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Protocol

Use of Virtual Reality in the Reduction of Pain After the Administration of Vaccines Among Children in Primary Care Centers: Protocol for a Randomized Clinical Trial

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Abstract

Background: Pain and anxiety caused by vaccination and other medical procedures in childhood can result in discomfort for both patients and their parents. Virtual reality (VR) is a technology that is capable of entertaining and distracting the user. Among its many applications, we find the improvement of pain management and the reduction of anxiety in patients undergoing medical interventions.

Objective: We aim to publish the protocol of a clinical trial for the reduction of pain and anxiety after the administration of 2 vaccines in children aged 3 to 6 years.

Methods: We will conduct a randomized, parallel, controlled clinical trial with 2 assigned groups. The intervention group will wear VR goggles during the administration of 2 vaccines, while the control group will receive standard care from a primary care center for the procedure. Randomization will be carried out by using the RandomizedR computer system—a randomization tool of the R Studio program. This trial will be an open or unblinded trial; both the subjects and the investigators will know the assigned treatment groups. Due to the nature of the VR intervention, it will be impossible to blind the patients, caregivers, or observers. However, a blind third-party assessment will be carried out. The study population will include children aged 3 to 6 years who are included in the patient registry and cared for in a primary care center of the region of Central Catalonia. They will receive the following vaccines during the Well-Child checkup: the triple viral+varicella vaccine at 3 years of age and the hepatitis A+diphtheria-tetanus-pertussis vaccine at 6 years of age.

Results: The study is scheduled to begin in January 2022 and is scheduled to end in January 2023, which is when the statistical analysis will begin. As of March 2022, a total of 23 children have been recruited, of which 13 have used VR during the vaccination process. In addition, all of the guardians have found that VR helps to reduce pain during vaccination.

Conclusions: VR can be a useful tool in pediatric procedures that generate pain and anxiety.

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Introduction

Pain is defined as a complex and multidimensional sensory experience that comprises cognitive, behavioral, and psychological elements [1,2]; it is usually associated with unpleasant and subjective experiences and involves an adaptive function that allows for the initiation of protective responses [2]. Fear and stress influence the perception of pain, and the failure to apply appropriate pain reduction techniques exposes patients to unnecessary negative experiences, which can lead to long-term consequences, such as needle phobia or anxiety about medical procedures [2-4].

Pediatric patients seen in primary care settings frequently experience negative reactions, such as fear, anxiety, pain, or feelings of aggression, during routine invasive procedures, such as vaccinations, blood draws, wound sutures, or nursing care.

According to the World Health Organization, the possible adverse reactions to vaccination that are linked to procedural stress include fainting, hyperventilation, vomiting, and seizures [5]. Further, 19% of patients aged 4 to 6 years have needle phobia [6], with the average age of onset being 5.5 years [7]. Additionally, 7% of children experience syncope (fainting) during the administration of a medical injection, and 5% avoid treatment [8]. In a study on the impact of the fear of needles on adherence to vaccination, it was estimated that fear was the cause of nonadherence in 8% of children [9].

For all of these reasons, different mechanisms have been developed to try to minimize or eliminate adverse reactions to vaccination [2]. In the clinical practice guidelines for reducing pain during the administration of vaccines in the pediatric age group [10,11], the following main recommendations are made: breastfeeding during the procedure, offering sweet solutions before vaccine administration to those older than 1 year if they cannot be breastfed, and comfortably positioning patients if they can be held by their parents or using a rapid vaccination technique without aspiration.

Distractions help to reduce anxiety because they prevent painful stimuli from being transmitted either to the thalamus (ie, to the limbic system) or to the sensory cortex in such an effective way [12,13], thereby helping one to focus their attention on external and internal stimuli and not on nociceptive stimuli [14,15]. Distractions sometimes surpass local anesthetics' ability to control pain and discomfort associated with medical interventions [12]. Distractions can be active (immersive), which involves patient participation through the manipulation of the environment, or passive (nonimmersive), which involves observation only [13].

Current technological advances, especially in the field of virtual reality (VR), have resulted in new types of distractions, which can be used along with traditional distractions [14] to achieve better pain control in pediatric patients for procedures such as vaccination, according to the *Protocol of Preventive and Health Promotion Activities in Pediatric Patients: Healthy Childhood* [15].

VR is a term that was proposed in the mid-1980s by Jaron Launier, and it refers to a computer technique that allows for the creation of a simulated environment by means of a device with sensors that can be connected to a computer, mobile device, or tablet [1,3]. Its effectiveness is based on the psychological theory of "presence" [2,3]. This theory posits that people interact with their environments via the following three types of components: auditory, visual, and tactile components [1,2]. VR technology redirects one's attention to a more pleasant environment [2] by replacing real stimuli with virtual stimuli. This activates users' higher cognitive and emotional brain regions, resulting in the dissociation of pain [2,3].

The idea behind VR-generated analgesia was probably inspired by the intercortical modulation of pain matrix signaling pathways via attention, emotion, memory, and other senses [12,13].

In a systematic review published by the Cochrane Library in 2019 on VR distraction for reducing acute pain in children, it was concluded that the use of VR had low evidence regarding its benefits. However, in that review, due to the limited amount of data available, no conclusions could be drawn about the side effects of VR, satisfaction with VR, the level of parental anxiety, or the cost of VR use [12].

Many aspects remain to be clarified; however, the use of VR for pain management has shown great benefit in hospital procedures. Our study seeks to introduce VR as an analgesic tool in pediatric primary care services and daily procedures, such as vaccination, thereby combining new technologies with traditional concepts, such as distraction [1-3].

Methods

Study Design

Trial Design

We will conduct a randomized, single-center, open, parallel, and controlled clinical trial with 2 assigned groups (intervention group and control group).

Scope and Period of the Study

The study population will include children aged 3 to 6 years who are included in the patient registry and are being seen in a primary care center of the Catalan Institute of Health in Central Catalonia.

The study will be conducted during the period of January 2022 to January 2023. If the minimum sample size is not achieved, the study period will be extended until it is achieved.

Participants

Inclusion Criteria

The patients who will take part in the study will be those from the pediatric population (ie, those aged 3 to 6 years) in the register of patients from a primary care center of the Catalan Institute of Health in Central Catalonia who, according to the vaccination schedule, are due to receive 1 of the following 2 vaccinations: (1) the triple viral+varicella vaccine at 3 years of age and (2) the hepatitis A+diphtheria-tetanus-pertussis vaccine at age 6.

Exclusion Criteria

The exclusion criteria will include the following: (1) patients who have already received 1 of the 2 vaccines to be administered; (2) patients and accompanying persons who do not understand and speak Catalan or Spanish; (3) patients with physical or mental illnesses, as well as those with blindness or deafness; (4) patients with a known history of epileptic episodes or severe motion sickness; (5) patients with any infections, burns, or injuries to the face, head, or neck that may interfere with the placement of the VR device; and (6) the absence of legal guardians for signing the informed consent form.

Intervention

The intervention group will use the Pico G2 VR goggles (Pico Interactive Inc) during the administration of the two vaccines, together with an Android AOYODKG tablet, which will be connected to the goggles as a controller.

The control group participants will receive traditional distractors, such as being held by the parent or guardian who accompanies them to the appointment, receiving stickers at the end of the appointment, or receiving rewards that the parent or guardian has prepared from home.

Eligible patients will be invited to participate in the study on an ongoing basis, and the assignment to study groups will be randomized.

Randomization

Sequence Generation

Randomization will be carried out by using the RandomizedR computer system—a randomization tool of the R Studio program.

Implementation

The participants will be selected from a patient diary register. Both the sequence and the allocation of participants to the interventions will be generated by using the RandomizedR computer system.

Masking

Due to the nature of the study, it will not be possible to mask patients or health care professionals. Therefore, the trial will be open or unblinded. However, a blind evaluation by third parties will be carried out, as the person in charge of data analysis will not be involved with the intervention.

Sample Size Determination

To detect a 1-point difference between the two groups on the pain level scale, a sample of 150 boys and girls in each group is required, assuming an SD of 3 points, an α risk of 5%, a power of 80%, and an estimated loss to follow-up rate of 5% [16].

Data Collection and Sources of Information

Recruiting Patients to Participate in the Study

The procedure will be carried out by 1 pediatric team consisting of a pediatrician and a nurse of the primary care center in Súria (Spain). The families will be contacted by telephone to schedule the patients for the checkup at 3 and 6 years of age, as is currently done. The nurse will administer the vaccines and will continue to be part of the Well-Child checkup team.

Information on the purpose, risks, and benefits of the study will be provided, and any queries will be answered. In addition to verbal information, an information document about the study will be provided.

Prior to the start of the study, training on the use of the devices will be given to all of the health care personnel involved.

If a family agrees to be included in the study, the informed consent form must be signed by at least 1 of the parents or legal guardians. The signing parent or guardian will agree to inform the other parent or guardian.

Data Collection, Sources of Information, and Intervention

Study data collection will begin once informed written consent has been obtained from the legal guardian. For patients' assignment to a study group, randomization will be carried out by using the RandomizedR computer system. The person responsible for data collection will indicate the patients' age, gender, and study group and the type of intervention performed. Prior to administering the vaccine, the patients' condition and heart rate on arrival at the clinic will be recorded, regardless of their assigned study group.

For patients in the intervention group, it will be explained to them that they will be able to use the VR device; they will be assisted in fitting the device and will be given a brief explanation of the content that will be played. The *Leia's World* (VRPharma Immersive Technologies SL) content, which was specially designed for vaccination, will be used, and data will be collected before and after the procedure for each of the first 2 vaccinations.

The Wong-Baker Faces Pain Rating Scale, which ranges from 0 to 10, and the Children's Fear Scale, which ranges from 0 to 4, will be used to evaluate the reduction of pain and anxiety. The data collected from the control group will be compared with those collected from the intervention group (heart rate, the level of pain perception, the level of distress and fear, and the length of visits) [17-19]. In addition, to understand the perceptions of the tutors on the use of VR, a satisfaction survey will be conducted [20].

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The aforementioned data will be collected by the nursing or pediatric professional via a web questionnaire generated by the Microsoft Forms tool on the tablet and will be hosted in a computer server of the Institut Català de la Salut de la Catalunya Central.

Statistical Analysis

An intention-to-treat analysis will be performed; the subjects will be analyzed according to the group to which they were initially assigned and not the group in which they finally participated.

The data will be obtained through Microsoft Forms (an application included in Office 365 [Microsoft Corporation] that allows one to create customized questionnaires, surveys, and records) and analyzed with R software (version 4.0.3) [21,22]. Categorical variables will be described with absolute frequencies and percentages, and continuous variables will be described with means and SDs or medians and quartiles. A 2-tailed *t* test will be used to compare the values related to pain, anxiety, and satisfaction across the two groups. The correlations between pain perception and anxiety values reported by the children and those reported by their caregivers and nurses will be evaluated by means of a Pearson correlation. The significance level will be set at 5%, and all CIs will be set at 95%.

The data will be stored in a database. The Pearson chi-square test will be used for the calculation of statistical significance.

Ethics Approval

The University Institute for Research in Primary Health Care Jordi Gol i Gurina (Barcelona, Spain) ethics committee approved the trial study protocol (approval code: 21/233). Written informed consent will be requested from all parents or legal guardians participating in the study.

Results

The study is scheduled to begin in January 2022 and is scheduled to end in January 2023, which is when the statistical analysis will begin. As of March 2022, a total of 23 children have been recruited, of which 13 have used VR during the vaccination process. In addition, all of the guardians have found that VR helps to reduce pain during vaccination.

We hope that sufficient evidence can be obtained to demonstrate that the use of VR is effective in reducing anxiety and pain. In this context, the Catalan health system could introduce the use of VR in usual practices and extend its use to other potentially painful processes. Statistically significant differences in heart rate and decreased pain perception that are in favor of the intervention group will be considered a satisfactory result.

Discussion

Our study aims to demonstrate that the use of VR goggles reduces the pain reported by children aged 3 to 6 years during the administration of 2 vaccines. The use of VR goggles may also reduce anxiety after such a procedure and thus result in greater satisfaction among the parents or legal guardians.

There are studies that have already used VR with children for painful procedures and during the administration of vaccines [12-14]. However, to date, there is no literature describing studies that focus on the population of children aged 3 to 6 years who are administered 2 vaccines at the same visit and also record the adverse effects of the use of VR goggles. In this context, our study may provide further support for the use of VR in the management of pediatric patients. Obtaining favorable results could lead to the use of VR as a standard practice for painful procedures performed in the primary care centers of Catalonia. The use of VR for pain reduction is likely to result in a decrease in visit duration. To demonstrate the efficacy of the use of VR, the professionals will note the length (in minutes) of the visits in order to evaluate whether VR reduces or increases the duration of the visits.

Our study has several limitations. The main limitation of the study is the pressure of care and time management in the pediatric consultations conducted by the Well-Child Programme. The time available for caring for a patient is limited. The time required for secluding the participants and obtaining consent and questionnaire data is estimated to be 5 minutes. This means that if the burden of care is high, the quality of care will have to be prioritized, and the recruitment of patients who are eligible to participate in the study will have to be paused.

Another limitation is that parents (or legal guardians) and minors who do not speak Catalan or Spanish cannot participate in the study. The use of VR could be highly advantageous if the VR content is translated into the native languages of these children, because they are usually more fearful and anxious when they cannot understand the pediatrician or nurse.

There are other limitations associated with the study design, patient recruitment, and the inclusion and exclusion criteria. First, patients receiving vaccines from their private pediatricians will be excluded. Second, the study population will be limited to a specific age range. Third, evaluations will only be conducted for vaccination and not for other invasive procedures. Fourth, patients who have already received 1 of the 2 scheduled vaccines will be excluded, since they would have previously presented the related pathology (eg, patients who have already been vaccinated for chickenpox). Fifth, parents or legal guardians who do not agree with vaccination in general or are associated with the masking process may introduce bias when they report their experiences in the survey.

Data Availability

The principal study researchers will have access to the full data set, and the data generated and analyzed during the study will be available from the corresponding author. The results obtained are expected to be published in peer-reviewed journals and at national and international conferences.

Authors' Contributions

All authors contributed to the design and content of the study protocol. MDLCH is responsible for the coordination of the study. JVA, MCM, PAP, AFC, and QMC are responsible for the design and writing of the initial draft of the manuscript. MDLCH is responsible for data collection, and JVA, QMC, and AFC are responsible for data processing and exploitation. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

MCM is the cofounder and CEO of VRPharma Immersive Technologies SL—a company that offers a virtual reality (VR) kit system for hospital use—and has an economic interest in the study, as the VR kit system is offered by VRPharma as a service. In order to minimize the conflict of interest, VRPharma's staff will not be involved in the data collection, the statistical analysis, and the results representation phase.

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Abbreviations

VR: virtual reality

Protocol

Comparing Online and On-Site Cognitive Behavior Therapy in Major Depressive Disorder: Protocol for a Noninferiority Randomized Controlled Trial

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2022/4/e38720

Abstract

Background: The incidence of mental health disorders in Canada is increasing with costs of CAD $51 billion (US $40 billion) per year. Depression is the most prevalent cause of disability while cognitive behavioral therapy (CBT) is the best validated behavioral depression treatment. CBT, when combined with mindfulness meditation (CBT-M), has strong evidence for increased efficacy. While randomized controlled trials (RCTs) have demonstrated online CBT-M efficacy, comparisons with in-office delivery are lacking.

Objective: The aim of this research is to assess whether online group CBT-M (with standard psychiatric care) is non-inferior in efficacy and more cost-effective than office-based, on-site group CBT-M at post-intervention and 6-months follow-up in major depressive disorder. The study will also assess whether digitally recorded data (ie, online workbooks completed, Fitbit step count, and online text messages) predict depression symptom reduction in online participants.

Methods: This single-center, two-arm, noninferiority RCT employs assessor-blinded and self-report outcomes and economic evaluation. The research site is the Centre for Addiction and Mental Health (Toronto), a research-based psychiatry institution where participants will be identified from service wait lists and through contacts with other Toronto clinics. Inclusion criteria are as follows: (1) aged 18-60 years, any ethnicity; (2) Beck Depression Inventory-II (BDI-II) of mild severity (score ≥14) with no upper severity limit; (3) Mini-International Neuropsychiatric Interview-confirmed, psychiatric major depressive disorder diagnosis; (4) fluent in English. All patients are diagnosed by staff psychiatrists. Exclusion criteria are as follows: (1) receipt of weekly structured psychotherapy; (2) observation of Diagnostic and Statistical Manual of Mental Disorders (5th Edition) criteria for severe alcohol or substance use disorder (in past 3 months), borderline personality disorder, schizophrenia (or other primary psychotic disorder), bipolar disorder, or obsessive-compulsive disorder; (3) clinically significant suicidal ideation (imminent intent or attempted suicide in the past 6 months); and (4) treatment-resistant depression. All participants receive standard psychiatric

care, experimental participants receive online group CBT-M, and controls receive standard care in-office group CBT-M. The online group program (in collaboration with NexJ Health, Inc) combines smartphone and computer-accessed workbooks with mental health phone counselling (16 hours in 16 weeks) that coordinates software interactions (eg, secure text messaging and Fitbit-tracked walking). The primary outcome is BDI-II, and secondary outcomes are anxiety (Beck Anxiety Inventory), depression (ie, Quick Inventory of Depressive Symptomatology and 17-item Hamilton Depression Rating Scale), mindfulness (Five-Facet Mindfulness Questionnaire), quality of life (European Quality of Life Five Dimension), and pain (Brief Pain Inventory).

Results: Based on prior studies with the BDI-II and 80% power to reject an inferiority hypothesis with a 1-sided type I error rate of 5%, a sample of 78 per group is adequate to detect small-to-medium–effect sizes.

Conclusions: This study assesses online CBT-M efficacy and noninferiority in relation to in-person CBT, and the cost-effectiveness of both interventions.

Trial Registration: ClinicalTrials.gov NCT04825535; https://www.clinicaltrials.gov/ct2/show/NCT04825535

International Registered Report Identifier (IRRID):   DERR1-10.2196/29726

Introduction

Mental health disorders are Canada's most costly chronic health problem for both health systems and patients, and they are increasing in incidence. The current economic costs of mental health are estimated at CAD $51 billion annually (US $40 billion), with CAD $42.3 billion (US $33 billion) in direct costs to the Canadian health care system [1]. Depression is a commonly diagnosed mental health disorder, representing the most prevalent cause of disability worldwide [2]. Cognitive behavioral therapy (CBT) is the best validated psychotherapy for the treatment of depression, with decades of research demonstrating its efficacy [3]. Despite demonstrated efficacy, many individuals are not able to access adequate CBT treatment due to the limitations of face-to-face delivery. Improving access to CBT services is crucial to overcoming the treatment barriers (including geographic distance, cost, time, and perceived stigma) that currently prevent access to necessary mental health care for individuals with depression [4-6]. Recent research projects have focused on internet-based CBT (with internet-delivered or telephone-based interventions) as a means of delivering cost-effective treatment to populations that are unable to access high-quality psychotherapy services within traditional in-office environments. The structured and goal-directed modules of CBT are well suited to online delivery, and numerous randomized controlled trials (RCTs) have indicated that internet-delivered CBT is highly effective in symptom reduction and depression remission [7-9]. In recent years, CBT has been integrated with mindfulness meditation (CBT-M) following strong evidence for the increased efficacy when CBT and mindfulness meditation are combined [10]. While other trials support online CBT and mindfulness efficacy versus control groups [11-18], no prior trial, to our knowledge, has compared the efficacy and cost-effectiveness of online group CBT-M versus standard office-based group CBT-M.

Previous noninferiority RCTs have indicated that guided online CBT can be at least as effective as in-person CBT for the treatment of depression; however, these studies are limited by the use of small, nonclinical samples and do not include cost-effectiveness comparisons [19-21]. Research is now required with an adequate sample size and in-depth cost comparisons to fully establish noninferiority and cost-effectiveness [22]. This study has been registered with ClinicalTrial.gov (NCT04825535).

Methods

Aim

This study has the 3 following aims: (1) to evaluate whether online group CBT-M (with standard psychiatric care) is noninferior in efficacy compared with office-based group CBT-M (with standard care) as measured by the BDI-II (Beck Depression Inventory-II) score in the treatment of adults with major depressive disorder (MDD) [23]; (2) to evaluate whether online group CBT-M is more cost-effective than office-based group CBT-M post intervention and at 6 months post-intervention follow-up; (3) to assess, within the online group CBT-M intervention group, whether digitally recorded adherence data (ie, online workbooks completed, Fitbit tracked steps, online text messages exchanged, and phone sessions completed) predict outcome benefits as indicated by the changed BDI-II score [23].

Ethical Considerations, Recruitment, and Randomization

The study has been approved by the Research and Ethics Board at the Centre for Addiction and Mental Health (CAMH) (reference 087/2020). The participants will be identified from the wait lists within the CAMH General Adult Psychiatry and Health Systems Division, which annually services thousands of MDD patients. The attending physician or clinician identifies prospective participants and asks for their verbal consent to receive more information about the research. Once the patient's attending physician or clinician obtains verbal consent for more information about the research project, he or she can refer eligible participants to the research analyst who explores interest with the participant, and after an expressed interest, reviews and explains the study. Eligibility screening and written consent are undertaken in person prior to randomization. The study

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biostatistician performs electronic randomization with study IDs blindly assigned to intervention (online CBT-M plus standard psychiatric care) and control (office-based group CBT-M plus standard psychiatric care) groups. The study ID information with the respective group allocation will be transferred onto cards placed in opaque, individual, sealed envelopes. After a participant completes baseline questionnaires, the research analyst opens the next envelope in sequence to determine group allocation and study ID. Based on the results of previously successful RCTs, including the one conducted at the identical study site, we will recruit 100 participants per group or 200 overall (N=200). One-sided type 1 error rate is set at 5%. We chose a margin of 3 and a correlation of 0.70, indicating a sample size of 78 per group in 2 groups, which is more than adequate for the detection of small-to-medium effect sizes. The 16-week intervention entails 16 weekly group CBT in-person sessions (control group) (1.5 hours in duration) and 16 weekly, phone-based navigator-health coach sessions (16 hours in duration per subject in group or individual formats). Participants are assigned to review 1-2 workbooks and related videos per week (16-32 workbooks per 16 weeks). Assessments take place at post-intervention and 6 months follow-up. Given the recruitment, consent, and intervention target of 48 participants per year, we expect to complete the study within 2.5 to 3 years.

Inclusion Criteria

The inclusion criteria are as follows: (1) individuals 18-60 years of age; (2) BDI-II of at least mild severity (score ≥14) with no upper severity limit [23]; (3) MINI (Mini-International Neuropsychiatric Interview)-confirmed diagnosis of MDD [24]; and (4) fluency in English. All participants are diagnosed by a CAMH staff psychiatrist with diagnosis confirmed via the MINI [24], administered at the screening visit.

Exclusion Criteria

The exclusion criteria are as follows: (1) individuals currently receiving weekly structured psychotherapy; (2) individuals who meet DSM-V (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition) criteria for severe alcohol or substance use disorder (in the past 3 months), borderline personality disorder, schizophrenia, or any other primary psychotic disorder, bipolar disorder, or obsessive-compulsive disorder; (3) individuals who manifest clinically significant suicidal ideation defined as imminent intent or attempted suicide (in the past 6 months); and (4) individuals who are judged to have treatment-resistant depression, as defined by failure in at least 2 trials of antidepressant medications or a course of psychotherapy during the current depressive episode [25].

Interventions

Online Intervention

The online group CBT-M program combines online-accessed workbooks with phone-based navigator coaching that assists with the coordination and support of multiple software interactions (eg, secure text messaging, Fitbit tracked walking, and food monitoring via photography). Each participant is loaned a Fitbit HR Charge 4 (Fitbit Inc), which assesses physical steps and 24-hour heart rate, averaged in 5-second intervals.

Intervention content builds on 6 online RCTs with students [26-32], 1 RCT with adults with type 2 diabetes [11,33,34] (where significant mental health and blood glucose benefits resulted), and 1 online RCT with youth diagnosed with MDD [22]. The content contains 24 workbook chapters on multiple topics derived from the focus group study (eg, Living By Your Truths, Overcoming Wired-ness and Tired-ness, Mindfulness and Relationships, Loss and Grief, Resilience, Befriending Ourselves, Befriending Your Body with Exercise, Body Image, Intimacy, Forgiveness, Overcoming Procrastination, Dealing with Negative Moods, Stress Resilience, Reducing Performance Anxiety, and Cultivating Inspiration), addressed in sequences mutually agreed on by the participants and navigator-coaches.

The online CBT-M groups address structured tasks that elevate mood and decrease anxiety. Depressive social withdrawals are identified and reflected on while corrective emotional experiences are elicited, structured, and supported. Healthy internet interactions are reinforced by the web-based program content (24 workbooks and 56 videos), with priorities guided by participant interests. While internet-based contacts are sometimes distracting "escapes" (eg, Netflix movies and video game playing), they can be productive, socially engaging events (eg, TED Talks, CBT discussion, and mindfulness instructions) where role-modeling coordinates with learning. Group members stimulate and reinforce health behavior adoptions (exercise, CBT, mindfulness, sleep hygiene, diet, and text message encouragement) and transformations from distractive media fixations to positive learning and enjoyment. Internet-based contacts integrate with face-to-face professional and familial contacts and social intimacy development. Group online CBT-M tasks emphasize applying CBT-M methods in accord with content themes, which are decatastrophizing, overcoming perfectionism, sound sleep, self-befriending, courage development, forgiveness, interpersonal mindfulness, and autonomous generosity. This progression coordinates physical and cognitive changes that integrate interpersonal contacts with self-management. The tracking of walking exercise and heart rate (HR), on a 24-hour basis, captures HR elevations that reflect episodes of anxiety and negative affect (elevated HR with minimal movement). There is selective sharing of Fitbit bio-behavioral data with designated staff and group members. Reduced HR often accompanies mindfulness practice while mildly elevated HR is closely associated with walking (ie, movement-affected HR). Self-modification goals involve improving autonomic nervous system balance through appropriate exercise, improved sleep hygiene, and restorative sleep [35].

Office-Based Intervention

The on-site, usual-care CBT group follows the structure of the "Mind Over Mood" workbook in reviewing CBT concepts and procedures [36]. A series of worksheets assist participants in differentiating moods from thoughts and situational influences, leading to modifications of thinking, behavior, emotion, and mood.

Difficulties with cognitive change are assumed to be associated with self-acceptance deficits and negative mood dominance. Increased self-acceptance is linked with mindfulness

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experiences, which involve "more focusing on the present moment" and on nonjudgmental acceptance of ongoing experience. Mindful breathing awareness is described in content on "balanced deep breathing" and in tension releases achieved via progressive muscle relaxation practice [37].

An emphasized structure is the automatic thought record by which negative, disturbing thoughts are identified, and attention directed to alternate thoughts evaluated as clearer and less distorted. These transitions are more difficult when immersions in negative moods diminish the confidence in finding a "better" thought. Accordingly, self-efficacy is an important goal, emphasized in exchanges of support between group members and in enhanced experiences of self-acceptance.

Behavioral activations are structured for the development of increased awareness and observations of how self-control resources elicit gratifying activities. On the basis of behavioral activation practices, cognitive restructuring strategies utilize the automatic thought record or experiential approximations of the automatic thought record [38].

Another major component of group CBT-M at CAMH involves examinations of core beliefs where multiple techniques are employed (eg, self-observation logs and historical self-reviews) in the group setting and in individual homework assignments between sessions [38].

Hypothesis

Online group CBT-M will be noninferior to standard, office-based group CBT in the treatment of MDD (as indicated by BDI-II score change) when online and office-based treatment groups are compared, using both intention-to-treat and per-protocol analyses. Online group CBT-M will be more cost-effective than standard, office-based group CBT, as measured by cumulative costs and quality-adjusted life years (QALY) calculated in the cost utility analysis. Within the online CBT-M intervention participant group, digitally recorded adherence data will predict outcome benefits (as reflected in the BDI-II score change). Adherence over time will be compared within each participant using a generalized estimating equation logistic regression model with an autoregressive 1 (AR1) correlation structure.

Outcome Measures

Primary Outcome

The primary outcome measure is the BDI-II [23]. It is a 21-item self-report scale, measuring symptoms of depression with a 4-point Likert scale (0 to 3), with higher scores indicating more severe depressive symptoms. The customary cut-off scores for mild depression are 14 to 25, moderate depression 26 to 30, and severe depression 31 and greater.

Secondary Outcomes

The secondary outcomes assess the following: anxiety (Beck Anxiety Inventory) [39]; depression (QIDS [Quick Inventory of Depressive Symptomatology] [40] and HDRS-17 [17-item Hamilton Depression Rating Scale], consisting of an interview with a blinded-assessor rater) [41]; mindfulness (FFMQ [Five-Facet Mindfulness Questionnaire]) [42]; quality of life

(EQ-5D [European Quality of Life Five Dimension]) [43,44]; patient costs (health care cost diary for major depression) [45]; and pain (brief pain inventory) [46].

All self-report measures and the HDRS-17 interview are carried out at the same CAMH mood and anxiety research clinic in identical assessment rooms. The HDRS-17 interviewer-assessor is blinded to intervention and control conditions for the trial duration and is experienced in the blinded-assessor role with similar conditions conducted at the identical study site used in this trial [22].

Results

Analyses

Primary Outcome

The primary analysis will be a Bayesian analysis of covariance (ANCOVA), with change in BDI-II between baseline and 16 weeks as the outcome and 2 covariates, the baseline score and the intervention group variable, coded as "O" (for online) and "I" (for in-office). We refer to the parameter of interest as Δ, the baseline-adjusted difference between the 2 groups in the change in BDI-II from baseline to 16 weeks, coded such that $\Delta<0$ means that the online group has a smaller decrease in the level of depression over the course of the study. Then, if $\Delta>-3$, the improvement in the online group is at most 3 points worse than the improvement in the in-office group, and the online group is noninferior to the in-office group. Using noninformative priors for all study parameters in the ANCOVA model, we will compute and plot the full posterior distribution of Δ, presenting the lower 95% credible interval for Δ, and then calculating the posterior probability that $\Delta>-3$; in other words, the probability (after observing the study data) that online CBT is noninferior, according to our definition. One advantage of a Bayesian approach is that it allows the assigning of posterior probabilities of noninferiority at other margins; notably, other margins near 3 may have equal levels of evidentiary support. For example, without a penalty for multiple testing, we can compute the probability that $\Delta>-2$ or $\Delta>-4$. Another advantage of the Bayesian approach is that it involves a more useful presentation of results than a simple confidence interval or *P* value. Finally, the outputs of the Bayesian model can be used as probabilistic inputs for the economic analysis. Since this is a noninferiority approach, the primary analysis will be per protocol, which, in the presence of intervention nonadherence, is more conservative than intention-to-treat (ie, less likely to conclude that groups are similar when they are not). Three secondary analyses of the primary outcome will be conducted. First, we will make the above between-group comparison of the changes in BDI-II scores from baseline to each follow-up time point. Secondly, we will perform an intention-to-treat analysis, including outcomes on participants who were nonadherent to their program (standard care CBT vs CBT online) using established cut-offs. Finally, to assess for sensitivity to random imbalance in baseline characteristic, the following covariates will be added to the ANCOVA model: age, baseline anxiety, baseline depression (HDRS-17), baseline pain, and baseline mindfulness. If more than 5% of the participants included in the per protocol are missing outcome data, that analysis will use multiple imputations

within the Bayesian model with full baseline covariate data used to impute missing outcomes. In a second approach, we will assume that missing follow-up data are missing not at random and replace missing values by values randomly sampled from the upper half (high BDI-II) of their predictive distribution. This represents the assumption that those who have no follow-up BDI-II have values lower than the median predicted by their baseline characteristics. This will be repeated within the intention-to-treat analysis, where missing outcome data will be more common.

Secondary Outcomes

A similar modeling approach will be used for each secondary outcome (Beck Anxiety Inventory, QIDS, and HDRS-24), mindfulness (FFMQ [Five-Facet Mindfulness Questionnaire]), pain (brief pain inventory), health care cost diary for major depression, and quality of life (EQ-5D). While noninferiority margins per outcome are nonexistent, we will present probabilities for a range of margins based on fractions of the minimally clinical important difference for these scales (where available) or fractions of a standard deviation. All primary and secondary outcomes will be analyzed as continuous variables, with outcomes modelled as normal, *t*, rescaled beta, log-normal, or gamma distributions, whichever is most appropriate.

Postintervention Period Outcomes

We will examine BDI-II changes over time across the 2 intervention delivery models during a 6-month post-intervention period. To give a quantitative overview of changes between and within groups over 6 months, all study outcomes will be assessed using linear mixed effects models incorporating within-person correlation. Mixed effects models allow for including partial data (eg, from participants with missed visits or who dropped out prematurely) while accounting for repeated within-person data [47]. The baseline and follow-up scores (up to 10 months from baseline) will form the dependent variable and intervention group, time, and the time-treatment interactions will be the independent variables. Within-person correlation of residuals will be handled by an AR1 error structure. Through the examination of estimated model parameters and their 95% confidence intervals, we can assess whether changes over time are similar between groups and whether differences between groups at any given time are clinically important.

Adherence

Multiple analyses are used to assess adherence in the online group CBT-M program and the relationship of adherence to both time and potential predictors. Adherence is cumulatively and quantitatively defined as a binary variable (adherent or nonadherent). We will assess adherence over 2 distinct periods—0 to 2 months and 2 to 4 months—so each participant has up to 2 adherence measures. Our first analysis of adherence will simply be the calculation of percentages adhering in each of the time windows. The chi-squared or Fisher exact tests will compare adherence within each of the time windows. All further analyses will be carried out on the sequence of 2 adherence measures on each participant using a generalized estimating equation logistic regression model with an AR1 correlation structure. A series of models will be run, which is as follows:

to check adherence changes over time, we will use time as a categorical predictor variable and assess its importance using a Wald test; to examine predictors of adherence, variables (steps per day or HR, workbooks completed, text messages exchanged, videos watched, and phone counselling calls completed) measured at the start of each of the 2 time periods will be added as predictors for the corresponding adherence outcome. These time-varying predictors help us assess whether the most recent assessment of a given predictor predicts adherence over the following 2 months.

Missing Data

Missing data may occur when participants miss an assessment or outcome measure but continue the study participation or because participants drop out prematurely. In the first case, regression-based imputation at the individual patient level will be used to impute the missing outcomes. In the second case, imputing data using bottom quintile scores of responders will be used as a worst-case sensitivity analysis. Loss to follow-up is unavoidable in MDD studies and can reflect poor intervention response. It was a relevant comparison variable in the recently completed RCT where loss to follow-up in the intervention arm was 10%, compared to 60% in the standard psychiatry control arm [22]. While differences may be more modest in the proposed trial (eg, 40% in group in-office CBT versus 10% in group online CBT), they will be carefully monitored and, as previously mentioned, represented in the cost-effectiveness and intention-to-treat analyses.

Cost-effectiveness

We will conduct a full economic evaluation following the design of a cost-utility analysis conducted from a societal and health care consumer or payer's perspective. We will adopt the following time horizons: within trial (4 and 10 months) and the lifetime of the trial cohort. A within-trial cost utility analysis will focus only on interventions directly evaluated in the trial. We will estimate costs for (1) the interventions; (2) physician services; (3) emergency department visits and hospitalizations; (4) outpatient diagnostic tests; (5) drugs, including those unrelated to MDD; (6) home care; (7) long-term care; (8) out-of-pocket costs; and (9) productivity costs. The intervention cost will be estimated by estimating the value of time of those administering the intervention, facility-use costs, and device or equipment costs, amortized over an appropriate period. Resource utilization, out-of-pocket costs, and productivity costs will be estimated using a patient cost diary. We will assess health outcome data in QALY using the EQ-5D at each time point [48-52]. Cumulative costs and QALY will be estimated and compared in order to calculate the incremental cost utility ratio, and incremental net health benefit. We will plot the cost-effectiveness acceptability curves and confidence ellipses to demonstrate variability in a trial sample and illustrate probability of online CBT-M being cost-effective compared with a standard CBT program at a range of willingness-to-pay thresholds.

Discussion

If the hypothesized results are obtained, online group CBT-M for the treatment of MDD can be used by health care providers

to deliver high-quality psychotherapy to more people in need. Online group CBT-M may be a primary treatment option for individuals currently unable to access standard office-based care due to distance, time, or cost. The cost-effectiveness analysis of online versus office-based group CBT-M will provide policy makers with definitive evidence to appropriately budget for internet-delivered CBT services. Acknowledged study limitations include the lack of blinding of self-report measures other than the interview-delivered HDRS-17 assessment [41].

Conflicts of Interest

Multimedia Appendix 1
CONSORT eHEALTH Checklist (V 1.6.1.).
[PDF File (Adobe PDF File), 879 KB - resprot_v11i4e29726_app1.pdf]

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Abbreviations

ANCOVA: analysis of covariance
AR1: autoregressive 1
BDI-II: Beck Depression Inventory-II
CAMH: Centre for Addiction and Mental Health
CBT: cognitive behavioral therapy
CBT-M: cognitive behavioral therapy with mindfulness
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EQ-5D: European Quality of Life Five Dimension
FFMQ: Five-Facet Mindfulness Questionnaire
HDRS: Hamilton Depression Rating Scale
HR: heart rate
MDD: major depressive disorder
MINI: Mini-International Neuropsychiatric Interview
QALY: quality-adjusted life years

QIDS: Quick Inventory of Depressive Symptomatology
RCT: randomized controlled trial

Protocol

Coordinating Health Care With Artificial Intelligence–Supported Technology for Patients With Atrial Fibrillation: Protocol for a Randomized Controlled Trial

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Abstract

Background: Atrial fibrillation (AF) is an increasingly common chronic health condition for which integrated care that is multidisciplinary and patient-centric is recommended yet challenging to implement.

Objective: The aim of Coordinating Health Care With Artificial Intelligence–Supported Technology in AF is to evaluate the feasibility and potential efficacy of a digital intervention (*AF-Support*) comprising preprogrammed automated telephone calls (artificial intelligence conversational technology), SMS text messages, and emails, as well as an educational website, to support patients with AF in self-managing their condition and coordinate primary and secondary care follow-up.

Methods: Coordinating Health Care With Artificial Intelligence–Supported Technology in AF is a 6-month randomized controlled trial of adult patients with AF (n=385), who will be allocated in a ratio of 4:1 to AF-Support or usual care, with postintervention semistructured interviews. The primary outcome is AF-related quality of life, and the secondary outcomes include cardiovascular risk factors, outcomes, and health care use. The 4:1 allocation design enables a detailed examination of the feasibility, uptake, and process of the implementation of AF-Support. Participants with new or ongoing AF will be recruited from hospitals and specialist-led clinics in Sydney, New South Wales, Australia. AF-Support has been co-designed with clinicians, researchers, information technologists, and patients. Automated telephone calls will occur 7 times, with the first call triggered to commence 24 to 48 hours after enrollment. Calls follow a standard flow but are customized to vary depending on patients' responses. Calls assess AF symptoms, and participants' responses will trigger different system responses based on prespecified protocols, including the identification of red flags requiring escalation. Randomization will be performed electronically, and allocation concealment will be ensured. Because of the nature of this trial, only outcome assessors and data analysts will be blinded. For the primary outcome, groups will be compared using an analysis of covariance adjusted for corresponding baseline values. Randomized trial data analysis will be performed according to the intention-to-treat principle, and qualitative data will be thematically analyzed.

Results: Ethics approval was granted by the Western Sydney Local Health District Human Ethics Research Committee, and recruitment started in December 2020. As of December 2021, a total of 103 patients had been recruited.

Conclusions: This study will address the gap in knowledge with respect to the role of postdischarge digital care models for supporting patients with AF.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12621000174886; https://www.australianclinicaltrials.gov.au/anzctr/trial/ACTRN12621000174886

International Registered Report Identifier (IRRID): DERR1-10.2196/34470

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Introduction

Background

Atrial fibrillation (AF) is a chronic health condition that is increasing in prevalence and is associated with substantial morbidity. In 2010, the number of individuals with AF globally was estimated to be 33.5 million, and this number is expected to double by 2050 [1]. AF places a significant burden on the health care system, particularly because of hospitalizations, with health care costs rising faster than those for any other heart rhythm condition [2]. AF is a substantial contributor to stroke, heart failure, cardiovascular events, dementia, and all-cause mortality [3], and in addition to the morbidity associated with these sequelae, symptomatic AF also contributes significantly to reduced quality of life [4].

Integrated care for AF that is both patient-centric and multidisciplinary is now recommended by several guidelines as the optimal way to manage AF and thereby improve quality of life, patient experience, and health outcomes [5-8]. Despite the push for integrated care, implementation of this model of care in a standardized way is difficult for many centers to achieve. Digital health tools have the potential to facilitate the integration and coordination of care between different clinicians (eg, cardiologist and general practitioner [GP]) and the patient [8], as well as provide standardized pathways of care, support, and education that are customizable and with the added potential for delivery at scale. The inclusion of mobile health (mHealth)—delivery of health care and support through mobile technologies—can enhance health care accessibility. Simultaneously, mHealth can improve the reach of clinical services to provide care to remote and isolated patients above and beyond face-to-face clinical service offerings. mHealth interventions have shown promise in prevention and management of cardiovascular conditions [9-21].

Automated telephone calls are a type of mHealth intervention with wide reach because anyone with a telephone—landline, mobile phone, or smartphone—can potentially receive these types of telephone calls [21-23]. *First-generation* automated telephone calls do not have voice recognition capabilities and include unidirectional calls where the person only listens to a recorded or automated script without the option to interact (eg, a reminder to take prescribed medications) or first-generation interactive voice response (IVR), where the user interacts by using the telephone's keypad (eg, pressing 1 for *Yes* or entering a number for their systolic blood pressure reading using the keypad). Existing systematic reviews of automated telephone calls have focused predominantly on these first-generation interventions, without voice recognition, showing promising but inconsistent effects in promoting medication adherence, physical activity, immunization, screening, and appointment attendance [22-24].

Recent developments in the field of artificial intelligence (AI) have led to the growing use of conversational AI–driven technologies [25-27]. Conversational technologies simulate human conversation with appropriate responses to dialogue using text or voice. Voice-based conversational technologies include smartphone assistants (eg, Apple's Siri and Amazon's Alexa) and AI-driven automated telephone calls, such as more recent IVR systems with voice recognition capabilities. These technologies can analyze verbal speech using voice recognition software and natural language processing, and because they are able to interact with users conversationally, they can potentially promote engagement with health interventions [22,25]. Some potential advantages of the voice recognition software are that it might further enhance the acceptability, engagement, and effectiveness of the IVR system [22,28].

To date, only a few randomized controlled trials have assessed the use of AI-driven automated telephone calls with voice recognition in health care. These studies have shown mixed results in screening interventions and pediatric care [29-31] and improvements in postdischarge care and outcomes of patients with acute coronary syndrome (eg, medication adherence and adverse events) [32]. Interventions had wide variation in voice recognition abilities (ie, from understanding only *yes* or *no* responses to understanding more complex phrases), and studies rarely evaluated patient perspectives and satisfaction with the intervention. So far, in AF, our literature search has identified no AI-driven automated telephone interventions; most digital solutions have focused on screening and basic support in smartphone apps, and the success of such solutions has been inconsistent [10-16,33].

Objectives

In this study, we will evaluate an intervention —*AF-Support*—designed to support patients with AF, which comprises a series of AI-driven automated telephone calls (IVR with voice recognition ability), emails, SMS text messages, and an educational website. We will conduct a randomized controlled trial to evaluate the efficacy of this intervention in improving the primary outcome of AF-related quality of life compared with usual care. Measures of engagement with the intervention and semistructured interviews with intervention participants will be used to evaluate the feasibility of the intervention.

Methods

Study Design

The study will be a 6-month randomized controlled trial (4:1 allocation ratio) among adults with AF to evaluate the efficacy of the intervention *AF-Support* in improving AF-related quality of life compared with a control group receiving usual care. It will be complemented by a mixed methods process evaluation to evaluate feasibility, uptake, and implementation. The 4:1 allocation ratio has been chosen to increase the number of

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participants exposed to the intervention to enrich data for the assessment of engagement with the intervention, including feasibility, uptake, and acceptability ([Figure 1](#)). The trial has been registered in the Australian New Zealand Clinical Trials Registry (trial number: ACTRN12621000174886).

Figure 1. Study flow diagram. AF: atrial fibrillation.
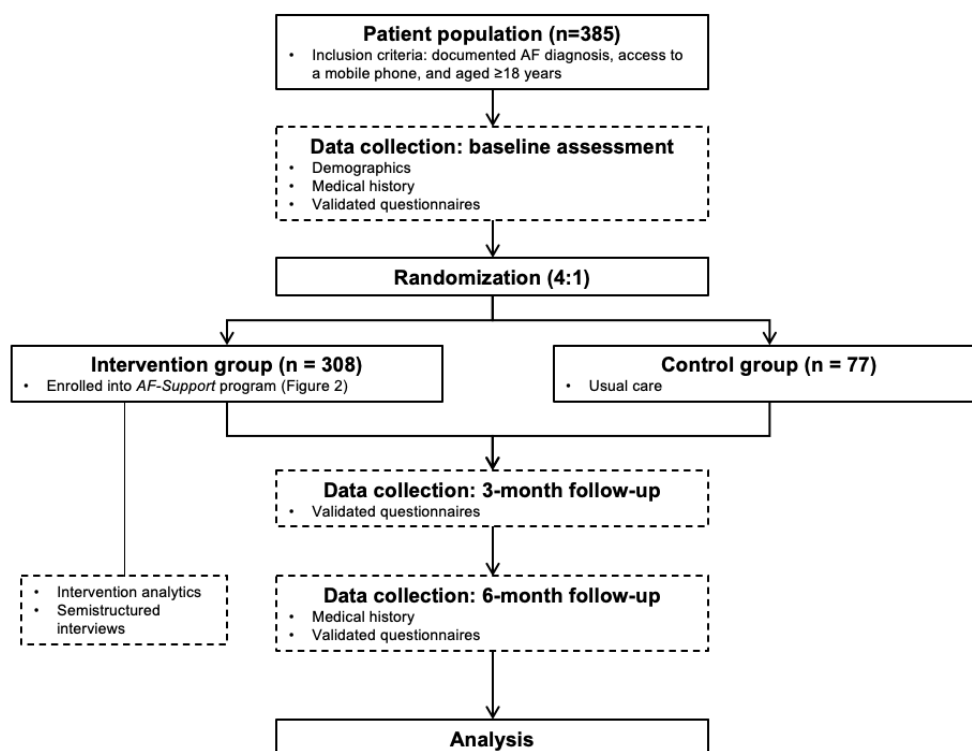
Study Setting

This study will be conducted in Western Sydney, New South Wales, Australia, with the initial sites proposed to be Westmead Hospital and Blacktown Hospital. Western Sydney serves a culturally, linguistically, and socioeconomically diverse population, with 35% of its population born overseas. Participants will be recruited from cardiology inpatient and outpatient services within the 2 hospitals.

Participants

Patients will be eligible to participate if they (1) are aged ≥18 years, (2) have a documented diagnosis of AF (including recently diagnosed AF, chronic AF, or paroxysmal or persistent AF), (3) have a mobile phone that is able to receive calls, (4) are able to receive SMS text messages or emails and open weblinks embedded in them, and (5) are competent with the English language as ascertained by the study researchers. Participants will be excluded from the study if they (1) are participating in another AF clinical trial; (2) are pregnant; (3) have a medical illness with anticipated life expectancy of <3 years; (4) are unable to provide written consent; or (5) have a concomitant illness, physical impairment (eg, hearing impairment), or mental condition that in the opinion of the study team or the primary physician could interfere with the conduct of the study, including outcome assessment.

Randomization and Blinding

The randomization sequence will be generated in R (using the randomizeR package; R Foundation for Statistical Computing)

and uploaded to REDCap (Research Electronic Data Capture, Vanderbilt University) software [34]. Allocation concealment will be ensured using management systems in REDCap. We will create separate data access groups to ensure that blinded researchers (eg, outcome assessors and data analysts) will not be able to see randomization lists or access the randomization form in REDCap. A nonblinded researcher will manage randomization of the participants within REDCap as they are recruited. The software will automatically allocate participants to the intervention or control group according to the randomization sequence, ensuring allocation concealment. Randomization will be stratified by center and sex. The allocation sequence will be in a 4:1 ratio (intervention:control). Because of the nature of the study, research study staff involved in recruitment, data collection, and follow-up (eg, semistructured interviews), along with participants and cardiologists, will not be blinded to the randomization outcome.

Control Group

The control group will receive usual care. Usual care for patients with AF consists of postdischarge instructions from the cardiologist regarding medications, lifestyle modification recommendations, encouragement of follow-up with a GP to be organized by the patient, and additional cardiologist appointments, as needed.

Intervention: AF-Support Program

Overview

The AF-Support program comprises 7 patient outreaches (digital *visits*) over 6 months through automated voice calls (IVR with

voice recognition) and SMS text messages or emails, supplemented by an educational website ([Figure 2](#)). The automated telephone system uses AI to interact with patients and simulate human conversation. The AI underpinning the automated telephone system (ie, conversational AI) [35] includes two main components: automatic speech recognition, which is able to recognize patient voice responses and translate them into text, and natural language processing and understanding, which identifies the semantic and syntactic elements from the user utterance. The system was culturally adapted to Australia and trained to recognize the Australian accent in uttered speech (see *Intervention Development and Patient Involvement* section). In addition, the system has a back-end feature called *Pardon*

Me; if the patient's verbal response is not understood, it will repeat the complete question and ask the patient to press a button corresponding to their response (eg, "please press 1 for always, 2 for often, and 3 for sometimes"), ensuring that the user hears the question more than once and has a chance to respond either verbally or with a number option.

The intervention aims to support patients with AF in self-managing their condition and coordinate primary and secondary care follow-up. The AF-Support program provides education and information on how best to navigate AF care, as well as facilitates risk assessment and provides clinician support as needed, triggered by *red flag* responses to the outreaches.

Figure 2. Overview of the AF-Support program. After leaving the hospital or clinic, patients will receive 7 outreaches consisting of automated telephone calls, emails, or SMS text messages, along with access to an educational website. AF: atrial fibrillation; BP: blood pressure; GP: general practitioner.
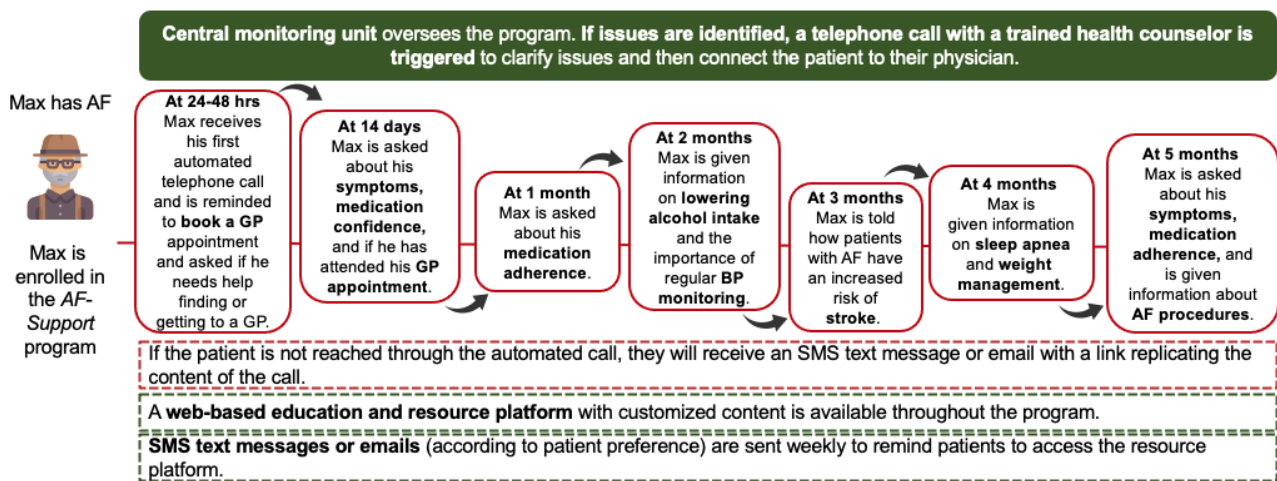
Digital Visits

Outreaches will occur at 24 to 48 hours, 14 days, 1 month, and then monthly until the end of the 6-month program. The automated telephone calls have an average duration of 4 minutes and will start with ensuring that the intended patient has answered the call, with options to call back or reschedule, and assessing their general health. During the automated telephone calls patients will receive AF education and support, as well as verbally respond to risk assessment queries ([Figure 3](#)). On the basis of their answers, patients will be presented with information that is tailored to their individual needs. The system is programmed to refer to prior content areas, that is, if a patient has reported in a previous telephone call that they have made a GP appointment, the system will know not to ask again. Each outreach will vary slightly in the information delivered and the risk assessment queries ([Table 1](#)).

On the basis of patient responses to risk assessment queries, certain answers will trigger an alert to the central monitoring team and lead to an escalation pathway with clinician support,

where needed. Triggering responses include the following: poor overall health status (options ranging from *excellent* to *poor*, where *poor* triggers an alert), impact of AF symptoms on daily life (options ranging from *not at all* to *extremely*, where *extremely* triggers an alert), medication confidence rated 1 or 2 on a scale of 1 to 7 (where 1 is *not confident at all* and 7 is *very confident*), nonadherence to medication ("Are you taking your medications as instructed?"; options are *yes* or *no*), and not having booked or attended a GP appointment within 1 month of hospital discharge. These alerts will be seen and actioned by the central monitoring team and addressed within 24 to 48 hours.

If participants are unable to be reached in the first call attempt, the technology has the capability to leave voicemails directing individuals to a 24/7 telephone number that they can use to complete the call at a more suitable time. If the system is unable to connect with the patient after 3 failed call attempts, an SMS text message or email (depending on patient preference) will be sent containing a link replicating the content of the call, including the option for patients to respond to the queries using a multiple-choice response format ([Figure 4](#)).

Figure 3. Example of the automated telephone call flow and content. GP: general practitioner.

Table 1. Educational information and risk assessment queries delivered in each outreach.

	Outreach number						
	1	2	3	4	5	6	7
Educational information							
General lifestyle information (eg, diet and physical activity)	✓		✓	✓	✓		✓
Importance of GP[a] support	✓						✓
Medication adherence		✓					
Limiting alcohol intake				✓			
Blood pressure control				✓	✓		
Warning signs and risk of stoke					✓		
Sleep apnea						✓	
Weight management						✓	
AF[b] procedures							✓
Risk assessment queries							
Overall health status	✓	✓	✓	✓	✓	✓	✓
Regular GP or medical center	✓						
Transportation barriers to accessing appointments	✓	✓					
Booked or attended GP appointment		✓	✓		✓		
AF symptoms and impact on daily life		✓					✓
Medication confidence and adherence		✓	✓				✓

[a]GP: general practitioner.

[b]AF: atrial fibrillation.

Figure 4. Webpage substitute for the automated telephone call. It replicates content from automated telephone calls, including queries presented in a multiple-choice response format, as seen on a smartphone.
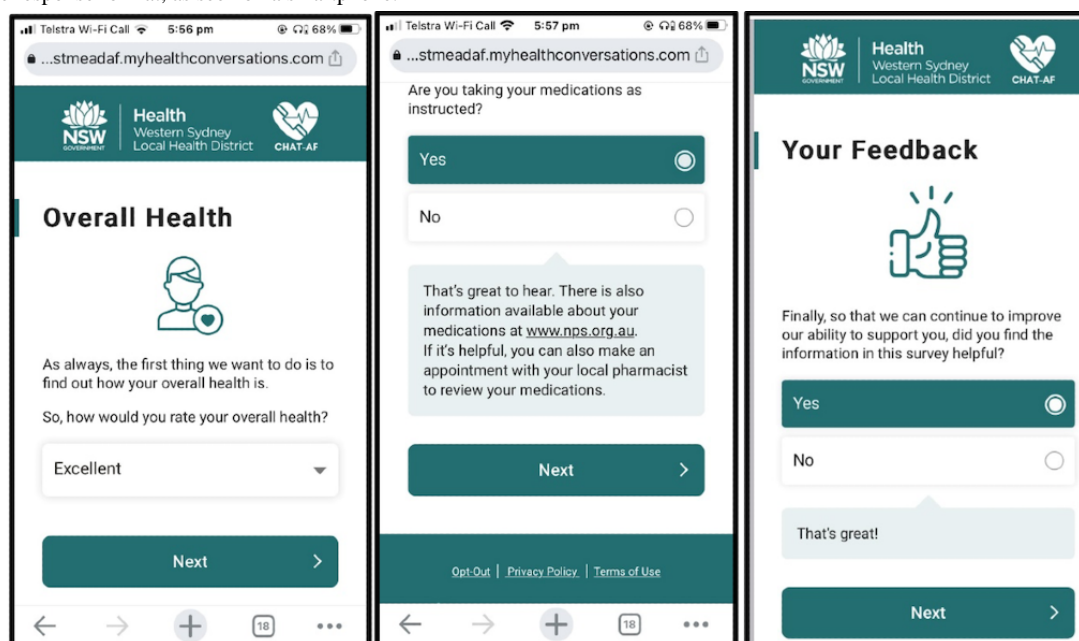
Education Website

In addition to these outreaches, an SMS text message or email will be sent to intervention group participants every week to encourage them to visit the educational website ([Figure 5](#)). The information on this website will be personalized based on participant information collected at baseline (smoking status, alcohol intake, diagnosis of hypertension, and prescription of anticoagulants or warfarin). The website will consist of various modules, covering general AF information, AF procedures, medications, alcohol, blood pressure, smoking, and weight management, as well as providing general resources. Content will be in the form of embedded videos, text, and images as well as external links to web-based resources, videos, webpages, and brochures from reputable sources (eg, the Heart Foundation and National Prescribing Service). An additional feature of this website is the embedded quiz questions that prompt patients to test their knowledge at the end of each module.

Figure 5. Personalized education website, as seen on a smartphone. It includes information about atrial fibrillation, medications, weight management, alcohol, smoking, physical activity, blood pressure, treatment options (not shown in figure), and other lifestyle information (not shown in figure). The website also has embedded quiz questions to test patients' knowledge of the educational content. The images contained in these screenshots are stock images; no potentially identifiable patient information is shown.
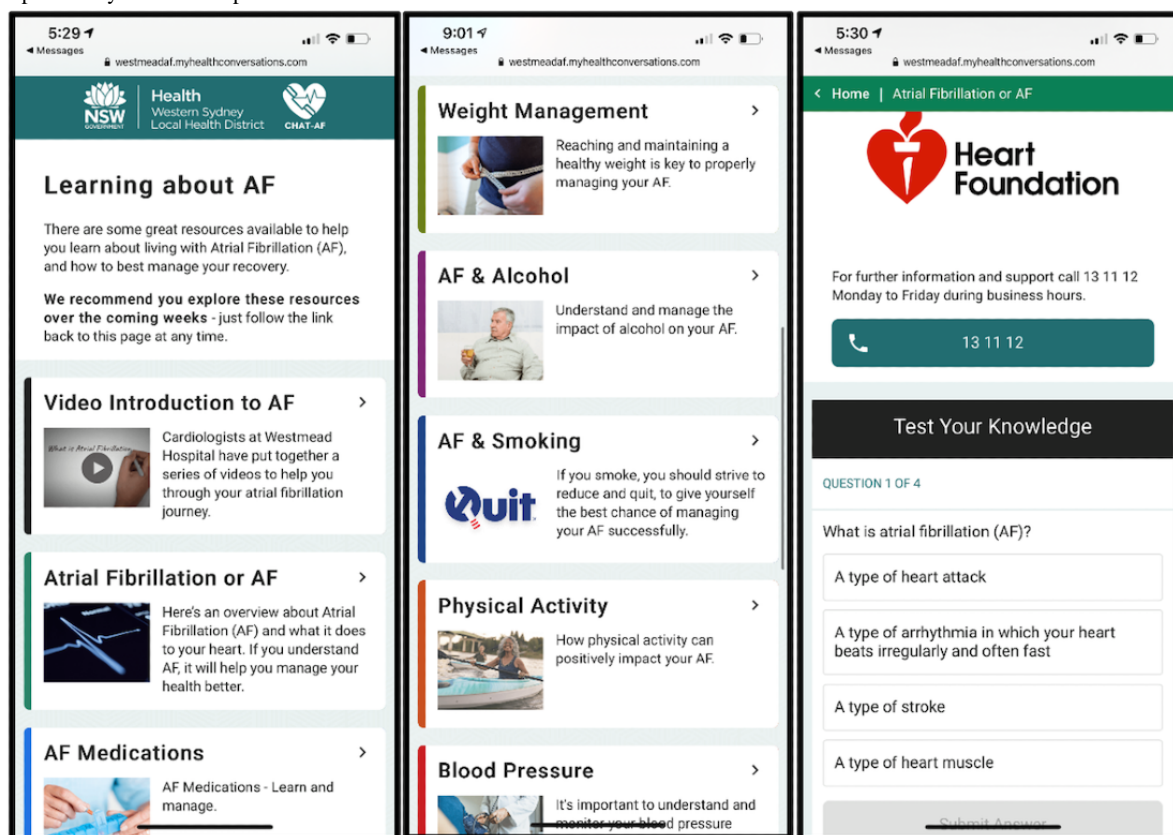
Intervention Development and Patient Involvement

The intervention was co-designed with patients, a multidisciplinary group of health care providers, behavioral scientists with experience delivering conversational technology–based health management and wellness programs, and technologists.

The rationale for including automated telephone calls in addition to emails and SMS text messages as part of the intervention was based on 2 recent promising trends to engage patients in health care. First, in the past couple of years, there has been a growing use of conversational AI–driven technologies such as automated telephone calls in health care [25-27], following a similar trend that began in industry and government organizations, with good acceptability and results [36]. These technologies have been applied in different health domains such as mental health support and chronic disease management to enable a conversational interaction with patients and promote engagement with health interventions with the aim of increasing intervention acceptability, use, and effectiveness [22,25-28]. Nevertheless, few randomized controlled trials have assessed their effectiveness so far [29-32], and none in AF.

Second, it has become increasingly common to use multichannel communication to take advantage of different available technologies to interact with users. Having started in marketing and commerce [37], and with growing use in health care [38], multichannel communication aims to improve service quality and user experience by engaging users through several technology channels, depending on preference and the goal of the interaction (eg, bookings, reminders, and education). Therefore, our multidisciplinary team decided to use a combination of automated telephone calls and emails or SMS text messages, according to patient preference, to deliver the intervention. The frequency of the interactions was decided based on the experience of our technology partner in delivering conversational technology–based programs and our own experience in delivering SMS text messaging programs [39-41].

We worked closely with a consumer representative with AF as well as approached patients in cardiology waiting rooms at Westmead Hospital. Patients were approached regardless of whether they had been diagnosed with AF, given that we wanted to ensure that the language in the call scripts was accessible to a lay audience without specific knowledge about AF. Patients were involved in intervention development and refinement, as well as in reviewing the scripts and content of automated calls. Scripts went through several iterations before finalization. Patient feedback was overall positive (eg, "clear and straightforward" and "straightforward and easy to understand"). We received suggestions to use more lay language and avoid the use of medical terminology; for example, the use of *heart specialist* instead of *cardiologist*. Health care providers had input into the content and scripting of the IVR calls, as well as the educational website, to ensure that the information was in accordance with current AF clinical guidelines. We adapted the intervention to incorporate the comments and suggestions received from all stakeholders. The system was culturally

adapted to Australia by using a custom voice with an Australian accent and by co-designing the call scripts with Australian patients and health care professionals. The automatic speech recognition engine was trained to recognize different Australian accents in uttered speech. Although the AI models were not specifically trained on a Western Sydney population data set, as part of our process evaluation we aim to assess the adequacy and acceptability of the intervention in this population.

Study Outcomes

The primary outcome of the study is AF-related quality of life at 6 months in the intervention group compared with the control group, measured using the AF Effect on Quality-of-Life (AFEQT) questionnaire (total score) [42]. The secondary outcomes include AFEQT domain scores (symptoms, daily activities, treatment concerns, and treatment satisfaction), medication adherence, lifestyle behavioral outcomes, AF knowledge, patient activation, patient care experience, health outcomes, and health care service use. We will also assess the feasibility of the intervention, focusing on acceptability and engagement with different intervention components.

Data Collection and Study Procedures

Overview

A regular screening of upcoming patient appointments and scheduled procedure lists will be conducted by the research team and physicians to identify potential participants. We will approach these participants (1) face-to-face during their visit to obtain consent, (2) over the telephone before they attend their scheduled appointment, (3) or within 48 hours of their visit to the hospital. Eligible individuals who have provided informed consent will be asked to complete a baseline assessment that will consist of study-specific and validated questionnaires. After baseline data collection, patients will be randomized into the study groups. Both control and intervention group participants will complete study-specific surveys and validated questionnaires at baseline, 3 months, and 6 months (Table 2), using a link delivered through SMS text message or email, according to the participants' preferences. For the purposes of study data collection, SMS text message delivery will be managed by TextCare software (Westmead Applied Research Centre, University of Sydney) [40,41] and email delivery will be managed using REDCap [34]. At 6 months, a purposive sample of participants from the intervention arm will be invited to participate in a semistructured interview. We will also collect patient-specific program analytics throughout the duration of the intervention.

Table 2. Data and outcome measures collected at baseline, 3 months, and 6 months.

Outcomes	Data collected	Baseline	3 months	6 months
Primary outcome: AF[a]-related QoL[b]	AFEQT[c] Questionnaire [42]	✓	✓	✓
Secondary outcomes				
Medication adherence	Self-reported	✓		✓
Lifestyle behavioral outcomes	Self-reported	✓		✓
AF knowledge	AF knowledge scale [43]	✓		✓
Patient activation measure	PAM[d]-13 Questionnaire [44]	✓		✓
Patient experience measure	PACIC[e] Questionnaire [45]	✓		✓
Health events	Self-reported and medical records	✓		✓
Health care services use	Self-reported and medical records	✓		✓
Feasibility (acceptability and engagement)	Semistructured interviews			✓[f]
Feasibility (acceptability and engagement)	Program analytics	✓[f]	✓[f]	✓[f]

[a]AF: atrial fibrillation.

[b]QoL: quality of life.

[c]AFEQT: Atrial Fibrillation Effect on Quality-of-Life.

[d]PAM-13: Patient Activation Measure, 13 items.

[e]PACIC: Patient Assessment of Chronic Illness Care.

[f]Intervention group participants only; program analytics collected throughout the 6 months.

Study-Specific Questionnaires

Study-specific questionnaires will collect data on demographics, medication adherence, lifestyle behavioral outcomes, health events, health care service use in past 6 months, and patient medical history (Multimedia Appendices 1-3). Health events, health care service use, and medical history will be collected through study-specific questionnaires (self-reported) and consolidated with hospital medical records.

Validated Questionnaires

The primary outcome will be measured using the AFEQT Questionnaire, a reliable and validated 21-item questionnaire measuring self-reported health-related quality of life specific

to AF [42]. It consists of scores in four domains (symptoms, daily activities, treatment concerns, and treatment satisfaction), along with a global measure. Scores range from 0 to 100 (higher scores associated with better quality of life). The overall AFEQT score is calculated using a total of the domain scores.

Other validated questionnaires will include the AF Knowledge Scale [43]; the Patient Activation Measure, 13 items (PAM-13) [44]; and the Patient Assessment of Chronic Illness Care (PACIC) Questionnaire [45]. The AF Knowledge Scale [43] will be used to assess patients' knowledge of AF (1 point is given for each correct response, with the potential total score ranging from 0 to 10; the last item was removed, given that *thrombosis center* is not a term commonly used in Australia). The PAM-13 [44] evaluates patients' perceived knowledge, skills, and confidence in self-management activities. Question responses are structured according to a Likert scale from 1 (strongly disagree) to 4 (strongly agree), and total scores range from 0 to 100 (higher scores representing more patient activation in disease self-management). To assess patient satisfaction with quality of care, the PACIC Questionnaire [45] will be administered to all study participants at baseline and to intervention group participants only at 6 months. This instrument is a reliable and validated 20-item questionnaire that consists of 5 subscales (patient activation, decision support, goal setting, problem solving, and follow-up) and an overall summary score ranging from 20 to 50 [45].

Process Evaluation: Semistructured Interviews and Program Analytics (Intervention Group Only)

A process evaluation will be conducted following the Medical Research Council framework [46] to assess feasibility, engagement, and implementation through the use of semistructured interviews with a sample of intervention participants and program engagement metrics.

At the end of the 6-month program, a sample of participants from the intervention arm will be invited to participate in semistructured interviews. Interviews will explore acceptability and usability, as well as barriers and enablers to engagement; user preferences and patient perspectives regarding specific intervention components (eg, voice calls vs text-based interaction); and impact of the intervention on the patient journey and care integration. Interviews will follow a pilot-tested interview guide (Multimedia Appendix 4). We will use the maximum variation sampling method based on sociodemographic characteristics and engagement metrics to obtain a broad range of views for the semistructured interviews. A minimum of 20 interviews will be conducted; however, additional interviews will be conducted if needed until thematic saturation is reached. Interviews will be conducted through telephone, audio recorded, and manually transcribed for subsequent analysis using NVivo 12 software (QSR International).

Program engagement metrics will be collected and analyzed (eg, number of completed telephone calls, number of queries answered during each telephone call, and number of visits to the educational website). Intervention use metrics will be automatically collected through the IVR system and website analytics. In addition, a log will be kept of responses triggering escalation and subsequent contacts with the research team and clinical resolution.

Analysis

A sample size of 385 is required to detect a between-group difference of 7 [47] in the total score (100 points) of the AFEQT Questionnaire [42] with 80% power (α=.05; SD 19), accounting for a dropout rate of 10%. All continuous data will be checked for normality before performing parametric tests (2-tailed t tests). Appropriate nonparametric tests (eg, Mann-Whitney U test) will be used where data are not normally distributed. Continuous variables will be presented as means and SDs unless they are skewed, in which case medians and IQRs will be used. Categorical variables will be presented as frequencies and percentages. Effect estimates will be reported with 95% CIs. The primary analysis will be by the intention-to-treat principle. In addition, per-protocol analyses will be performed and reported. For the primary outcome (AFEQT total score), groups will be compared using analysis of covariance adjusted for corresponding baseline values. Similarly, other continuous variable secondary outcomes will be adjusted using the corresponding baseline measures (AFEQT domain scores: symptoms, daily activities, treatment concerns, and treatment satisfaction; AF knowledge score; PAM-13 score; PACIC score; BMI; number of cigarettes smoked daily; number of alcoholic drinks consumed per week; exercise minutes per week; daily fruit servings; and daily vegetable servings). For dichotomous outcomes (proportion of self-reported medication adherence; stroke and myocardial infarction rates; proportion of GP, cardiologist, and emergency department visits; and proportion of hospitalizations, catheter ablations, and cardioversions), groups will be compared using a log-binomial regression also adjusting for corresponding baseline values as fixed effect. A statistical analysis plan will be finalized before data lock and unblinding. P<.05 will be considered statistically significant. All statistical analyses will be performed using R (version 4.0.2).

Data from interviews will be analyzed using thematic analysis [48] of transcribed audio recordings in NVivo 12 software. Themes will be identified using an inductive data-driven approach, that is, inductive thematic analysis [49]. Inductive thematic analysis is a process of coding the data without trying to fit it into a preexisting coding frame or to analytic preconceptions so that the themes identified are strongly linked to the data [49]. First, we will select relevant information in the data, generating open codes in a codebook (first-cycle coding) [50]. As the analysis progresses, several codes will be added inductively. Second-cycle coding will involve focused coding (ie, to find thematic similarity) and axial coding (ie, to find relationships among the codes) [50]. Identification of themes will occur by sorting the different codes into potential themes and collating all the relevant coded data extracts within the identified themes. Themes will be identified at a semantic level, with analysis starting by organizing data to show patterns in semantic content and then moving to the interpretation of the patterns and their broader meanings and implications [49]. Revisions of the codebook by the authors will be conducted iteratively through comparing and revising codes and emerging themes. After a candidate thematic *map* is reached, the data set will be reread to ensure the quality of the themes and refine

them as needed. Reporting will follow the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist [51].

Ethics and Dissemination

Written and informed consent will be obtained from all study participants before commencing any study procedures. Participation in this study will be entirely voluntary, and participants will have the option to withdraw at any point.

The digital technology platform will be hosted on the Amazon Web Service Asia Pacific Region in Sydney, New South Wales, Australia. Data handling and storage will be conducted in accordance with the National Health and Medical Research Council guidelines and Australian Code for Responsible Conduct of Research. Identifiable data collected from this study will be stored on the secure research data store server provided by the University of Sydney and will only be accessible to study researchers. Questionnaire data will be collected electronically and stored on REDCap.

With participant consent, medical history data will be collected from patient medical files for the purpose of this study. As per the Health Records and Information Privacy Act 2002 No 71 (Schedule 1, Section 10 [1a]), the individual to whom the information relates will provide consent for use of their information, in line with the National Health and Medical Research Council's National Statement.

Results

Ethics approval was obtained from the Western Sydney Local Health District Human Ethics Research Committee (2020/ETH02546; November 4, 2020). Recruitment started in December 2020, and as of December 2021, a total of 103 patients had been recruited. Results are expected to be published in 2023.

Discussion

Anticipated Findings

This study will provide initial data on the efficacy of a novel *AF-Support* program comprising a preprogrammed set of digital visits and conversational AI to provide automated but customized postdischarge AF care designed to support integrated care for patients with AF. It will also provide a detailed evaluation of the implementation, uptake, and overall acceptability of this multichannel digital care intervention. The design of the evaluation has been matched to the goals of the study to both provide new data to enable a better estimate of the efficacy of such a digital care intervention and inform further development of chronic disease digital care interventions. Digital care programs for postdischarge care have the potential to meet the need for increasing management of chronic disease in the community; yet, there is little research on the effectiveness on health outcomes, patient-reported experience, and cost-effectiveness of digital care models.

Strengths and Limitations of This Study

To the best of our knowledge, this will be the first detailed evaluation of an AI conversational technology to support AF integrated care. The intervention has been co-designed with researchers, multidisciplinary clinicians from tertiary and primary care, informaticians, and patients. The trial is designed with a 4:1 allocation ratio such that most participants will receive the intervention to enable a detailed examination of feasibility and uptake, as well as the implementation process.

The limitations of the study include the 6-month duration and not being powered to assess impact on clinical outcomes such as cardiovascular hospitalizations and events.

Implications

If successful in this trial, conversational AI interventions may be able to complement clinical care by supporting patients between clinical visits with the GP and cardiac care team. Future software development in this area should explore the integration of such a system with existing electronic medical records in primary and secondary care—a major challenge for the health information technology industry. Enabling seamless clinician access to the data collected by the system (eg, risk assessments such as symptom evaluation) would be an important step toward better integration of AF care. This research will contribute to addressing the gap in knowledge with respect to the role of postdischarge digital care models for supporting patients with chronic disease.

Authors' Contributions

TS and CKC secured the funding for this project. LL, TS, RT, ST, EC, AT, and CC were involved in the intervention planning and design. LL, TS, SM, and CC developed the study design and statistical plan. LL, TS, RT, EC, and CC prepared the ethics and governance application. LL and RT prepared the first draft of this manuscript, with critical input from CC. LL, TS, RT, SR,

EC, AT, SK, TCT, TNN, SM, and CC provided critical input and reviewed and approved the final version of this protocol for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Self-reported study-specific questionnaire 1 (at baseline only).
[DOCX File , 17 KB - resprot_v11i4e34470_app1.docx]

Multimedia Appendix 2
Self-reported study-specific questionnaire 2 (at baseline and 6 months).
[DOCX File , 17 KB - resprot_v11i4e34470_app2.docx]

Multimedia Appendix 3
Medical history from hospital records (at baseline and 6 months).
[DOCX File , 17 KB - resprot_v11i4e34470_app3.docx]

Multimedia Appendix 4
Interview guide.
[DOCX File , 17 KB - resprot_v11i4e34470_app4.docx]

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Abbreviations

AF: atrial fibrillation
AFEQT: Atrial Fibrillation Effect on Quality-of-Life
AI: artificial intelligence
COREQ: Consolidated Criteria for Reporting Qualitative Research
GP: general practitioner
IVR: interactive voice response
mHealth: mobile health

PACIC: Patient Assessment of Chronic Illness Care
PAM-13: Patient Activation Measure, 13 items
REDCap: Research Electronic Data Capture

Protocol

App-Based Mindfulness Meditation for People of Color Who Experience Race-Related Stress: Protocol for a Randomized Controlled Trial

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Abstract

Background: People of color (POC) who experience race-related stress are at risk of developing mental health problems, including high levels of stress, anxiety, and depression. Mindfulness meditation may be especially well suited to help POC cope, given its emphasis on gaining awareness and acceptance of emotions associated with discriminatory treatment. However, mindfulness meditation rarely reaches POC, and digital approaches could reduce this treatment gap by addressing traditional barriers to care.

Objective: This study will test the effectiveness of a self-directed app-based mindfulness meditation program among POC who experience elevated levels of race-related stress. Implementation outcomes such as treatment acceptability, adherence, and satisfaction will be examined.

Methods: Participants (n=80) will be recruited online by posting recruitment materials on social media and sending emails to relevant groups. In-person recruitment will consist of posting flyers in communities with significant POC representation. Eligible participants will be block randomized to either the intervention group (n=40) that will complete a self-directed 4-week mindfulness meditation program or a wait-list control condition (n=40) that will receive access to the app after study completion. All participants will complete measures at baseline, midtreatment, and posttreatment. Primary outcomes include changes in stress, anxiety, and depression, and secondary outcomes constitute changes in mindfulness, self-compassion, rumination, emotion suppression, and experiential avoidance. Exploratory analyses will examine whether changes in the secondary outcomes mediate changes in primary outcomes. Finally, treatment acceptability, adherence, and satisfaction will be examined descriptively.

Results: Recruitment began in October 2021. Data will be analyzed using multilevel modeling, a statistical methodology that accounts for the dependence among repeated observations. Considering attrition issues in self-directed digital interventions and their potential effects on statistical significance and treatment effect sizes, we will examine data using both intention-to-treat and per-protocol analyses.

Conclusions: To our knowledge, this will be the first study to provide data on the effectiveness of a self-directed app-based mindfulness meditation program for POC recruited based on elevated race-related stress, a high-risk population. Similarly, meaningful clinical targets for POC affected by stressors related to race will be examined. Findings will provide important information regarding whether this type of intervention is an acceptable treatment among these marginalized groups.

Trial Registration: ClinicalTrials.gov NCT05027113; https://clinicaltrials.gov/ct2/show/NCT05027113

International Registered Report Identifier (IRRID):   DERR1-10.2196/35196

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Introduction

Background

In the United States, people of color (POC) are disproportionally affected by stressors related to race and ethnicity compared with their non-Latinx White counterparts, with approximately 70% of POC reporting having experienced some form of discrimination in their lives and 60% reporting facing day-to-day discriminatory treatment [1,2]. The prevalence of these discriminatory experiences varies across POC groups, with Black individuals (70%) experiencing more instances of discrimination compared with their Asian (57%) and Latinx (45%) counterparts [1]. Notably, approximately 60% of Black, 49% of Asian, and 45% of Latinx individuals state that these experiences make their lives harder [2]. Race-related stress is the psychological distress associated with appraising a situation as disturbing or burdensome because of negative racial bias [3]. Race-related stressors have multiple forms, such as direct interpersonal discrimination (ie, perceived differential and unfair treatment among individuals), vicarious discrimination (ie, observing members of one's race or ethnicity being victimized), and institutional practices (ie, laws and policies that limit access to services and opportunities) [4,5]. Common race-related stressors experienced by POC include being treated with less courtesy or respect, receiving poorer service, receiving unfair treatment in the workplace, and negative interactions with police [2].

Race-Related Stress and the Mental Health of POC

When differential or unfair treatment is perceived as racially motivated, it triggers physiological (eg, cardiovascular reactivity, dysregulated hypothalamic-pituitary-adrenal axis activity), cognitive-affective (eg, rumination, emotion suppression), and behavioral (eg, avoidance, aggression) responses that prepare the individual to confront the situation [6-8]. The chronic and unpredictable nature of race-related stressors often depletes individuals' psychological resources and increases their vulnerability to developing mental health disorders [8]. Meta-analytic work shows that based on effect sizes, stress (r=.27), anxiety (r=.22-.25), and depression (r=.21-.26) are the mental health problems most strongly correlated with experiencing race-related stress, and these associations seem to be stronger among Asian and Latinx individuals compared with Black individuals [9-11]. This disproportionate exposure to race-related stressors may partly explain the higher prevalence and persistence rates of mood and anxiety disorders among Black, Asian, and Latinx groups compared with non-Latinx White groups [12,13]. These adverse mental health outcomes are especially concerning considering current social events, including instances of police brutality [14], recent political discourse [15], the COVID-19 pandemic [16], and an increase in hate crimes [17] that have made race-related stressors even

more salient, further affecting the mental health of POC communities.

Considering POC exposed to race-related stress are at high risk of developing a mental health disorder, there is a clear need for treatments that allow individuals to cope effectively with these stressors. Among numerous evidence-based treatments available, mindfulness meditation may be particularly well suited to help POC cope.

Mindfulness Meditation for Race-Related Stress in POC

Mindfulness is a psychological trait associated with staying in the present moment with one's experience (ie, physical sensations, thoughts, emotions, behaviors), endorsing a nonjudgmental and curious attitude, and cultivating acceptance and self-compassion [18]. Self-compassion refers to an attitude of openness to one's own suffering without avoiding it, cultivating the desire to alleviate it without self-judgment [19]. Multiple meta-analyses have shown that increases in mindfulness and self-compassion are two of the mechanisms by which mindfulness meditation leads to decreases in overall stress, anxiety, and depression [20-24].

Furthermore, mindfulness meditation could be particularly effective in helping POC cope with race-related stress by reducing experiential avoidance. Experiential avoidance is the inability to remain in contact with distressing physical sensations, thoughts, and emotions, even when doing so causes harm in the long term [25]. POC exposed to race-related stressors often develop emotional (eg, unwillingness to experience sadness after being discriminated against) and behavioral (eg, evading places or situations where discrimination is anticipated to occur) avoidance that maintain mental health symptoms [5,6,8]. As such, mindfulness meditation, with its emphasis on bringing awareness to all experiences regardless of their negative valence, may serve as an exposure strategy that reduces avoidance, leading to decreases in psychological distress [26].

Considering that rumination (ie, the passive and repetitive focus on the causes and consequences of one's distress) [27] and emotion suppression (ie, the active reduction of emotionally expressive behavior when emotionally aroused) [28] are maladaptive emotion regulation strategies often used by POC exposed to race-related stressors [5,6,8,29], researchers and clinicians have hypothesized that mindfulness meditation may be particularly well-suited for this population [30-32]. Research suggests that mindfulness meditation disrupts ruminative tendencies by cultivating acceptance of and nonjudgmental engagement with thoughts [33]. In the case of emotion suppression, mindfulness meditation may help individuals identify, describe, and healthily engage with emotions triggered by race-related stressors rather than suppress these feelings, leading to decreases in mental health symptoms [34].

Although research to date supports the effectiveness of mindfulness meditation in reducing mental health problems, most studies have relied on almost exclusively non-Latinx White samples [35], which significantly differ from POC on critical demographic variables, such as level of education, income, and culture (ie, norms, language, beliefs, customs). For example, even in a meta-analysis where the primary aim was to examine mindfulness meditation's effectiveness among underserved populations, less than 30% of studies included had POC samples [30]. A more recent systematic review surveying literature from 1990 to 2016 found only 24 studies examining the effectiveness of mindfulness meditation in POC samples, and just 25% of these studies were conducted with adults [36].

Improving Access to Mindfulness Meditation for POC via Technology

Despite the significant mental health need among individuals who experience race-related stress and the existence of promising interventions such as mindfulness meditation, POC face numerous barriers to care, including limited access to providers [37], financial and transportation constraints [38], and stigma [39]. Although no single approach will eliminate all barriers driving mental health disparities, using technology to provide care could reduce this treatment gap [40,41].

Among many technological resources available, smartphones represent a promising vehicle for providing mental health services. The feasibility of this approach is supported by extensive ownership of mobile devices in the United States. For instance, approximately 85% of Americans have a smartphone, with POC having similar ownership rates as non-Latinx White individuals [42]. Compared with non-Latinx White people, POC are also more likely to be smartphone-dependent, meaning they rely on these devices to access the internet in the absence of a broadband connection at home. As such, interventions using smartphones may be well positioned to reach those affected by the digital divide observed in low-income households, as these interventions capitalize on technology already owned by POC [40,43].

In addition to their feasibility, there is a growing body of evidence supporting the efficacy of app-based mental health interventions [44,45]. Although somewhat limited, existing data with POC samples are promising [40]. In the case of app-based mindfulness meditation, multiple meta-analyses show that these interventions effectively reduce overall stress, anxiety, and depression [46-48] and increase mindfulness and self-compassion [47,48]. To our knowledge, experiential avoidance, rumination, and emotion suppression have not been examined as potential clinical targets in app-based mindfulness meditation. Furthermore, similar to face-to-face mindfulness meditation research, there is a lack of POC representation in app-based mindfulness meditation studies.

Issues of Engagement in App-Based Mental Health Interventions

Despite their feasibility and empirical support, there are significant concerns regarding treatment engagement in app-based mental health interventions. Enrollment rates are low, with a meta-analysis showing that 8% to 58% of participants never download the intervention app [49]. Even when the app is downloaded, studies show that some users never use it, and those who engage with the app are unlikely to do so more than a few times, showing a decrease in use over time [49,50]. Similarly, attrition rates range from 24% to 53%, with higher rates found in longer programs (ie, more than 8 weeks) [49]. Importantly, programs without guidance (eg, via human coach, automated reminders) seem to lead to even poorer treatment engagement [51]. This limited treatment engagement in app-based mental health interventions is concerning as users may not receive enough treatment dosage to promote behavioral change.

Considering the importance of promoting treatment engagement for the success of app-based interventions, researchers and clinicians have proposed multiple strategies to increase acceptability, improve adherence, and reduce attrition. Among numerous approaches to promote app user engagement, cultivating a sense of guidance and support may be especially effective. Onboarding procedures in which users interact with providers before starting the intervention, asking questions about the intervention, problem-solving potential barriers to engagement, and building a relationship with the team have shown to be associated with higher treatment engagement [52]. Similar procedures in app-based interventions for POC seem to be effective as users can ask questions about the program and request assistance with technology [53]. As a whole, studies show that onboarding procedures decrease treatment attrition in app-based mental health interventions [49].

Among POC who have more limited access to technology, the use of text messaging notifications could be a especially well-suited strategy to increase treatment engagement. Text messages capitalize on the high phone ownership rates among POC while minimizing costs, as most phone plans include unlimited text messages. The feasibility of this approach is supported by previous studies showing that receiving simple text messaging reminders increases attendance to face-to-face treatment sessions among POC [54,55]. Importantly, this engagement strategy is well tolerated by participants [56]. These findings among POC are consistent with other studies showing that receiving prompts (eg, text messages, app notifications) leads to higher treatment engagement in digital interventions [57]. In app-based interventions, the use of prompts has also been found to be associated with lower attrition rates [49]. Therefore, exploring treatment acceptability, adherence, and satisfaction in these programs is crucial to determining whether mindfulness meditation programs are relevant for POC who experience race-related stress.

This Study

Considering the lack of research examining the effectiveness of mindfulness meditation among POC, especially those who experience elevated levels of race-related stress, this study will use a randomized controlled trial (RCT) approach to examine whether receiving an app-based mindfulness meditation intervention leads to decreases in the adverse mental health outcomes more often associated with exposure to race-related stress (ie, stress, anxiety, depression) among POC. Similarly, this RCT will test whether the intervention engages hypothesized

mechanisms of change (ie, mindfulness, self-compassion, experiential avoidance, rumination, emotion suppression). As an exploratory aim, this study will examine whether decreases in the primary outcomes of interest (ie, stress, anxiety, depression) occur via hypothesized mechanisms of change (ie, mindfulness, self-compassion, experiential avoidance, rumination, emotion suppression). Finally, acceptability, adherence, and satisfaction will be analyzed descriptively. Results from this trial will contribute to the nascent data on mindfulness meditation's acceptability and effectiveness with POC. To our knowledge, this study will be the first to include a sample of POC recruited based on elevated levels of race-related stress, a high-risk population that is not commonly targeted in mindfulness meditation research.

Methods

Participants

A power analysis using G*Power [58] indicated that, based on 2 groups (ie, control vs active treatment), 3 repeated measurements (ie, baseline, midtreatment, posttreatment), a conservative $r=.60$ correlation among repeated measures, and a small $d=0.2$ treatment effect size, a sample of n=54 provides 95% power to detect a treatment by time interaction using the most conservative outcome in this study. Considering recent meta-analytic work suggesting an approximately 24% attrition rate in short-term (ie, 4 weeks or less) mindfulness meditation app trials with at-risk samples [49], we plan to recruit 80 POC individuals for this study.

Individuals interested in participating in this study will complete an online screening questionnaire using Qualtrics, a platform that is smartphone compatible. For study inclusion, participants are required to (1) self-identify as a member of a POC group (eg, Black/African American, Asian/Asian American/Pacific Islander, Latinx, Native American/Native Alaskan, multiracial, other), (2) report experiencing elevated levels of race-related stress (ie, a score of 55 or higher on the Index of Race-Related Stress–Brief [IRRS-B] [4] or a score of 12 or higher on the Multicultural Discrimination Module [MDM] [59]), (3) speak and read English, (4) not receive psychological services currently (ie, individual or group therapy, any type of counseling), (5) not have practiced mindfulness meditation for more than 2 hours in the month prior to study commencement, (6) own a smartphone with access to the internet, (7) be willing to install the mindfulness meditation app and accept daily

notifications and text reminders, and (8) be aged 18 years or older.

Those individuals who meet eligibility criteria will be contacted by a research team member to obtain verbal consent and randomize them to either the intervention group (n=40) or a wait-list control group (n=40) using block randomization. During this onboarding procedure, participants in the intervention group will be assisted in installing the mindfulness meditation app, setting app notifications, understanding daily text messaging reminders, and getting familiar with the intervention content. Similar onboarding procedures have been shown to improve treatment adherence in app-based mindfulness meditation studies [49,51]. Participants in the control condition will be reminded of the scheduled assessments and when they will receive access to the mindfulness meditation app (ie, 4 weeks after randomization). Individuals who endorse self-harm or suicidal ideation during the onboarding procedure or in their replies to the text messages will be further assessed and referred to crisis support services.

Ethical Approval

All procedures have been approved by the University of California, Los Angeles' institutional review board (21-001426). This study was registered at ClinicalTrials.gov [NCT05027113].

Procedures

Participants are being recruited through social media, sending emails to relevant groups, and posting physical flyers in communities with significant POC representation. Considering the current COVID-19 pandemic, data are being collected using an online procedure (ie, Qualtrics) at baseline (ie, randomization or week 0), midtreatment (ie, 2 weeks after randomization), and posttreatment (ie, 4 weeks after randomization) via online questionnaires. These assessments were piloted among POC to improve survey clarity and minimize participant fatigue before starting recruitment. These remote assessment strategies have shown to be effective in app-based intervention research with low-income POC [53].

Participants in both conditions will receive a free subscription to the mindfulness meditation app intervention as an incentive to participate. Additionally, participants will be compensated with US $10, $15, and $25 for completing baseline, midtreatment, and posttreatment questionnaires, respectively. There is evidence that monetary compensation significantly reduces attrition in app-based mindfulness meditation studies [49]. Figure 1 shows the study design flow.

Figure 1. Study flow diagram.
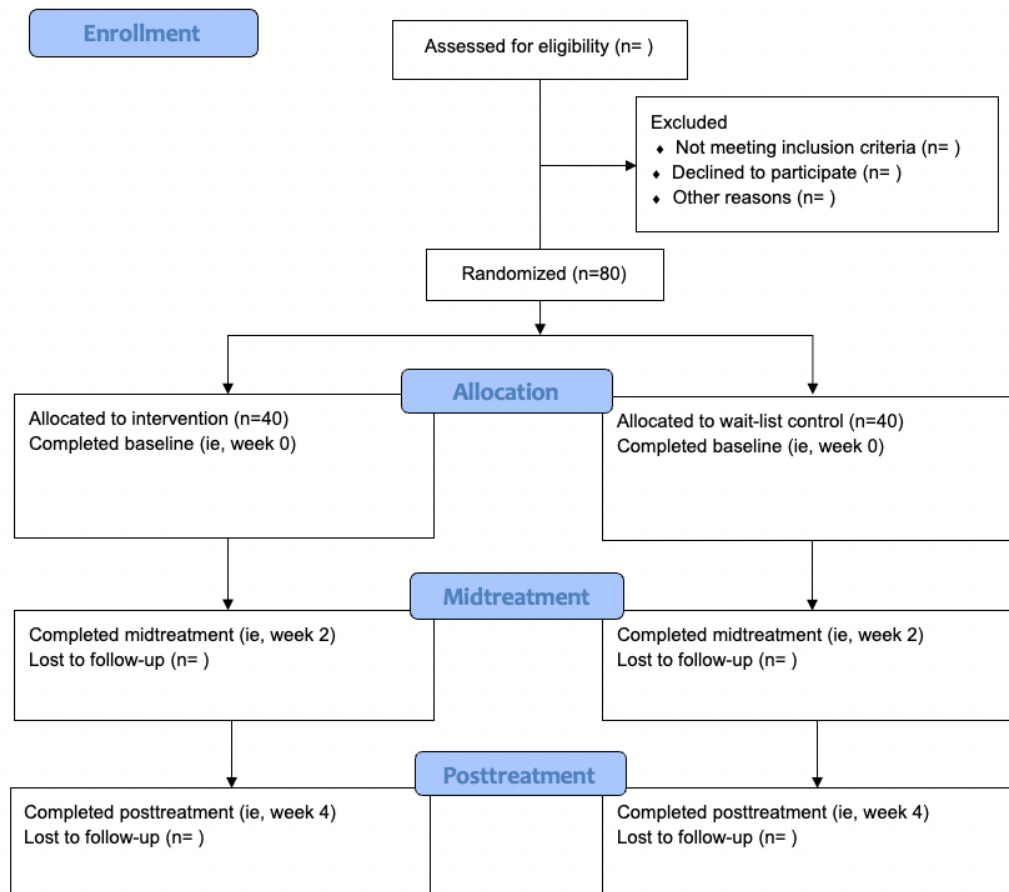
Mindfulness Meditation Intervention

This study will use the Ten Percent Happier app, a consumer-based mindfulness meditation app that offers a wide range of meditation practices developed and guided by renowned experts in the field. Among the many mindfulness apps available in the market, we chose this app because it has been shown to be an effective intervention to increase mindfulness and decrease anxiety and depressive symptoms in previous studies [60-62]. It is important to note that samples in these studies were almost exclusively non-Latinx White.

The intervention will consist of using the Ten Percent Happier app to complete at least 1 meditation daily—with the possibility of exceeding this goal by choosing additional meditations—for 4 weeks. More specifically, participants will be asked to complete The Basics and The Basics II courses to familiarize themselves with the principles of mindfulness meditation. Each audiorecorded session begins with a short video providing psychoeducation around mindfulness meditation and teaching specific techniques (eg, using the breath as an anchor, redirecting attention, noting thoughts and emotions). These 2 introductory courses comprise 15 sessions, in which the meditation length gradually increases from 5 to 17 minutes. For the last 2 weeks of the program, participants will be invited to complete the Essential Advice course, which dispels common myths around mindfulness meditation (eg, "meditators empty their minds," "successful meditations are those without distractions") and teaches participants how to deal with common obstacles in their practice (eg, difficult emotions, strong physical sensations).

This additional course comprises 14 sessions ranging in length from 15 to 18 minutes. For any additional practice, participants will be able to select any meditation from the Ten Percent Happier library based on their preferences. This highly structured 4-week introductory course may be more likely to provide the foundation necessary for participants to benefit from mindfulness meditation compared with less structured programs often seen in app-based mindfulness meditation research [46]. Moreover, short-term app-based mindfulness meditation interventions (ie, 4 weeks or less) lead to lower attrition rates compared with longer programs [49].

Given the evidence of low treatment adherence in self-directed app-based mindfulness meditation [49-51], we will use a combination of app and text messaging reminders. The Ten Percent Happier app allows users to set a daily notification that can be personalized. Similarly, users will receive daily text messages reminding them to complete their daily meditation. Similar procedures have been hypothesized to foster a therapeutic relationship that keeps the user engaged and promotes a sense of accountability [50,52]. Text messaging reminders have proven effective in increasing treatment adherence among POC community samples [54-56,63], including those in app-based mindfulness meditation studies [49].

Measures

Screening

Race-Related Stress

The 22-item IRRS-B [4] measures multiple sources of race-related stress, including individual, institutional, and cultural sources. Participants rate items on a scale ranging from 0 (this never happened to me) to 4 (this event happened and I was extremely upset), with higher scores indicating more race-related stress. Items include "You notice when POC are killed by the police, the media informs the public of the victims' criminal record or negative information in their background, suggesting they got what they deserve," "You have been subject to racist jokes by non-POC people in positions of authority and did not protest for fear they might have held it against you," and "You were refused an apartment or other housing; you suspect it was because you are a POC." The IRRS-B was developed with a POC sample (ie, Black individuals), showing adequate reliability (α=.78) for both cultural and individual subscales and acceptable reliability (α=.69) for the institutional subscale. The wording of the IRRS-B will be slightly adapted to capture the experience of multiple POC groups rather than only Black individuals. For study inclusion, participants need to obtain a score of 55 (range 0-88), which represents elevated race-related stress.

Perceived Discrimination

The 8-item MDM [59] measures perceived discrimination across different racial, ethnic, and cultural groups. Participants rate items on a scale ranging from 1 (never) to 4 (often), with higher scores indicating more levels of perceived discrimination. Items include "How often have you been treated with less respect than other people?" "How often have people acted as if they think you are not smart?" and "How often have you been threatened or harassed?" The MDM was developed using a sample representative of the US population (approximately 40% POC) and has shown good internal consistency (α=.81-.88) in a previous study [59]. For study inclusion, participants need to obtain a score of 12, which represents the 75th percentile of the population distribution.

Primary Outcomes

Stress

The 10-item Perceived Stress Scale (PSS) [64] is the most widely used measure of perceived stress. Participants rate items on a scale ranging from 0 (never) to 4 (very often), with higher scores indicating more stress. The measure includes items such as "How often have you felt that you were unable to control the important things in your life?" "How often have you felt confident about your ability to handle your personal problems?" and "How often have you been able to control irritations in your life?" The PSS has shown good reliability (α=.84-.86) and validity [64], and it is commonly used in mindfulness meditation research [22]. The PSS will be administered at baseline, midtreatment, and posttreatment.

Anxiety

The General Anxiety Disorder (GAD-7) scale [65] is one of the most widely used measures of anxiety symptoms. Participants rate items on a scale ranging from 0 (not at all) to 3 (nearly every day), with higher scores indicating more severe anxiety symptoms. The scale includes items such as "Feeling nervous, anxious or on edge," "Not being able to stop or control worrying," and "Feeling afraid as if something awful might happen." The GAD-7 has shown good internal consistency (α=.89-.90) and validity in POC samples [66]. The GAD-7 will be administered at baseline, midtreatment, and posttreatment.

Depression

The 8-item Patient Health Questionnaire (PHQ-8) [67] is one of the most widely used measures of depressive symptoms. Participants rate items on a scale ranging from 0 (not at all) to 3 (nearly every day), with higher scores indicating more severe depressive symptoms. This measure includes items such as "Little interest or pleasure in doing things," "Feeling down, depressed, or hopeless," and "Feeling bad about yourself or that you are a failure or have let yourself or your family down." Although the PHQ-8 omits an item assessing suicidal ideation and self-harm, meta-analytic work shows this version is practically equivalent to the original PHQ-9 measure [68]. The PHQ-8 has good reliability (α=.86-.89) and has shown validity across different racial and ethnic groups [69]. The PHQ-8 will be administered at baseline, midtreatment, and posttreatment.

Secondary Outcomes

Mindfulness

The 15-item Mindful Attention Awareness Scale (MAAS) [70] measures mindfulness. Participants rate items using a scale ranging from 1 (almost always) to 6 (almost never), with higher scores indicating more mindfulness. Items include "I find it difficult to stay focused on what's happening in the present," "I tend not to notice feelings of physical tension or discomfort until they really grab my attention," and "I could be experiencing some emotion and not be conscious of it until sometime later." The MAAS is one of the most used measures of mindfulness [71], showing good internal consistency (α=.80-.87) during its development [70]. The MAAS will be administered at baseline, midtreatment, and posttreatment.

Self-compassion

The 12-item Self-Compassion Scale–Short Form (SCS-SF) [19] measures self-compassion. Participants rate items using a scale ranging from 1 (almost never) to 5 (almost always), with higher scores indicating more self-compassion. Items in this measure include "I try to be understanding and patient toward those aspects of my personality I don't like," "I try to see my failings as part of the human condition," and "When I'm going through a very hard time, I give myself the caring and tenderness I need." In the development study of the SCS-SF, this scale showed good internal consistency (α=.86) and validity in a sample with significant POC representation [19]. The SCS-SF will be administered at baseline, midtreatment, and posttreatment.

Experiential Avoidance

The 15-item Brief Experiential Avoidance Questionnaire [25] measures experiential avoidance. Participants rate their responses on a scale ranging from 1 (strongly disagree) to 6 (strongly agree), with higher scores indicating more experiential

avoidance. Items include "I'm quick to leave any situation that makes me feel uneasy," "I would give up a lot not to feel bad," and "I work hard to keep out upsetting feelings." The BAEQ has shown good internal consistency (α=.80-.86) and construct validity [25]. The BAEQ will be administered at baseline, midtreatment, and posttreatment.

Rumination

The 5-item brooding subscale of the short version of the Ruminative Response Scale (RRS-SF) [27] measures rumination. Participants rate their responses on a scale ranging from 1 (almost never) to 4 (almost always), with higher scores indicating more rumination. Items include "Why can't I handle things better?" "Why do I have problems other people don't have?" and "What am I doing to deserve this?" The RRS-SF brooding subscale has shown adequate internal consistency (α=.79) and validity in studies with POC samples that experience discrimination [72]. This subscale will be administered at baseline, midtreatment, and posttreatment.

Emotion Suppression

The 4-item expressive suppression subscale of the Emotion Regulation Questionnaire (ERQ) [28] measures emotion suppression. Participants rate their responses on a scale ranging from 1 (strongly disagree) to 7 (strongly agree), with higher scores indicating more emotion suppression. Items include "I keep my emotions to myself," "When I am feeling positive emotions, I am careful not to express them," and "I control my emotions by not expressing them." The expressive suppression subscale of the ERQ has shown adequate reliability (α=.68-.76) and validity in samples with significant POC representation [28]. Furthermore, this subscale has been used in mindfulness research with POC [29]. The ERQ will be administered at baseline, midtreatment, and posttreatment.

Descriptive Outcomes

Acceptability and Appropriateness of the Intervention

The Attitudes Toward Psychological Online Interventions (APOI) [73] is a 16-item measure of experiences with digital interventions with 4 subscales (ie, skepticism and perception of risks, confidence in effectiveness, technologization threat, anonymity benefits). Participants rate items on a scale ranging from 1 (totally agree) to 5 (totally disagree), with higher scores indicating more perceived acceptability and appropriateness. The skepticism and perception of risks subscale includes items such as "By using the app, I do not expect long-term effectiveness" and "It is difficult to implement the suggestions of the app effectively in everyday life." The confidence in effectiveness subscales contains items such as "I have the feeling that the app can help me" and "I believe that the concept of app interventions makes sense." The technologization threat subscale includes items such as "I am more likely to stay motivated with a therapist rather than when using an app" and "I learn skills to better manage my everyday life from a therapist rather than from an app." The anonymity benefits subscale has items such as "An app is more confidential and discreet than visiting a therapist" and "I would be more likely to tell my friends than I use an app than that I visit a therapist." The APOI has shown good reliability (α=.83) and validity in a previous study [74].

The wording of the APOI will be slightly modified to refer to app-based interventions rather than online interventions. The APOI will be administered to participants in the intervention group at baseline, midtreatment, and posttreatment.

Treatment Satisfaction

The 7-item satisfaction with therapy subscale of the Satisfaction with Therapy and Therapist Scale–Revised [75] assesses treatment satisfaction with the app program. Participants rate items on a scale ranging from 1 (strongly disagree) to 5 (strongly agree), with higher scores showing more treatment satisfaction. Examples of items include "I am satisfied with the quality of the therapy I received," "My needs were met by the program," and "I would recommend this program to a friend." The satisfaction with therapy subscale has shown excellent reliability (α=.92) and validity in a digital intervention study with a racially and ethnically diverse sample [76]. The wording of the satisfaction with therapy subscale will be adapted to suit the app-based format of the intervention better. The satisfaction with therapy subscale will be administered to participants in the intervention group at baseline, midtreatment, and posttreatment.

Treatment Adherence

Number of meditations completed, number of days with at least one meditation completed, and total time meditated in minutes will be used as behavioral measures of treatment adherence. This information is tracked by the Ten Percent Happier app and will be obtained by asking participants in the intervention group to share a screenshot of their app profile via text message. Previous studies have shown that this methodology allows researchers to obtain accurate behavioral indicators of treatment adherence [60,77]. These behavioral indicators will be collected at midtreatment and posttreatment.

Results

Recruitment began in October 2021. This study will use multilevel modeling, a statistical methodology that allows time-varying predictors and handling dependence among repeated observations. We will examine changes in primary outcomes (ie, stress, anxiety, depression), hypothesized mediators (ie, mindfulness trait, self-compassion, experiential avoidance, rumination, emotion suppression), and treatment effects from baseline to midtreatment and posttreatment, and from midtreatment to posttreatment within each group. Test of mean differences will be calculated by fitting models with group condition (ie, intervention vs control) as the predictor, time as a within-group factor (ie, baseline, midtreatment, posttreatment), and a group-by-time interaction. To explore whether changes in primary outcomes are mediated by changes in the hypothesized mechanism of change, we will conduct mediation analyses. Relevant demographic variables (eg, income, age, gender) will be added to the models as covariates. These models will include random intercepts to capture potential differences in the starting points of each outcome and an autoregressive error structure to account for dependence among repeated measures. Given the relatively small sample size in this study, random slopes will be fitted when possible. Although our primary interest is in group-by-time interactions corresponding

to differential treatment effects, should significant interactions or main effects be found, follow-up contrasts can be used to examine within-group changes over time and between-group differences at each time point.

Considering issues of attrition and their potential effects on statistical significance and treatment effect sizes in app-based mindfulness meditation research [49], we will examine data using both intention-to-treat and per-protocol analyses [78]. In intention-to-treat analyses, group comparisons include all patients originally allocated after randomization, regardless of participant adherence to the intervention or withdrawal. Missing data will be handled using the last-observation-carried-forward method, which is considered a conservative approach. In per-protocol analyses, group comparisons include only those participants who completed the treatment as planned originally. Measures of treatment acceptability, satisfaction, and adherence will be examined by calculating descriptive statistics.

Discussion

Principal Findings

Despite extensive evidence showing the negative mental health effects of race-related stress in POC [6-11,14-17] and the promise of mindfulness meditation to help these individuals cope [20-24,26,30-32,79], this evidence-based treatment continues to be understudied among this high-risk population in both traditional [30,35,36] and digital formats [46-48]. As such, this study seeks to address gaps in the literature by (1) recruiting a sample exclusively composed of POC who report elevated levels of race-related stress and (2) testing the acceptability and effectiveness of a self-guided app-based mindfulness meditation intervention.

The main goal of this study is to determine whether POC who receive this self-directed app-based mindfulness meditation intervention experience reductions in mental health symptoms often associated with experiencing race-related stress. Based on previous meta-analyses [46,47,79], we hypothesize that POC who receive the intervention will experience significant decreases in overall stress, anxiety, and depression compared with those in the control group.

An additional goal of this study is to examine whether this self-directed app-based mindfulness meditation program engages potentially relevant clinical targets for POC exposed to race-related stress. Based on previous meta-analyses [20-24], we hypothesize that POC who receive the intervention will experience significant increases in mindfulness and self-compassion compared with those in the control group. Although increases in mindfulness are a well-established mechanism of change in mindfulness meditation programs, the role of self-compassion is less understood, warranting further investigation [20,21,23,24]. Considering previous studies showing the crucial role of experiential avoidance [80,81], rumination [20,23,24,82,83], and emotion suppression [29,83,84] as mediators in the development of mental health

problems among individuals exposed to stressors related to race, we hypothesize that POC who receive the intervention will experience significant decreases in these 3 variables compared with those in the control group.

Although mediation analyses are exploratory in nature, given the relatively small sample in this study, we hypothesize that changes in the secondary outcomes (ie, mindfulness, self-compassion, experiential avoidance, rumination, emotion suppression) will mediate changes in the primary outcomes (ie, stress, anxiety, depression). These analyses will provide novel information regarding potentially meaningful mechanisms of change in mindfulness meditation interventions among POC exposed to race-related stressors.

Finally, information regarding treatment acceptability, satisfaction, and perceived appropriateness may be especially important, given researcher and clinician concerns regarding potential cultural mismatches between mindfulness meditation and the needs of POC [32,85]. Similarly, data on treatment adherence in self-directed app-based mindfulness meditation are crucial to understanding whether this digital approach can indeed reduce unmet mental health need among POC while capitalizing on technology already available in households with more limited technological device ownership [40]. Issues of treatment adherence are significant considering extensive evidence of low enrollment, poor use, and high attrition rates in self-directed app-based interventions [49-51]. As such, descriptive information regarding number of individuals enrolled versus those eligible, number of meditations completed, total time meditated in minutes, survey completion rate, and number of dropouts is essential to determine the feasibility of this type of program and the potential impact of the engagement strategies used in this study (ie, short program length, onboarding procedure, text messaging reminder system, app notifications, financial incentives).

Conclusion

To our knowledge, this will be the first study to include a sample of exclusively POC presenting with elevated levels of race-related stress, contributing to the nascent data on the acceptability and effectiveness of self-directed app-based mindfulness meditation among marginalized groups. This study may help reduce disparities in mindfulness meditation among POC by testing an innovative delivery method and identifying relevant clinical targets for this at-risk population. Findings from this study could also inform the design of future studies using methodologies that provide more nuanced information about contextual and cultural factors influencing the success of digital mindfulness meditation interventions among POC (eg, qualitative, mixed methods). Similar approaches have provided relevant data on factors facilitating the provision of traditional face-to-face mental health services for communities of color [86]. This line of research is necessary to guarantee that app-based interventions for POC attend to issues of diversity, equity, and inclusion, reducing inequities already present in brick-and-mortar mental health services [43].

Acknowledgments

Authors' Contributions

All authors made substantial contributions to the design and implementation of this randomized controlled trial (RCT). GR is the principal investigator, designed the original RCT, and wrote all drafts of this manuscript. AA helped with the design of the text messaging reminder system and provided the technology necessary for its implementation. AM assisted with the RCT design and data analytic plan. AL identified treatment outcomes relevant to people of color populations. CYW designed the data collection strategy and managed the initial implementation of this RCT. VCT assisted with recruitment efforts. DC was involved in the original design of this RCT, reviewed all drafts of this manuscript, and provided funding for the execution of this project.

Conflicts of Interest

None declared.

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Abbreviations

APOI: Attitudes Toward Psychological Online Interventions
ERQ: Expressive Suppression of the Emotion Regulation Questionnaire
GAD-7: General Anxiety Disorder
IRRS-B: Race-Related Stress–Brief
MAAS: Mindful Attention Awareness Scale
MDM: Multicultural Discrimination Module
PHQ-8: Patient Health Questionnaire
POC: people of color
PSS: Perceived Stress Scale
RCT: randomized controlled trial
RRS-SF: Ruminative Response Scale, short form
SCS-SF: Self-Compassion Scale–Short Form

Protocol

A Web-Based Well-being Program for Health Care Workers (Thrive): Protocol for a Randomized Controlled Trial

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Abstract

Background: Mental health has come to be understood as not merely the absence of mental illness but also the presence of mental well-being, and recent interventions have sought to increase well-being in various populations. A population that deserves particular attention is that of health care workers, whose occupations entail high levels of stress, especially given the ongoing COVID-19 pandemic. A neuroscience-based web-based well-being program for health care workers—the Thrive program—has been newly developed to promote habits and activities that contribute to brain health and overall mental well-being.

Objective: This paper describes the protocol for a randomized controlled trial whose objective is to evaluate the Thrive program in comparison with an active control condition to measure whether the program is effective at increasing well-being and decreasing symptoms of psychological distress in health care workers at a designated Australian hospital.

Methods: The trial will comprise two groups (intervention vs active control) and 4 measurement occasions over a 12-week period. A survey will be administered in each of weeks 0, 4, 8, and 12, and the well-being program will be delivered in weeks 1-7 (via web-based video presentations or digital pamphlets). Each of the 4 surveys will comprise a range of questionnaires to measure well-being, psychological distress, and other key variables. The planned analyses will estimate group-by-time interaction effects to test the hypothesis that mental health will increase over time in the intervention condition relative to the active control condition.

Results: The Thrive program was delivered to a small number of wards at the hospital between February 2021 and July 2021, and it will be delivered to the remaining wards from October 2021 to December 2021. A power calculation has recommended a sample size of at least 200 participants in total. A linear mixed model will be used to estimate the interaction effects.

Conclusions: This trial seeks to evaluate a new web-based well-being program for health care workers at a major public hospital. It will contribute to the growing body of research on mental well-being and ways to promote it.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12621000027819; https://tinyurl.com/58wwjut9

International Registered Report Identifier (IRRID):   DERR1-10.2196/34005

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Introduction

Background

In recent decades, the medical and behavioral sciences have recognized that mental health is not merely the absence of mental illness but also the presence of mental well-being [1]. Thus, mental illness and well-being are distinct albeit related constructs that need to be considered in research and clinical practice. In a seminal study of the US adult population, Keyes [2,3] delineated three categories of mental well-being: flourishing, moderately healthy, and languishing. Those with high well-being and no mental illness are described as flourishing, whereas those with low well-being may be free of illness (*pure languishing*) or not (eg, *depressed and languishing* in the case of those with major depression). In the representative sample of >3000 adults, less than one-fifth were flourishing, and a comparable proportion were languishing. Of those with low well-being, over half did not meet criteria for a major depressive episode, generalized anxiety disorder, panic disorder, or alcohol dependence over the preceding 12 months. On average, those who were purely languishing reported less than one symptom of each of these disorders, suggesting that low well-being is not a proxy for subclinical illness but rather a distinct condition. This was supported by confirmatory factor analyses that indicated that a correlated 2-factor model was the best way to account for the data on mental illness and well-being. Furthermore, it was found that pure languishing was not only as prevalent as pure illness (ie, illness without low well-being) but also associated with more severe psychosocial outcomes (relative to pure illness) on 9 out of 11 measures. Clearly, low mental well-being can place a substantial burden on the individual and on society that stands apart from the costs of illness alone and needs to be targeted in its own right in health promotion strategies.

More recently, there have been important advances in the measurement and understanding of mental well-being. Gatt et al [4] developed a composite measure of well-being—the Composure, Own-worth, Mastery, Positivity, Achievement, and Satisfaction for Wellbeing (COMPAS-W) scale—that assesses both hedonia (ie, positive affect and life satisfaction) and eudaimonia (ie, fulfillment of one's potential and having a sense of life purpose) across six subcomponents: Composure (dealing effectively with stress or adversity), Own-worth (a sense of autonomy and self-respect), Mastery (self-confidence and perceived control over one's environment), Positivity (happiness and optimism), Achievement (setting and pursuing goals), and Satisfaction (with one's life, health, and relationships). This factor structure was confirmed in a major twin study of Australian adults, as was the scale's reliability and validity. For example, well-being was associated with lower levels of depression, anxiety, and stress symptoms; higher work productivity; and healthier diet, exercise, and sleep habits [4]. The COMPAS-W measure has allowed researchers to explore the genetic and neural underpinnings of mental well-being [5-7] and, crucially, to determine the extent to which well-being might be modifiable through interventions and other environmental influences. From their twin study, Gatt et al [4] derived heritability estimates between 24% and 48% across the 6 subcomponents of well-being, with the remaining variance attributed to the unique environment. This indicates that, although well-being is significantly influenced by genetic factors, it is certainly subject to external influences as well, which is encouraging for practitioners who would seek to raise levels of well-being in a given population.

As mental well-being has been recognized as a key construct in its own right and one that is substantially determined by nongenetic factors, it has become the focus of interventions that aim to elevate it or at least prevent its decline. To date, there have been 2 randomized controlled trials (RCTs) investigating the effects of an intervention on COMPAS-W scores. In a trial involving a subsample from the aforementioned twin study, Routledge et al [8] evaluated a 30-day *brain training* (ie, computerized cognitive training) program comprising games and exercises related to cognitive and affective processing as well as emotional regulation. Relative to a waitlist control group, training participants exhibited changes in explicit emotion identification and implicit emotion bias for a number of facial expressions, but these alterations did not lead to changes in well-being or psychological distress. However, the brain training program did not exclusively target mental health but rather comprised a broader set of cognitive and emotional activities, and many participants did not complete the minimum amount of training recommended by the researchers. Furthermore, the recruitment process excluded participants with current or lifetime psychiatric disorders or substance abuse. Therefore, there may have been a ceiling effect whereby many participants were already functioning well enough that they had little to gain from the intervention in that regard, especially if they did not complete the recommended amount of training.

In the second RCT study, Chilver and Gatt [9] evaluated a 6-week positive psychology intervention relative to an active control condition in 326 university students. They found that the intervention led to significant increases in subjective well-being and—in those who had low resiliency resources at the outset—increases in composite well-being and decreases in psychological distress (ie, depression and anxiety symptoms). Again, this is consistent with the possibility that a ceiling effect exists to some degree whereby those who are more mentally healthy at the outset have less to gain from an intervention. However, across all the participants, the intervention by Chilver and Gatt [9] resulted in significant increases in the well-being subcomponent of Satisfaction, suggesting that certain aspects of well-being may be more responsive to training even in those with higher resilience at baseline. Together, these studies suggest that it is possible to improve well-being outcomes via particular intervention approaches and that they may be more efficacious in populations that are less resilient or more exposed to stress and other kinds of adversity.

One such population to target is hospital-based health care workers, who work under demanding and stressful conditions. There is extensive literature on nurses' experiences in the workplace, highlighting a range of demands and hardships that can compromise staff well-being. For instance, in a survey of >40,000 nurses from >700 hospitals across 5 countries, Aiken et al [10] found that the proportion of nurses who reported job dissatisfaction was >40% in the United States; >30% in Canada,

England, and Scotland; and approximately 20% in Germany. For comparison, the researchers pointed out that job dissatisfaction in the general population of American professionals was only 10%, indicating that dissatisfaction was markedly higher among nurses. Furthermore, a large proportion (15%-40% depending on the country) of the surveyed nurses reported that they were planning to leave their job in the following year. In a more recent survey of >3000 Australian health care workers, >70% stated that their workloads exceeded what they were capable of doing well at least once or twice a week, and >25% stated that they were thinking of leaving their profession [11]. The typical sources of psychological distress reported by health care workers include heavy workloads, time pressures, role ambiguity, lack of control or flexibility, and lack of participation in decision-making [12].

The COVID-19 pandemic has placed additional demands on health care workers [13]. In Australia, a survey of 637 primary health care nurses [14] revealed that most respondents (nearly 75%) did not always have access to sufficient personal protective equipment, almost half had concerns about a lack of support from their employers, and over one-third stated that the quality of care at their workplace had diminished (at least slightly) since the start of the pandemic. In addition, the government of New South Wales (Australia's most populous state) published a summary of worldwide research on the impact of the pandemic on the mental health of health care workers [15], finding that the pandemic had placed these workers at increased risk of psychological distress, including anxiety about contracting the virus. Of 433 Australian health care workers surveyed, approximately 50% reported increased workloads, anxiety, and tiredness, and >70% reported higher stress at work.

The mental well-being of nurses and other health care workers is vitally important not only for the workers themselves but also for the health and safety of their patients. Structural equation models have suggested that well-being mediates the relationship between organizational factors and patient care. For example, a study of 324 Hong Kong nurses [16] found that nurses' perceptions of support from their workplace, supervisor, and colleagues predicted their psychological well-being, which in turn predicted their safety performance. Similarly, a study of 345 Iranian nurses [17] found that organizational support predicted psychological well-being, which in turn predicted both job satisfaction and quality of care, and a study of 474 Taiwanese nurses [18] concluded that well-being predicted safety attitudes. In addition, a study of 325 Pakistani nurses found that those with higher levels of negative emotion were judged by their peers to engage in higher levels of "deviant" workplace behavior such as deliberately arriving late to work or taking undeserved breaks to avoid doing work, which could compromise patient care in numerous ways [19]. Furthermore, in a study of 637 US nurses, Dyrbye et al [20] observed that those who scored lower on a well-being index were more likely to have made a patient care error in the previous 3 months. Although the relationship between well-being and patient care may go in either direction (or be attributable to a third variable), it is eminently plausible that low well-being (and the psychosocial dysfunction that comes with it) can result in suboptimal job performance and more frequent errors (cf Keyes

[3], who found that lower well-being was related to higher absenteeism and reduced workdays, and Gatt et al [4], who found that lower well-being was associated with higher absenteeism and lower productivity on the job). Clearly, there are substantial benefits that may be gained by addressing shortfalls in health care workers' well-being.

Fortunately, there is some research to suggest that interventions for health care workers can lead to reductions in stress and improvements in mental well-being [21], although the evidence base is relatively limited at present. For instance, Orly et al [22] administered a cognitive behavioral intervention for nurses that resulted in benefits related to stress and mood, but the sample size was small (N=36), the participants were not randomly allocated to the intervention and control conditions, and there was no follow-up (ie, no testing beyond the end of the intervention). Tveito and Eriksen [23] conducted an RCT of a health and fitness program for nursing home staff, finding benefits in terms of self-reported health and stress but, again, the sample was small (N=29), and there was no follow-up. Similarly, Daigle et al [24] conducted an RCT of a mindfulness-based stress-reduction program for nurses, finding improved mood in the intervention group but, yet again, the sample was small (N=52), and there was no follow-up. Similarly, Bolier et al [25] carried out an RCT of a web-based mental health program for health care workers, but the randomization was conducted at the ward level rather than the individual level and, of the 178 participants allocated to the intervention group, only 9 actually engaged in the web-based activities. Hence, our study seeks to address some of the gaps in the literature on well-being programs for health care workers.

This paper outlines the protocol for an RCT evaluating the effects of a new well-being program—the *Thrive* program—for health care workers at a large public hospital in metropolitan Sydney, New South Wales, Australia. Thrive is a web-based psychoeducational program that provides information and guidance within seven areas of life related to mental well-being: sleep, exercise, nutrition, stress management, social connection, cognitive challenge, and life purpose. The program is innovative in that it covers how these 7 aspects of life affect not only well-being in general but also brain health in particular. With advances in neuroscience and neuroimaging in the 21st century, there is now a sufficient knowledge base to underpin this specialized intervention, which is aimed at promoting well-being via healthy habits and lifestyle decisions that directly affect the organ on which mental health ultimately depends—the brain. Another key strength of this study is that the COMPAS-W well-being scale [4] will be used as the primary outcome measure, allowing for a comprehensive assessment of the participants' subjective and psychological well-being and an opportunity to detect whether one or more of the 6 subcomponents of well-being is more or less responsive to the intervention. To the authors' knowledge, this will be the first intervention for health care workers to use an empirically derived measure of well-being that has also been validated with regard to genetic [7,26-28] and neural [5,6,29] markers as well as psychological factors, including resilience, trauma, and coping strategies [30,31].

Objectives

This study has 2 main objectives. First, it aims to determine whether the Thrive program results in significant gains in well-being—as measured by the COMPAS-W scale—in the intervention group compared with an active control group and, if so, which of the specific COMPAS-W subcomponents is most responsive to the program. Second, from the baseline measurements, the study will inform researchers, hospital staff, and other stakeholders of the current levels of overall mental health and well-being among the health care workers at the target hospital.

Methods

Design

The Thrive program will be evaluated in an RCT with 2 conditions and 4 measurement occasions. Thus, there will be two main independent variables—one between-group factor and one repeated-measure factor—as well as a selection of covariates and dependent variables. The two conditions will be the intervention (ie, the Thrive webinar program) and an active control condition (only an abbreviated pamphlet version of the educational components of the program). The study will take place over a 12-week period, and a web-based survey will be administered at each of the 4 measurement occasions. In week 0 (ie, 1 week before the program commences), the participants will complete the baseline survey (before the intervention). The Thrive program (and the parallel active control program) will run for 7 weeks, from week 1 to week 7. The participants will complete the second survey in week 4 (at the midpoint of the program), the third survey (after the intervention) in week 8 (ie, 1 week after the conclusion of the program), and the fourth survey (follow-up) in week 12 (ie, 4 weeks after the intervention). Each survey will take approximately 20 to 30 minutes to complete. Once all 4 surveys have been administered and the study period has concluded, all the participants in the active control condition will be given access to the full version of the Thrive program. The study timeline is illustrated in Figure 1.

Figure 1. Study timeline.
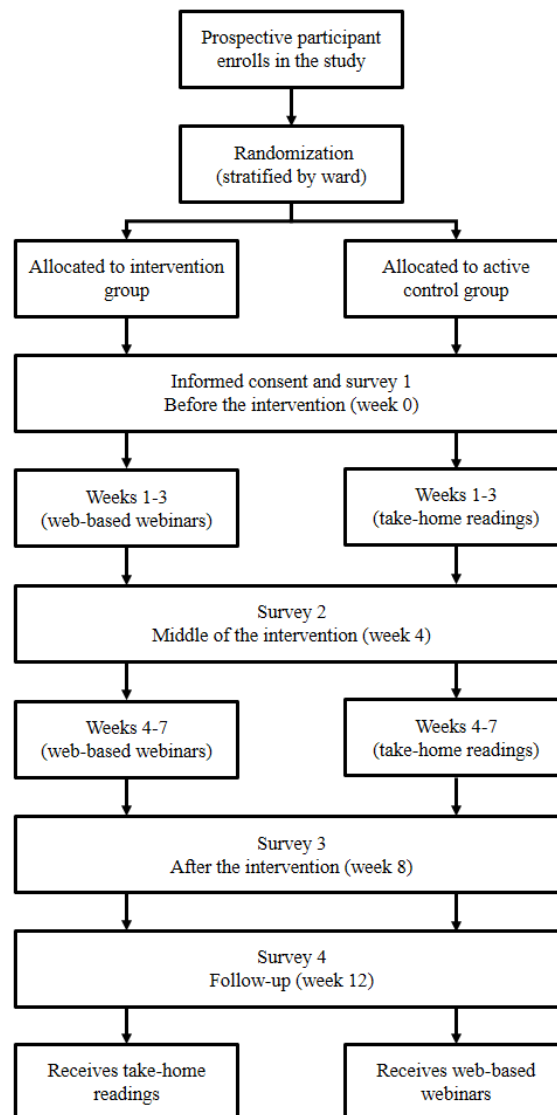
Participants

The participants will be health care workers from the Prince of Wales Hospital (POWH), a large public hospital in metropolitan Sydney, New South Wales, Australia. The participants will be recruited via flyers displayed around the hospital, emails sent to hospital staff mailing lists, and announcements from management (eg, Nursing Unit Managers). All health care workers from the hospital (eg, nurses, physicians, and allied health professionals) will be welcome to sign up for the study.

Eligibility Criteria

Prospective participants will be eligible to enroll in the study provided that they are health care workers at POWH, comfortable using written English to complete the program and surveys, willing to take four 20-to-30–minute web-based surveys across the 12-week study period, willing to complete the 7-week well-being program, and able to access the internet for the surveys and program content.

Recruitment

Study advertisements will invite POWH staff to sign up for the 12-week study and notify them that participants will be randomly assigned to one of two conditions, labeled *online presentations* and *take-home readings*. Those assigned to the former condition will be the intervention group, and those assigned to the latter condition will be the active control group. Once assigned, the participants will know whether they are in the *online presentations* or *take-home readings* condition, but they will be blind to which condition is the true intervention versus the active control. They will also be assured that all participants in one version of the Thrive program will receive all the resources of the other version after the end of the 12-week study period. This assurance should reduce the incentive for participants in one group to share any course content with a participant from the other group (the participants will also be explicitly instructed not to share anything with anyone else throughout the program).

Potential participants will be informed that those who complete the Thrive program will be eligible to receive Continuing Professional Development (CPD) points. At POWH, nurses and other health care workers are expected to engage in ongoing professional development by attending workshops, completing courses, and participating in other such activities, with a certain number of CPD points awarded for each activity. Each worker has to earn at least 20 points per year, and each Thrive participant will receive 10 points after completing the program. As the control participants will gain access to the full Thrive program at the end of the 12-week study period, all the participants will receive 10 points regardless of the condition to which they are assigned. There are numerous ways outside the Thrive program in which a given health care worker can earn their required CPD points, so the offer of 10 points for completing the program is not an undue inducement to participate but rather fair compensation for the participants' time and effort. Each participant will also receive a Certificate of Completion from the research team.

Randomization and Informed Consent

Hospital staff interested in participating will sign up for the study by writing their details (ie, name, email address, and ward) on registration sheets posted around the wards, by registering on the web via the hospital's professional development website, or by emailing a designated member of the research team (MM). The final list of participants will be sorted according to ward to allow for stratified randomization. For each ward, a random number generator will be used to allocate half the participating staff to the intervention condition and half to the active control condition. Next, the participants will be notified by email as to the condition to which they have been assigned. This email will also provide the Participant Information Statement and Consent Form and a link to the first survey. After reading the form, those who are willing to participate will click on the link to access the first survey. The first item of this survey provides a button whereby the participant can digitally record their consent to participate. For the remainder of the study period, the participants will be sent the relevant survey links and program resources by email at the appropriate times.

All participants will be free to withdraw at any time from the surveys, the Thrive program, or both the surveys and the program without penalty and without having to give a reason, with the provision that only those who complete the Thrive program will receive the 10 CPD points and Certificate of Completion. However, completion of the surveys will not be required to earn the points and certificate. In other words, if a participant is enjoying the program and wishes to finish it but does not want to continue providing data via the surveys, they will be welcome to do so.

Sample Size

Power calculations suggest that at least 200 participants need to be recruited (100 per condition) to detect a small group-by-time interaction effect at 80% power. This sample size was calculated using the statistical software package G*Power (version 3.1.9.2) [32,33]. Assuming a small effect of 0.01 (partial η^2), a conventional type-1 error rate of 0.05, and a correlation of 0.5 among the repeated outcome measures, the study will be able to detect such an effect at 80% power with 69 participants in each group. However, considering an attrition rate of up to 30% by the final measurement occasion, it will be necessary to recruit at least 99 people per group, so we will aim for a total sample size of at least 200. The projected attrition rate of 30% is based on the attrition rates reported in previous RCTs [23-25] that examined interventions to increase well-being in hospital staff. Additional power calculations show that the study will be able to detect effects as small as 0.04 (partial η^2) even under the strictest nonsphericity correction and possible attrition of up to 65%.

Procedure and Materials

Intervention

The intervention participants will receive the full version of the Thrive program, comprising a 1-hour web-based presentation each week for 7 weeks. Each presentation will be a webinar (web-based seminar) delivered via the Zoom platform (Zoom

Video Communications Inc). Participants will view the webinars as prerecorded videos on a dedicated webpage, which will ensure uniform delivery of the intervention. Each webinar will be copresented by 2 members of the research team. One presenter (MM) is a Nurse Educator from the hospital with a Master's degree in Adult Education and extensive experience in providing professional development courses to health care workers. The other presenter (LAE) is a researcher from the Gatt Group at Neuroscience Research Australia (NeuRA) and the University of New South Wales (UNSW) with a PhD in Psychology and extensive experience in lecturing, tutoring, and counseling.

Each webinar will follow a 3-step sequence named *Inform, Inspire, Improve*. The *Inform* and *Inspire* sections will last approximately 25 minutes each, and the *Improve* section will last approximately 10 minutes. During the *Inform* section, the presenters will share scientific findings from the fields of neuroscience, medicine, and psychology to educate the participants on the links among brain health, mental well-being, and one of the 7 areas of life covered by the program. This section will provide knowledge only, as a background to the subsequent sections. During the *Inspire* section, the presenters

will provide advice, guidance, and recommendations on how to improve one's brain health and mental well-being in the relevant area of life. This section will build upon the preceding knowledge by offering practical suggestions to implement in one's daily life. Finally, during the *Improve* section, the webinar viewers will have an opportunity to reflect on the knowledge and suggestions shared in the preceding sections, and they will be invited to commit to enacting at least one of the suggestions in their own lives.

The knowledge and recommendations provided in each webinar are based on peer-reviewed empirical studies from the medical and behavioral sciences, with a special emphasis on neuroscientific findings. The webinars also draw upon other authoritative sources such as the US Department of Health and Human Services, the Australian Government National Health and Medical Research Council, and the World Health Organization. The full reference list for the Thrive program contains >250 peer-reviewed publications, and the participants will be provided with a reference list for each week of the program in case they wish to check anything or explore the literature themselves. Textbox 1 provides an overview of the program content for each of the 7 webinars.

Textbox 1. Overview of the Thrive webinar content for the intervention group.

Webinar topics and content

- Week 1 (sleep): impact of sleep quantity and quality on well-being and the brain; tips for improving sleep quality in relation to light exposure, exercise, meal timing, and nutrition; cognitive behavioral tips for sleeping better; and accessing treatment for a sleep-related disorder

- Week 2 (exercise): impact of physical activity on well-being and the brain; tips for increasing motivation to exercise in relation to social connection, natural environments, and novelty or variety; using the internet to find new ways to exercise; exercising in a way that suits one's personal preferences; and how to access an exercise physiologist through the publicly funded health care system

- Week 3 (nutrition): impact of nutrition on well-being and the brain; links among nutrition, human evolution, and chronic noncommunicable diseases; tips for improving one's diet in relation to avoiding empty calories, practicing mindful eating, and accommodating dietary restrictions; and how to get tested for micronutrient deficiencies

- Week 4 (stress management): impact of stress on well-being and the brain; how the stress system works; tips for managing and reducing stress using mindfulness, controlled breathing, and effective coping strategies; and how to access treatment for posttraumatic stress disorder or a stress-related disorder

- Week 5 (social connection): impact of social connections on well-being and the brain; tips for improving connections using compassionate communication, active listening, nonverbal communication, and acts of kindness; and how to use the internet to make new social connections

- Week 6 (cognitive challenge): impact of cognitive challenge on well-being and the brain; tips on challenging oneself using new knowledge, linguistic or mathematical puzzles, skill development, and novelty; and how to overcome anti-intellectual stigma and follow one's curiosity

- Week 7 (life purpose and meaning): impact of life purpose on well-being and the brain; the differences between hedonia and eudaimonia; the state of flow and how to achieve it; and tips for achieving a greater sense of purpose and fulfillment by targeting character strengths and weaknesses, setting meaningful goals, accepting unavoidable hardship, and identifying one's core values

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Each week, in addition to the reference list, the intervention participants will receive a 1-page *reflective sheet* and a 4-page infographic summary. The reflective sheet will prompt participants to write down their key learning from that week's webinar, what this learning means to them, and what they will do next to act on it. After viewing each webinar, the participants will be encouraged to fill in their reflective sheet and add it to their CPD portfolio, although this is not a requirement to complete the program. The infographic document will provide a summary of the *Inform* section of that week's webinar (ie, a summary of the neuroscience and other background information covered in the webinar).

Active Control

The active control participants will receive an extremely reduced version of the Thrive program. In each of the 7 weeks, they will be emailed the infographic summary on that week's topic and instructed to read it. The infographic documents will be identical to those received by the intervention participants. In short, the control participants will be provided with only the *Inform* section for each week's topic, in the form of the infographic summary only. They will not receive any tips and advice for promoting well-being. Thus, the intervention participants will receive knowledge plus practical advice and reflective opportunities (in webinar and document forms), whereas the control participants will receive knowledge only (in document form only). The

control participants will receive a reference list to accompany each infographic summary, but they will not receive the reflective sheets. To summarize, each week, the intervention participants will receive a webinar, reflective sheet, infographic, and reference list, whereas the active control participants will receive the infographic and reference list only.

Survey Measures

Overview

A range of questionnaires will be administered via the web-based surveys, but not all will be administered at each measurement occasion (see Table 1 for an outline of the questionnaire timings).

Table 1. Questionnaires delivered at each time point.

Questionnaire	Survey 1 (week 0)	Survey 2 (week 4)	Survey 3 (week 8)	Survey 4 (week 12)
Demographics	✓			
Medical history	✓			
Health and lifestyle	✓	✓	✓	✓
COMPAS-W[a]	✓	✓	✓	✓
RRC-ARM[b]	✓			
DASS-21[c]	✓	✓	✓	✓
Abbreviated POMS[d]	✓	✓	✓	✓
Brief COPE[e]	✓	✓	✓	✓
Self-Compassion Scale	✓			✓
Compassion Scale	✓			✓
MAAS[f]	✓			✓
HPQ[g] (work performance items)	✓			✓
UWES[h]	✓			✓
DLE[i] (trauma items)	✓			
DLE (COVID-19 items)	✓	✓	✓	✓
COVID-19 Exposure Survey	✓	✓	✓	✓
Thrive attendance items		✓	✓	✓
Thrive satisfaction items			✓	✓

[a]COMPAS-W: Composure, Own-worth, Mastery, Positivity, Achievement, and Satisfaction for Wellbeing Scale.

[b]RRC-ARM: Resilience Research Centre Adult Resilience Measure.

[c]DASS-21: Depression, Anxiety, and Stress Scale–21-item version.

[d]POMS: Profile of Mood States.

[e]COPE: Coping Orientation to Problems Experienced.

[f]MAAS: Mindful Attention Awareness Scale.

[g]HPQ: Health and Work Performance Questionnaire.

[h]UWES: Utrecht Work Engagement Scale.

[i]DLE: Daily Life Events.

Demographics

This questionnaire will measure age, sex, education, occupation, and other demographic characteristics.

Medical History

This questionnaire will ask whether the participant or anyone in their immediate family has ever been diagnosed with a learning or developmental disorder or diagnosed with and treated for a psychological or psychiatric disorder.

Health and Lifestyle

This questionnaire will ask about health-related habits, including questions on diet, exercise, sleep, and drug and alcohol use.

COMPAS-W Scale

The COMPAS-W scale [4] is a 26-item questionnaire that measures overall mental well-being as well as the six subcomponents of Composure, Own-worth, Mastery, Positivity, Achievement, and Satisfaction. Each item presents a statement with a 5-point response scale ranging from *strongly disagree* to *strongly agree*. The respondents are asked to answer the items in terms of how they feel *most of the time* but, in this study, the

instructions will be modified for the second, third, and fourth surveys to ask the respondents how they have felt *over the past month* (ie, since taking the previous survey).

Resilience Research Centre Adult Resilience Measure

The Resilience Research Centre Adult Resilience Measure [34] is a 28-item questionnaire that measures resiliency resources (eg, *I know where to get help in my community*). Each item presents a statement with a 5-point response scale ranging from *not at all* to *a lot*. This scale does not specify a period but simply asks the respondents to what extent each statement describes them.

Depression, Anxiety, and Stress Scale–21-Item Version

The Depression, Anxiety, and Stress Scale–21-item version [35,36] is a 21-item questionnaire that measures psychological distress (ie, symptoms of depression, anxiety, and stress). Each item presents a statement with a 4-point response scale ranging from *did not apply to me at all* to *applied to me very much or most of the time*. The respondents are asked to answer each statement in terms of how much it has applied to them *over the past week*.

Abbreviated Profile of Mood States (Revised Version)

The revised version of the Abbreviated Profile of Mood States [37] is a 40-item list of adjectives describing positive and negative mood states (eg, vigorous or unhappy), with a 5-point response scale ranging from *not at all* to *extremely*. The respondents are asked to what extent each adjective describes how they feel *right now*.

Brief Coping Orientation to Problems Experienced

The Brief Coping Orientation to Problems Experienced scale [38] is a 28-item questionnaire that measures 14 specific coping styles across the broader categories of approach coping (eg, *I've been taking action to try to make the situation better*) and avoidant coping (eg, *I've been refusing to believe that it has happened*). The 14 subscales are named *active coping*, *planning*, *positive reframing*, *acceptance*, *humor*, *religion*, *using emotional support*, *using instrumental support*, *self-distraction*, *denial*, *venting*, *substance use*, *behavioral disengagement*, and *self-blame*. Each item presents a method of coping with a 4-point response scale ranging from *I haven't been doing this at all* to *I've been doing this a lot*. The respondents are asked to answer each statement in terms of how much they have been using that coping style *in the past month*.

Self-Compassion Scale

The Self-Compassion Scale [39] is a 26-item questionnaire that measures self-compassion across six subscales named *self-kindness*, *self-judgment*, *common humanity*, *isolation*, *mindfulness*, and *overidentification*. Each item presents a statement with a 5-point response scale ranging from *almost never* to *almost always*. The respondents are asked to answer each statement in terms of how they *typically* act toward themselves in difficult times.

Compassion Scale

The Compassion Scale [40] is a 16-item questionnaire that measures compassion for others across four subscales named *kindness*, *common humanity*, *mindfulness*, and *indifference*. Each item presents a statement with a 5-point response scale ranging from *almost never* to *almost always*. The respondents are asked to answer each statement simply in terms of *how often* they feel or behave in the stated manner.

Mindful Attention Awareness Scale

The Mindful Attention Awareness Scale [41,42] is a 15-item questionnaire that measures mindfulness (ie, nonjudgmental consciousness of the present moment). Each item presents a statement with a 6-point response scale ranging from *almost never* to *almost always*. The respondents are asked to what degree each statement pertains to their *current experience*.

Health and Work Performance Questionnaire Scales (Employee Version)

Two sections from the employee version of the World Health Organization Health and Work Performance Questionnaire [43]—scale B9 and scale B12—will be used to measure work performance. Scale B9 contains 5 items asking how many days in the past 4 weeks the respondent missed an entire workday, missed part of a workday, or performed extra work outside their usual working hours. Scale B12 contains 7 items about the respondent's work performance in the past 4 weeks (referring to both overperformance and underperformance), with a 5-point response scale ranging from *none of the time* to *all of the time*.

Utrecht Work Engagement Scale

The Utrecht Work Engagement Scale [44] is a 17-item questionnaire that measures the respondent's level of engagement with their work (eg, *I am enthusiastic about my job*). Each item presents a statement with a 7-point response scale ranging from *never* to *always/every day*.

Daily Life Events

The Daily Life Events (DLE) scale [45] is a list of minor and major positive and negative life events, and the respondents are asked whether each event has happened to them and, if so, whether it has had a positive, neutral, or negative impact on them. For this study, we used the trauma items from the original DLE scale and adapted the other items to be answered in reference to COVID-19. The trauma section lists 7 potentially traumatic life events (eg, being physically or sexually assaulted) and asks the respondents whether each event has ever happened to them and, if so, how many years ago it last occurred. The COVID-19 section lists 15 life events (eg, separation from family and working from home) and asks the respondents whether each event has happened to them in the last 12 months (ie, during the COVID-19 pandemic) and, if so, how many months ago it last occurred and whether it had a positive, neutral, or negative impact on them, with a 7-point response scale ranging from −3 (*extremely negative impact*) to +3 (*extremely positive impact*). The DLE scale is provided in Multimedia Appendix 1.

COVID-19 Exposure Survey

The COVID-19 Exposure Survey is a compilation of items regarding the impact of the COVID-19 pandemic on the respondents and their workplace (ie, their ward at the hospital). The survey includes questions on how many times the

respondent has been tested for COVID-19, whether they have contracted the virus, whether they have had to care for a patient with the virus, whether the pandemic has affected their workload, and whether they have considered leaving their job during the pandemic. The COVID-19 Exposure Survey is provided in Multimedia Appendix 1.

Thrive Program Attendance and Satisfaction Survey

This survey asks the respondents which of the 2 versions of the Thrive program they received (this question will serve as a manipulation check), how much of the program they have completed (ie, their attendance), whether they enjoyed it, and how helpful they felt it was for both themselves and their patients. This survey will be administered only after the Thrive program has concluded (ie, in weeks 8 and 12); however, items 7 and 8 of the survey (Multimedia Appendix 1) will be administered in week 4 to measure attendance up to that point. When item 8 is administered in week 4, it will ask about attendance only for weeks 1 to 3. When administered in weeks 8 and 12, this item will ask about attendance across all 7 weeks of the program.

Primary and Secondary Outcomes

The primary outcomes for this RCT will be the participants' levels of well-being (as measured by the COMPAS-W) and their levels of psychological distress (as measured by the Depression, Anxiety, and Stress Scale–21-item version). Thus, the primary outcomes will encompass both dimensions of mental health: mental well-being and mental illness. The secondary outcomes will be health and lifestyle habits, mood states, compassion (for oneself and others), mindfulness, work performance, and work engagement. Program attendance, resiliency resources, medical history, trauma, coping styles, and pandemic-related variables will serve as potential moderator variables along with demographic variables such as age, sex, ward, and occupation. The primary end point for the analysis will be the third measurement occasion (week 8), and the secondary end points will be the second and fourth occasions (week 4 and week 12).

Anonymity and Confidentiality

Although each participant will provide their name, email address, and ward to enroll in the Thrive program, their survey responses will be completely anonymous and linked via a participant code number. At each measurement occasion, the participants will be emailed a link to the survey and, when they click on the link, they will be taken to the web-based Qualtrics (Qualtrics International Inc) platform that will be hosting the surveys. The web-based surveys will not ask for any information that could be used to identify any individual participant, and Qualtrics will not record any metadata from the respondents either. To match each participant's responses on one measurement occasion with their responses on the other occasions, each survey will ask the respondent to provide a self-generated code. The respondent will be instructed to take the last 3 digits of their mobile phone number and the last 2 digits of their birth year to create their own 5-digit code. For example, if a participant's phone number ended in the digits *123* and they were born in 1970, their code would be *12370*.

One might argue that someone familiar with a given participant could identify their survey responses from this code, but none of the researchers who will have access to the raw data will be personally acquainted with any of the participants. Furthermore, once all the data have been collected and all the responses have been matched, the 5-digit codes will be deleted from the data set and replaced with generic, arbitrary ID numbers.

At each measurement occasion, the survey link sent to the intervention participants will be different from the link sent to the active control participants (even though the surveys themselves will be identical). This will allow the researchers to keep track of which condition each participant is in without relying on self-reports.

Data Storage and Security

Once the data have been collected via Qualtrics, they will be downloaded directly from the Qualtrics servers onto the secure internal server at NeuRA. Only the research team will have access to the data. There will be no intermediaries (either human or technological) between Qualtrics and the research team.

Analysis

Missing values in the data set will be estimated via multiple imputation, and the initial analyses will be conducted on an intention-to-treat basis followed by per-protocol analyses to account for levels of treatment compliance (eg, program attendance). The data will be analyzed via a linear mixed model that will allow the group-by-time interaction effects to be estimated. It is hypothesized that levels of well-being will increase over time in the intervention condition relative to the active control condition. Similarly, it is hypothesized that levels of psychological distress (ie, symptoms of depression, anxiety, and stress) will decrease over time in the intervention condition relative to the active control condition. There may also be a group-by-time interaction effect on one or more of the secondary outcomes. For example, the intervention may promote increased compassion, mindfulness, or work engagement. Furthermore, any interaction effect may itself be moderated by a variable such as resilience or coping style (cf [9,31]).

Publication Policy

The results of this study will be shared with the hospital, the funding body, the overseeing organizations, and other relevant stakeholders. The results will also be published in peer-reviewed scholarly journals, presented at academic conferences, and publicized on the media platforms used by NeuRA and UNSW. In all publications and presentations of the findings, the data will be presented in aggregate, and no individual participants will be identifiable.

Ethics Approval

This study has received ethical approval from the Human Research Ethics Committee of the South Eastern Sydney Local Health District (approval granted on November 9, 2020; project 2020/ETH02090), and this approval was ratified by the UNSW Human Research Ethics Committee on November 12, 2020.

Results

The trial has been prospectively registered with the Australian New Zealand Clinical Trials Registry (registration approved on January 14, 2021; trial ID ACTRN12621000027819).

The Thrive program was developed between August 2020 and January 2021. For logistical reasons, it was decided that the program would be implemented incrementally throughout the hospital. The hospital comprises >50 wards, of which 5 were selected for the initial wave of recruitment, which occurred in December 2020 and January 2021. For the resulting cohort of participants, survey 1 was administered in February 2021, survey 2 was administered in March 2021, survey 3 was administered in April 2021, and survey 4 was administered in May 2021. The participants in the active control condition were provided with the full version of the program between May 2021 and July 2021. CPD points and certificates were awarded in August 2021. Since the successful administration of the Thrive program in the initial selection of wards, the research team and hospital management have decided to continue rolling out the program, and the staff from the remaining wards will be invited to participate in the trial from October 2021 to December 2021.

Discussion

This study contributes to the field of research on mental well-being in a number of important ways. It addresses a population—health care workers—whose occupations entail relatively high levels of stress and burnout and who may therefore especially benefit from a staff well-being program such as Thrive. This consideration is particularly salient in light of the COVID-19 pandemic, which has confronted health care workers with additional demands and dangers. This study also addresses the methodological shortcomings of previous RCTs of interventions for health care workers with a relatively large sample, stratified random allocation, and an active control condition.

This study will furnish an evidence base for the role of a comprehensive, neuroscience-based psychoeducational program in preserving or enhancing mental well-being in health care workers. The results of the trial will be used to evaluate and refine the Thrive program so that it may be implemented effectively not only at the target hospital but also at other hospitals and potentially other settings such as corporate workplaces or educational institutions.

This trial will also contribute to the knowledge base on well-being promotion more broadly. The 21st century has seen an evolution in the understanding of mental health, revealing that a lack of illness is not enough—one also needs sufficient well-being to flourish. The Thrive program represents an attempt at putting this understanding into practice, informed by a measure of well-being—the COMPAS-W—that has been validated in terms of not only behavioral outcomes but also neural and genetic markers. It is hoped that this line of research will lead to substantial advancements in our ability to promote greater well-being—and, thus, greater mental health overall—in health care workers and beyond.

Authors' Contributions

LAE (research assistant) coordinated this study in collaboration with MM and JMG. He helped co-design the Thrive program (content and delivery) and wrote the first draft of this paper. MM helped co-design the Thrive program (content and delivery) and assisted with participant recruitment and follow-up throughout the study. KT supported site setup for participant recruitment and facilitated approval of the program in the hospital. JMG obtained funding to support the project and conceived the project aims, assisted with co-design of the Thrive program, supervised LAE during the project, and edited the first draft of the paper. All authors reviewed and edited the manuscript revisions and approved the final version of the paper.

Conflicts of Interest

The Thrive program was developed entirely by the authors of this paper (LAE, MM, KT, and JMG) while employed at their respective institutions: LAE and JMG at Neuroscience Research Australia and the University of New South Wales, and MM and KT at Prince of Wales Hospital and the South Eastern Sydney Local Health District. The trial will be overseen by these institutions. The Mindgardens Neuroscience Network comprises four institutions—the Black Dog Institute, Neuroscience Research Australia, the University of New South Wales, and the South Eastern Sydney Local Health District. JMG is also a stockholder in MAP Biotech Pty Ltd, which had no contribution or role in this project. There are no other potential conflicts of interest to report.

Multimedia Appendix 1
Daily Life Events scale, COVID-19 Exposure Survey, and Thrive Program Attendance and Satisfaction Survey.

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[PDF File (Adobe PDF File), 215 KB - resprot_v11i4e34005_app1.pdf]

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Abbreviations

COMPAS-W: Composure, Own-worth, Mastery, Positivity, Achievement, and Satisfaction for Wellbeing Scale
CPD: Continuing Professional Development
DLE: Daily Life Events
NeuRA: Neuroscience Research Australia
POWH: Prince of Wales Hospital
RCT: randomized controlled trial
UNSW: University of New South Wales

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Protocol

Effectiveness of an Online Peer Gatekeeper Training Program for Postsecondary Students on Suicide Prevention in Japan: Protocol for a Randomized Controlled Trial

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Abstract

Background: Postsecondary student suicide is one of Japan's most severe public health problems. Gatekeeper training (GKT) programs are a generally recommended suicide prevention intervention in Japan. For suicide countermeasures, an online program tailored to students may enhance self-efficacy as a gatekeeper.

Objective: This study aims to describe a research protocol to investigate the effect of a newly developed internet-delivered online peer GKT program to improve postsecondary student self-efficacy as gatekeepers for suicide countermeasures in Japan.

Methods: This study is a 2-arm, parallel, randomized controlled trial with a 1:1 (intervention: waiting list) allocation. Participants (n=320) will be recruited, and those who meet the inclusion criteria will be randomly allocated to the intervention or waiting list control group. An approximately 85-minute, 6-section, internet-based gatekeeper program for postsecondary students has been developed that includes videos to help participants acquire skills as gatekeepers. The intervention group will complete the program within 10 days. The primary outcome, self-efficacy as a gatekeeper, is measured using the Gatekeeper Self-Efficacy Scale at baseline, immediately after taking the program, and 2 months after the survey after completing the program follow-up. To compare the primary outcomes, a *t* test, where the significance level is 5% (2-sided), will be used to test the intervention effect on an intention-to-treat basis.

Results: The study was at the stage of data collection at the time of submission. We recruited participants for this study during August and September 2021, and data collection will continue until December 2021. The data analysis related to the primary outcome will start in December 2021, and we hope to publish the results in 2022 or 2023.

Conclusions: This is the first study to investigate the effectiveness of an online GKT program for postsecondary students to improve self-efficacy as a gatekeeper using a randomized controlled trial design. The study will explore the potential of an online peer gatekeeper program for postsecondary students that can be disseminated online to a large number of students with minimal cost.

Trial Registration: University Hospital Medical Information Network Clinical Trials Registry UMIN000045325; https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000051685

International Registered Report Identifier (IRRID): DERR1-10.2196/34832

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Introduction

Background

According to the World Health Organization, every year about 700,000 people die by suicide [1]. Suicide is one of the most severe public health problems in the world. The high number of suicides in Japan has been a national issue since it transcended 30,000 per year in 1998 [2]. The number of suicides in 2020 was 21,081, an increase of about 4.5% compared to 2019 [3]. Although the number of suicides and suicide rate are declining compared to historic peak times in Japan, the Japanese suicide rate is the 5th highest among Organisation for Economic Co-operation and Development countries; additionally, the Japanese suicide rate is the highest among all Group of 7 (G7) members [4].

Furthermore, suicide was the leading cause of death among individuals aged 15 to 39 years in Japan [3]. This situation in Japan is serious, and among all G7 members, it is only in Japan that the leading cause of death among youth aged 15 to 34 years is suicide [5]. Suicide is the leading cause of death for college and university students in Japan [6]. Therefore, suicide prevention measures for young people, especially students, are urgently needed.

Recently, COVID‑19 has spread throughout the world. Problems associated with outbreaks of infections such as COVID-19 have an undesirable impact on learning and can also lead to mental health problems [7]. The effects of COVID-19 on the already-high suicide rate create an urgent need to deal with suicide among youth, especially students. A previous study showed that about 80% of college students who died by suicide had no prior contact with campus mental health professionals, and 85% of college students with moderate to severe depression did not get treatment [6,8]. Considering this fact, it is possible that students who have mental health problems cannot take measures by themselves (ie, help-seeking) or are not aware of the severity of their own condition. Therefore, awareness by other persons, such as gatekeepers who can detect and refer at-risk individuals, is essential for students experiencing difficulties.

A gatekeeper is someone aware of the signs of suicide who can take appropriate action (ie, be aware of people in need, speak to them, listen closely to them, direct those in need to resources for support, and watch over them) [9]. Gatekeeper training (GKT) is a program to foster the development of gatekeepers and aims to help nonprofessionals identify and respond to those at risk of suicidal behavior; it is the most general intervention in suicide prevention [10]. GKT programs are a generally recommended suicide prevention intervention in Japan, and the Japanese government and all local governments in Japan presently conduct GKT in various forms [11]. GKT builds the self-efficacy of those acting as a gatekeeper, such as speaking to people at risk of suicide. A recent meta-analysis in the United States reported the effectiveness of GKT in universities on suicide prevention knowledge, skills, and self-efficacy [12]. Thus, increasing a student's self-efficacy as a gatekeeper leads to more gatekeeper actions and, as a result, suicide prevention.

Students, however, may encounter obstacles in attending a GKT program. The most significant hurdle for students may be a lack of time and resources to participate in face-to-face training sessions. In addition, GKT programs conducted at a school or in a class unit often involve familiar acquaintances, and as GKT also includes private content such as sharing experiences and opinions in group work, some may not want to participate due to privacy concerns. As such, on-demand online GKT programs may be helpful in overcoming such hurdles for students. On-demand online GKT provides easy, fast, instant, and privileged access to needed knowledge about student suicide prevention at any time and from any location.

Most university GKT programs focus on teachers and related staff (eg, school counselors, nursing teachers) because of their daily interaction with students [13]. However, students have more opportunities to interact with other students than faculty members. Students may feel it is more challenging to talk to faculty staff than to other students (acquaintances). Suicidal college students tend to seek help from friends and family rather than from a mental health professional [14]. Past studies have shown that college students are most likely to talk to friends about suicidal ideation or ask for treatment when recommended by a friend [15,16]. Hence, students are especially advantageous as gatekeepers. GKT tailored to students is needed to increase the number of student gatekeepers.

Few programs have reported on the effectiveness of GKT programs for decreasing the number of suicides. Most studies have reported on suicide knowledge, attitudes, and skills of trainees instead of the number of suicides [17,18]. It is difficult to evaluate the effectiveness of GKT programs based on a decrease in suicide attempts or suicides. Therefore, in this study, we decided to use a surrogate outcome.

Behavior as gatekeeper has been conceptualized with the theory of planned behavior (TPB) [19,20]. According to TPB, "attitudes toward the behavior" may be our thoughts about the potency of, and our emotional reaction against, conducting the behavior [21]. TPB shows "perceived behavioral control" is the perceived controllability of a specific behavior, including a person's understanding and ability to perform the behavior [21]. These affect "intention to intervene" and lead to actual actions [21].

We hypothesized that self-efficacy as a gatekeeper affects attitudes toward the behavior and perceived behavioral control from this theory, leading to actual behavior as a gatekeeper. Past research has reported that GKT programs have improved self-efficacy as a gatekeeper [22-25]. Furthermore, self-efficacy was chosen as the primary outcome in this study because we

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thought self-efficacy in attitudes has the most significant impact on behavior among the commonly used surrogate items (knowledge, attitudes, and skills).

Assuming that encouraging action for suicide countermeasures as a gatekeeper lowers the suicide rate, a GKT program was created aimed at increasing self-efficacy, which affects behavior as a gatekeeper based on the attitude of TPB.

Objectives

To date, to the best of our knowledge, there has been no online GKT program for students in Japan. Moreover, no randomized controlled trials (RCTs) have been conducted to verify the effectiveness of online GKT programs for students. Accordingly, the aims of this research are to (1) create an online peer GKT program for students and (2) verify its effectiveness through RCTs.

Methods

Trial Design

Figure 1 shows the participant flow and study design. This study will be a 2-arm parallel-group nonblinded RCT with a GKT intervention group and a waitlist control group. Eligible participants are required to complete the baseline survey (t_0) and are randomly allocated at a 1:1 ratio either to the intervention group or the control group. All surveys will be conducted via online questionnaires. Online follow-up surveys will be implemented about 10 days after the t_0 survey (t_1: immediately after the intervention), and at 2 months after the t_1 survey (t_2). After the 2-month follow-up, the GKT program will be provided to participants in the control group who wish to attend. This manuscript has been written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [26].

Figure 1. Participant flowchart.
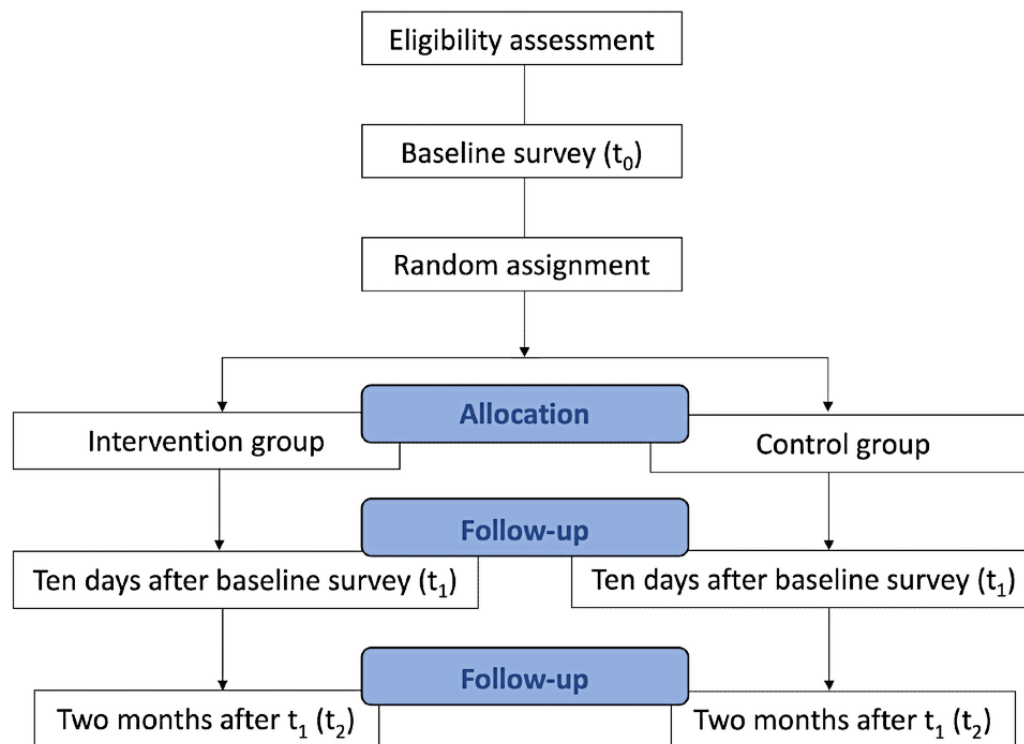
Participants and Setting

This study will target postsecondary school students (eg, college and university students) in Japan. The inclusion criteria for individuals will be students aged 18 to 29 years, in Japanese postsecondary school, with access to the internet via their own PC, smartphone, or tablet, and who acknowledge the program offered is a suicide prevention program. The exclusion criteria will be students who cannot read and write Japanese or who are full-time workers. The researchers asked their acquaintances to publicize this study through the mailing lists of their institutions. We also used social networking sites, our websites, and flyers to inform this study.

Procedure

Candidates will click the URL provided in the information about the invitation for GKT research and read a full explanation of the purpose and procedures of the study on the website. Students who are interested in participating will be asked to mark the consent option and type their name and their email address to give their consent. This consent information will be sent to the research center and preserved. Students who are not interested in participating will be asked to leave the website. Subsequently, participants who submitted the consent information will complete the baseline survey. After completing the baseline questionnaire, participants will be randomly assigned either to the intervention or the control group. Researchers will inform participants of their group assignment and send an email containing the GKT program's homepage URL and password

to participants in the intervention group. Participants in the intervention group will click the URL, enter the password, and receive the GKT program. They will be asked not to share this URL, password, and the GKT program content with others. Participants in the intervention group will be instructed to take the program within 10 days of receiving notification of group assignment. t_1 surveys will be administered to both the intervention and control groups. Participants in the intervention group are instructed to complete the t_1 survey immediately after attending the program. Participants in the control group are asked to respond to the t_1 survey 10 days after the t_0 survey. Those in the control group will receive the GKT program after the t_2 survey. Participants who answer all 3 surveys will get the chance to win a ¥1200 (US $10.14) gift card from Amazon as a monetary incentive to promote retention and follow-up completion by lottery.

Intervention Program

We developed a new GKT program using the following steps. First, we decided upon the composition of the program content by referring to existing GKT programs and the role of the gatekeeper advocated by the Ministry of Health, Labor, and Welfare. The first author then developed a preliminary program in consultation with researchers specializing in psychiatric nursing and psychiatry and in collaboration with experts in suicide prevention from a Japanese nonprofit organization. Next, the first author conducted a feedback session with 5 students and modified the program according to their recommendations. Last, a pilot trial was performed with vocational school students nested in one organization (n=18). Additionally, an opinion exchange meeting was held at the workshop for people involved in mental health and welfare to watch a part of the GKT and give their impressions. Based on these opinions and the results of the pilot trial, we modified the program and created the final version of the GKT program. The final version of the internet-based GKT program designed for postsecondary students was developed (Figure 2). The home page of the GKT program is the platform for participants to access the program. The content of this homepage includes an explanation of how to use the GKT program, videos of the GKT program (sections 1-6) via YouTube, a comment section (online discussion board), a text download page, and a contact form to the administrator.

The videos of the GKT program consist of the following 6 sections for a total of approximately 85 minutes (Table 1). The GKT program covers mental health basics (section 1), current status of suicide problems (section 2), danger sign features of suicide (section 3), how to appropriately respond (section 4), demo video (section 5), and referral information for appropriate resources (section 6). Each section takes 10-20 minutes to view and contains a voiceover, cases, personal work, and quizzes (except for section 5). We made videos of the GKT program for uploading to YouTube. Sections 1-4 and 6 were created by us in PowerPoint with lecture-style videos. Section 5 was shot with a video camera and edited with video editing software. The GKT program introduced a demo video (section 5) instead of role-playing. The demo video shows how to respond in situations students are likely to experience, and participants can learn how to respond concretely by imagining the characters appearing in the examples and replacing them with themselves. These are online videos but are unlisted and restricted to people who have the link to the video so only participants in the intervention group and researchers can view them. Because they are played on YouTube, the modules were designed so the participant controlled every aspect of the module, such as skipping or replaying a movie, adjusting playback speed, and switching the voiceover or subtitles on or off. Of course, during the intervention period, participants could watch the video at any time and place. Participants are instructed to watch sections 1 to 6 in order. Furthermore, participants have access to an online discussion board on the website, which gives them the opportunity to exchange thoughts with each other. On this online discussion board, participants can browse other participants' ideas and write their own opinions, but cannot reply to other participants' comments.

This GKT program does not have homework and is fully self-guided. However, participants are encouraged to voluntarily comment on their personal work responses and section impressions and read the opinions of other participants. Participants can download the text used in the videos of the GKT program on this homepage. In each section, an announcement is made to stop watching the video if they feel uncomfortable. The pages in each section provide a list of contacts available if they feel unwell.

Figure 2. Screenshots of the internet-based gatekeeper training program designed for postsecondary students.

Table 1. Contents of the online peer gatekeeper training program.

Section	Theme	Video viewing time	Contents
1	Mental health basics	09:59	• Concepts of the gatekeeper • Psychology of people who are mentally ill • Basic knowledge about depression
2	Current states of the suicide problem	12:56	• Statistics of suicide • Social isolation • The importance of consulting
3	Recognizing suicide risk	09:54	• Warning signs of suicide • Risk factors for suicide
4	Questioning	10:10	• How to call out • How to listening
5	Role play (demo video)	19:52	—[a]
6	Referral to care	21:11	• Concepts of referral to care • Case study • Resources available for suicide countermeasures

[a]Not applicable.

Outcomes

Table 2 summarizes the outcome measures. Only the participants in the intervention group are assessed regarding the process evaluation outcomes (eg, usability, satisfaction) at the t_1 survey.

All data are collected using web-based self-report questionnaires. At the t_1 and t_2 surveys, the researcher (KN) will send at least 2 emails reminding nonrespondents to complete the questionnaires.

Table 2. Assessment schedule of the outcome measures for the randomized controlled trial for the students' online peer gatekeeper training program.

Measurement	Aim	t_1	t_2	t_3
Primary outcome				
GKSES[a]	Self-efficacy as gatekeeper	✓	✓	✓
Secondary outcomes				
Short form of the LOSS[b]	Literacy of suicide	✓	✓	✓
SOC3-UTHS[c]	Sense of coherence	✓	✓	✓
MIDUS[d]	Stigma	✓	✓	✓
Scale for measuring help-seeking styles	Help-seeking	✓	✓	✓
K6[e]	Psychological distress	✓	✓	✓
Rosenberg Self-Esteem Scale–Japanese version	Self-esteem	✓	✓	✓
Tachikawa Resilience Scale	Resilience	✓	✓	✓
ACT	Behavior as gatekeepers	—[f]		✓
Process evaluation				
iOSDMH[g]	Acceptability, appropriateness, feasibility, satisfaction, adverse effect		✓	
Subgroup analysis				
FCV-19S[h]	Level of fear of COVID-19	✓		
CIUS[i]	Tendency toward internet dependence	✓		

[a]GKSES: Gatekeeper Self-Efficacy Scale.

[b]LOSS: Literacy of Suicide Scale.

[c]SOC3-UTHS: University of Tokyo Health Sociology version of the Sense of Coherence–3 scale.

[d]MIDUS: Mental Illness and Disorder Understanding Scale.

[e]K6: Kessler Psychological Distress Scale.

[f]Not applicable.

[g]iOSDMH: Implementation Outcome Scales for Digital Mental Health.

[h]FCV-19S: Fear of COVID-19 Scale.

[i]CIUS: Compulsive Internet Use Scale.

Primary Outcome

The primary outcome is confidence in students' gatekeeper skills, assessed using the Gatekeeper Self-Efficacy Scale (GKSES) [27]. The GKSES was developed to measure confidence in a person's own gatekeeper skills and consists of 9 items measured on a 7-point Likert scale. The GKSES is a 1-factor structure model. All items ask about confidence in their own gatekeeper skills. An example is, "I can understand the mental states of people who intend to die by suicide." Higher average scores for total items indicate a higher confidence in one's own gatekeeper skill. Reliability and validity have been confirmed among Japanese. Reliability of GKSES is very good with Cronbach α=.95 [27].

Secondary Outcomes

Literacy of Suicide Scale

The Japanese version of short forms of the Literacy of Suicide Scale (LOSS) will be used to assess suicide literacy; a 12-item short form of LOSS [28] will be used in this study. We obtained a license for the use of the LOSS by its creator, who also gave

us a Japanese translation of the short form. We have revised the Japanese version so that students can answer it more clearly. The scale provides a total literacy score (percentage correct) and can be broken down into the 4 literacy themes of risk factors, signs/symptoms, cause/nature, and treatment/prevention. Correct responses are scored 1, while incorrect or I don't know responses are scored 0. Literacy scores are the sum of correct items, with higher scores indicating higher suicide literacy.

Sense of Coherence

A sense of coherence (SOC) will be assessed using the University of Tokyo Health Sociology version of the SOC3 scale (SOC3-UTHS) [29]. SOC is defined as "individuals' perceptions of life and resources to help them overcome hardships in life" that relate to stress management ability [29]. The scale consists of 3 dimensions: manageability, meaningfulness, and comprehensibility. All items are rated on a 7-point Likert-type scale ranging from 1 (never) to 7 (always). The Japanese version of the SOC scale's reliability and validity was verified in a previous study. Cronbach alpha for SOC3-UTHS ranges from .80 to .98, indicating acceptable to high internal consistency [29]. The score is the average of the

3 items, which is then used for analyses. A higher score indicates a higher SOC.

Stigma

To assess community understanding of mental health and the stigma associated with mental illness and disorder, we will use the Mental Illness and Disorder Understanding Scale (MIDUS), consisting of 15 items measured on a 5-point Likert scale [30]. MIDUS has 3 factors: treatability of illness, efficacy of medication, and social recognition of illness. Lower total scores indicate better understanding. MIDUS's reliability and validity were verified in a previous study. Reliability of MIDUS is very good with Cronbach α=.78 [30].

Help-Seeking

To measure help-seeking, we will use a scale for measuring help-seeking styles [31]. The degree of help-seeking behaviors will be assessed by the Scale for Measuring Help-Seeking Styles, which consists of 15 items measured on a 7-point Likert scale. The scale consists of 3 dimensions: self-directed help-seeking, excessive help-seeking, and avoidant help-seeking. The Scale for Measuring Help-Seeking Styles' reliability and validity was verified in a previous study [31]. A high total score for each factor indicates a high possibility of taking help-seeking behaviors. In this study, we used the dimensions of self-directed help-seeking consisting of 4 items. Reliability of the dimensions of self-directed help-seeking is very good with Cronbach α=.79 [31]. A total score of this dimension (4 to 28) was calculated and used for analyses.

Psychological Distress

Psychological distress will be measured with the Japanese version of the Kessler Psychological Distress Scale (K6), which asks respondents how frequently they experienced symptoms of psychological distress during the previous 30 days using 6 items (α=.85) [32]. Responses are rated on a 5-point Likert scale ranging from 0 (none of the time) to 4 (all of the time). A total score of these items (0 to 24) will be calculated and used for analyses.

Self-Esteem

Self-esteem will be measured with the Japanese version of the Rosenberg Self-esteem Scale, which consists of 10 items measured on a 4-point Likert scale. This scale is a 2-factor structure. The reliability and validity of the Japanese version of the Rosenberg Self-esteem Scale were verified in a previous study. Reliability of the Rosenberg Self-esteem Scale is very good with Cronbach α=.89 [33].

Resilience

We will use the Tachikawa Resilience Scale [34], which consists of 10 items measured on a 7-point Likert scale. This scale measures an individual's resilience, or reactions to stressful life events. Higher scores reflect higher resilience. Reliability of the Tachikawa Resilience Scale is very good with Cronbach α=.82 [34].

ACT as Gatekeeper

We asked participants 2 months after the t_1 survey about their behavior as gatekeepers for the last 2 months (see Multimedia Appendix 1 for questionnaire). We asked the frequency of the following: asking acquaintances (friends) about suicidal thoughts, distress, or depressed mood; listening to an acquaintance (friends); providing appropriate information; taking acquaintance (friends) to the right resource; and noticing suicide danger signs.

Demographic Characteristics

Demographic data such as sex, age, grade, school type, school location, living status, international student status, part-time job situation, whether one goes to school, online class status, state of emergency or preemergency measures for COVID-19, and experience in contact with people who have suicidal ideation will also be collected.

Process Evaluation

Since the number of sections each participant follows could influence the scores on the questionnaires, participants in the intervention group are asked to answer for the section they watched in the questionnaire survey after the intervention program.

For process evaluation, we use the Implementation Outcome Scales for Digital Mental Health (iOSDMH) [35]. We will use the 19 items of implementation outcomes for digital health interventions. This measurement is based on 3 important concepts: acceptability (α=.67), appropriateness (α=.78), and feasibility (α=.83). Adverse effects (ie, harms [α=.78]) of eHealth interventions, such as physical symptoms (eg, tired eyes, stiff shoulders), mental symptoms (eg, insomnia), and dangerous experiences (eg, bumping into people while looking at a smartphone), will be covered in 5 items.

Subgroup Analysis

Impact of COVID-19

The researchers collected data about fears of COVID-19 to capture the impact of COVID-19 on daily life using the Japanese version of the Fear of COVID-19 Scale (FCV-19S), as the target population was recruited during the pandemic. The scale, which consists of 7 items measured on a 5-point Likert scale, consists of 2 dimensions: emotional fear reactions and symptomatic expressions of fear. The higher the score, the stronger the fear of COVID-19. The validity of the Japanese-language version of FCV-19S was verified in a previous study. Reliability of FCV-19S is very good with Cronbach α=.87 [36].

Internet Use

To assess levels of internet addiction, we will use the Japanese version of the Compulsive Internet Use Scale (CIUS), which consists of 14 items measured on a 5-point Likert scale [37]. CIUS has 3 factors: excessive absorption, difficulty in setting priorities, and mood regulation. The higher the total score, the stronger the dependence on internet use. Reliability and validity of the CIUS were verified in a previous study. Reliability of CIUS is very good with Cronbach α=.93 [37].

Sample Size Calculation

The sample size calculation is based on the difference between means of change in the primary outcome (self-efficacy as the gatekeeper) from baseline (preintervention) to postintervention

(t_1 survey) in both arms (complete case analyses). Based on previous studies on GKT, mean effect sizes of around d=0.5 are expected in per-protocol analyses for improving self-efficacy [12,22-25]. In order to detect such intervention effects in 2-tailed significance testing (α=.05) with a power of 80%, a sample size of 64 per group (total 128) participants is required. We assume the study dropout rate will be higher in web-based intervention and assessments compared to face-to-face research. The expected study dropout was about 60% (dropouts occur at random within each group), and this meant that 320 participants (160 per group) must be included in the study.

Randomization and Blinding

After baseline assessment, participants will be randomly assigned to either group using the permuted block method with a random block size of 2, and they will be informed of their assigned group by the first author (KN). Randomization will be stratified by sex. The computer-generated allocation list was made by an independent researcher (YM). The enrollment is conducted by the first author (KN), and the intervention starts immediately. The means for blinding in this study are limited. An independent researcher (YM) who will not analyze data will download data from the GKT database. An independent research staff person will mask the group variable before analysis, and then researchers (KN) will analyze data that is blinded to the group variable.

Statistical Analysis

The primary analysis for the GKSES score will be on a modified intention-to-treat principle, in which all available measurements are compared according to assigned groups. Baseline variables will be summarized by the groups using frequencies and proportions (for categorical variables) or mean and standard deviation (for continuous variables). The primary end points (difference of GKSES total score between presurvey and postsurvey) between the intervention group and the control group will be compared based on a t test. We will set the 2-sided significance level at 5%, and the 95% confidence interval of the average difference in differences of the scores will be estimated. Secondary end points will be compared similarly. As subgroup analysis for primary and secondary end points, we will stratify by highly dependent and lesser dependent groups for internet use, a group with high fear of COVID-19 and a group with low fear of COVID-19. To help interpretation, Cohen d and its 95% confidence intervals will be calculated at each assessment point; the values of 0.2, 0.5, and 0.8 are considered as small, medium, and large effects, respectively [38]. Statistical analysis will be performed using SPSS (version 27, IBM Corp) statistical software.

Data Monitoring

This study does not have an external data monitoring committee. The first author (KN) will manage participants' progress and completion of the intervention and the follow-up assessments.

Research Ethics and Approval

The Ethics Committee of the Faculty of Medicine and Graduate School of Medicine of the University of Tokyo approved this study (2020234NI). Before the baseline survey, candidates will

be fully informed that their participation is totally voluntary and they can withdraw consent if they want (they can send a withdrawal email to researchers). Informed consent by an explanation in the document will be conducted, and the marked consent option and full name will be obtained from all participants. Even if participants withdraw consent, they will not receive any disadvantage. In addition, they will be informed that the findings of this study will be disseminated without participants' personal information via publication and website. The participants will be told that the web-based program does not provide emergency support on the website and will be provided with corresponding contact information that can be used in case of emergency during the program. All data collected in this study are securely stored without the participants' personal information. Access to the data is encrypted and limited to research staff named on the ethics protocol. This study protocol was registered with the University Hospital Medical Information Network Clinical Trial Registry [UMIN000045325]. If there are important modifications of the protocol, we will obtain approval for the modifications from the Ethics Committee of the Faculty of Medicine and Graduate School of Medicine of the University of Tokyo and will revise the protocol on the trial registry website.

Data Confidentiality

Collected data will be stored as linkable anonymized data. The principal investigator will retain access to the final dataset after the trial and assume responsibility for data integrity and accuracy of the analysis.

Patient and Public Involvement

The first author conducted informal discussions with 5 students and nonprofit organization representatives that implement youth suicide countermeasures. Based on these conversations, adding 2 researchers to those mentioned, we modified the contents to reflect a real situation. One patient and public involvement (PPI) partner, a college student, reviewed the program's draft and noted some points that might be difficult for general students to understand. These PPI partners will participate in a discussion of the study results and in making the implementation strategy after finishing the RCT. We described the PPI process based on the PPI handbook and reporting checklists.

Results

At the time this paper was submitted, the study was at the stage of data collection. We recruited participants for this study during August and September 2021, and data collection will continue until December 2021. Data analysis will begin in December 2021 for the outcome variables. We expect to publish the results in 2022 or 2023.

Discussion

Strengths of the Study

We hypothesized that the online GKT program for students will increase self-efficacy as a gatekeeper. Moreover, we hypothesized that self-efficacy as a gatekeeper affects attitudes

toward the behavior and perceived behavioral control from TPB, leading to actual behavior as a gatekeeper.

The effects of an online gatekeeper program on self-efficacy will be examined for gatekeepers among postsecondary students in Japan. To the best of our knowledge, this study is the first RCT to examine the effectiveness of online GKT programs without face-to-face sessions targeting students rather than staff or faculty for their self-efficacy as gatekeepers. This online program will allow individuals to participate without worrying about their privacy anytime, from anywhere.

Dissemination of the Findings

An online GKT program requires less involvement by mental health specialists such as public health nurses. It can be provided at a low cost in a low-resource setting in which trained practitioners are seldom available. Thus, this online GKT program has much potential for dissemination as a practical tool for the prevention of suicide in schools such as universities. Once we find the online GKT program sufficiently effective, it will contribute to the dissemination of gatekeeper online training to a large number of students to prevent suicide at a low cost

and, as in the COVID-19 era, where close social contact is limited.

The main findings of this study will be disseminated via publications in peer-reviewed international journals. Study findings will also be presented at scientific conferences.

Limitations

Due to the intervention's nature, it is not possible for both the intervention implementer and participants to be blinded to group assignments. Because all the outcomes in this study will be obtained by the self-reported questionnaire, information bias could be introduced. Generalizability will be limited because snowball sampling will be used instead of random sampling.

Conclusion

This is the first study to investigate the effectiveness of an online GKT program for students to improve self-efficacy as a gatekeeper using an RCT design. The study explored the potential of an online peer gatekeeper program for students that can be disseminated online to a large number of students with minimal cost.

Authors' Contributions

KN and YM were responsible for study design, study setup, completion of the study, and finalizing of the manuscript. HA, MI, YK, and YO were responsible for study design and developing the contents of the intervention. AI developed the contents of the intervention. TS was involved in the study design and design of the statistical analyses. KI and NK worked on study design. KN wrote the first draft of the protocol manuscript. All authors revised the manuscript and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
ACT questionnaire.
[DOCX File , 15 KB - resprot_v11i4e34832_app1.docx]

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Abbreviations

CIUS: Compulsive Internet Use Scale
FCV-19S: Fear of COVID-19 Scale
G7: Group of 7
GKSES: Gatekeeper Self-Efficacy Scale
GKT: gatekeeper training
iOSDMH: Implementation Outcome Scales for Digital Mental Health
K6: Kessler Psychological Distress Scale
LOSS: Literacy of Suicide Scale
MIDUS: Mental Illness and Disorder Understanding Scale
PPI: patient and public involvement
RCT: randomized controlled trial
SOC: sense of coherence
SOC3-UTHS: University of Tokyo Health Sociology version of SOC3 scale
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TPB: theory of planned behavior

Protocol

Exercise and Creatine Supplementation to Augment the Adaptation of Exercise Training Among Breast Cancer Survivors Completing Chemotherapy: Protocol for an Open-label Randomized Controlled Trial (the THRIVE Study)

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Abstract

Background: In breast cancer survivors, chemotherapy-induced muscle loss has been shown to be attenuated with structured resistance exercise. Creatine supplementation can increase bioenergetics in skeletal muscle, which helps to improve overall strength and endurance and reduce muscular fatigue. Therefore, we hypothesize that adding creatinine supplementation to exercise training will accelerate improvements in strength, endurance, and bioenergetics in breast cancer survivors.

Objective: The primary objective is to determine the effects of combining creatine supplementation with exercise on modulating strength and physical function in breast cancer survivors by comparing these effects to those of exercise alone. The secondary objectives are to determine if creatine supplementation and exercise can increase the intramuscular storage of creatine and improve body composition by comparing this intervention to exercise alone.

Methods: We aim to test our hypothesis by conducting an open-label randomized controlled trial of 30 breast cancer survivors who have completed chemotherapy within 6 months of enrollment. Eligible participants will be equally randomized (1:1) to either a creatine and exercise group or an exercise-only group for this 12-week intervention. Individuals who are randomized to receive creatine will be initially dosed at 20 g per day for 7 days to boost the availability of creatine systemically. Thereafter, the dose will be reduced to 5 g per day for maintenance throughout the duration of the 12-week protocol. All participants will engage in 3 center-based exercise sessions, which will involve completing 3 sets of 8 to 12 repetitions on chest press, leg press, seated row, shoulder press, leg extension, and leg curl machines. The primary outcomes will include changes in strength, body composition, and physical function in breast cancer survivors. The secondary outcomes will be intramuscular concentrations of creatine and adenosine triphosphate in the vastus lateralis, midthigh cross-sectional area, and quality of life.

Results: As of October 2021, a total of 9 patients have been enrolled into the study. No unexpected adverse events have been reported.

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Conclusions: Creatine is being studied as a potential agent for improving strength, endurance, and bioenergetics in breast cancer survivors following chemotherapy. The findings from our trial may have future implications for supporting breast cancer survivors in reversing the muscle loss experienced during chemotherapy and improving their physical function and quality of life.

Trial Registration: ClinicalTrials.gov NCT04207359; https://clinicaltrials.gov/ct2/show/NCT04207359

International Registered Report Identifier (IRRID): PRR1-10.2196/26827

Introduction

Background

Survivorship after a breast cancer diagnosis is multifocal; it includes long-term care planning that is coordinated with a survivor's oncologist, primacy care provider, and social work support and should include an active lifestyle that is inclusive of exercise. Yet, individuals with breast cancer are at high risk for skeletal muscle wasting, which may be exacerbated by cancer treatment or tumor-related factors [1,2] and can negatively impact the ability to complete activities of daily living. Lower extremity muscle weakness is also associated with long-term fatigue in breast cancer survivors [3]. Studies on resistance exercise interventions have reported notable improvements in strength, endurance, and body composition in breast cancer survivors [4,5]; however, identifying strategies for enhancing adaptations to exercise among cancer survivors is of importance.

In the context of cancer survivorship, a large percentage of cancer survivors exhibit a loss of muscle mass that impacts their ability to perform activities of daily living [6]. The root causes of this loss of muscle mass are cancer treatment and tumor proteins [6,7]. Muscle wasting in patients with cancer, in combination with normal aging processes, dramatically increases the risk of disability and accelerates the aging process [8]. Certain cancer therapies can exacerbate this decline in physical function and result in disabilities that patients cannot independently manage [9]. Resistance training has been demonstrated to improve physical function, muscular strength, and endurance in breast cancer survivors. However, the relationship among body mass, treatment toxicity, and cancer recurrence requires those in the field of exercise oncology to identify modalities for promoting such exercise adaptations. Therefore, we hypothesize that adding creatine supplementation to a structured resistance training intervention can lead to better improvements than those resulting from exercise alone.

Creatine is a naturally occurring substance in the human body that is synthesized endogenously in the kidneys, pancreas, and liver from amino acids (ie, arginine, glycine, and methionine) at a rate of approximately 1 to 2 g per day [10]. An additional 1 g per day of creatine is typically consumed through the diet of those who eat meat and fish [11]. In total, the creatine pool in skeletal muscle averages at about 120 g for a 70-kg individual with a proposed creatine capacity of up to 160 g (via supplementation) [12].

Approximately 2 g of creatine are lost per day through urination. However, aging is associated with an incremental loss of intramuscular creatine stores [13,14]. Notably, creatine supplementation has been shown to reverse this loss [15]. Studies have demonstrated the efficacy of creatine supplementation in augmenting training adaptations and have reported positive outcomes, such as improved strength and physical function in a variety of healthy and clinical populations [11,12]. Although some publications suggest that creatine supplementation alone can increase strength and work capacity and delay the onset of fatigue in older men and women [16-19], the majority of studies suggest that the benefit of creatine supplementation is greatest when it is combined with hypertrophic stimuli, such as resistance exercise training [20].

Creatine supplementation has gained attention in the medical field because of the numerous health and quality of life benefits it has for people with muscular and neurological diseases, such as McArdle disease, Duchene dystrophy, myasthenia gravis, amyotrophic lateral sclerosis, and Parkinson disease, and its limited side effects [21]. Creatine is crucial to maintaining muscle energetics because of its role in rephosphorylating adenosine diphosphate to adenosine triphosphate (ATP). To date, few studies have examined the use of creatine supplementation to augment cancer treatment–associated declines in muscle mass and function [22-25]. Those that exist have generally failed to demonstrate its benefits for strength and function. A limitation to these studies is that most have investigated creatine supplementation alone. Only 1 study of cancer survivors has been published on combining creatine supplementation with resistance training, which resulted in improvements in lean body mass [22]. No such studies to date have been conducted on patients with breast cancer—a population that is particularly vulnerable to the loss of lean mass and function. Despite the benefits of exercise on reversing the anthracycline-related effects on muscle wasting, breast cancer survivors remain fatigued and deconditioned long into survivorship [26]. Therefore, there is a significant need to identify alternative strategies for reversing the known deleterious effects of chemotherapy in this population. The paucity of research in this area stems from the lack of awareness of the potential role that creatine supplementation plays in cancer survivors.

Safety and Toxicity of Creatine

Creatine has not been evaluated by the Food and Drug Administration for safety; however, it is a widely used over-the-counter supplement. Creatine is one of the most highly

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studied supplements, and numerous studies have demonstrated its safety and tolerability [12,27]. In the four papers published to date on creatine supplementation in patients with cancer [22-25], only 2 of the 333 patients who were taking creatine reported any adverse effects (muscle cramping and mucus production) [22]. Other commonly identified side effects of creatine supplementation include nausea, diarrhea, dizziness, and gastrointestinal pain, but their severity is often mild [12,27].

Study Objectives

The primary objective is to determine the effects of creatine supplementation, in combination with exercise, on modulating strength, body composition, and physical function in breast cancer survivors by comparing these effects to those of exercise alone. The primary hypothesis is that creatine supplementation will result in significantly greater gains in strength and physical function and improved body composition in breast cancer survivors compared to those resulting from exercise alone.

The secondary objectives are to determine if supplemental creatine can be used to increase intramuscular storages of creatine, alter energy storage, and improve quality of life. The hypothesis for these objectives is that creatine supplementation will significantly increase intramuscular concentrations of creatine and ATP in the vastus lateralis when compared to exercise-only controls. We also hypothesize that the creatine group will have significantly greater muscle cross-sectional areas and significantly lower levels of intramuscular fat compared to those of the exercise-only controls. Finally, we hypothesize that both groups will have a significantly better quality of life following the 12-week program.

Trial Design

Our prospective study is a single-center, open-label randomized controlled trial. Figure 1 shows the study design, and Table 1 presents the schedule of events. This study protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement recommendations [28].

Figure 1. Individuals randomized to the creatine group will exercise 3 times per week for 12 weeks and take creatine in powder form as indicated. Individuals in the control group will exercise 3 times per week for 12 weeks without creatine dosing.
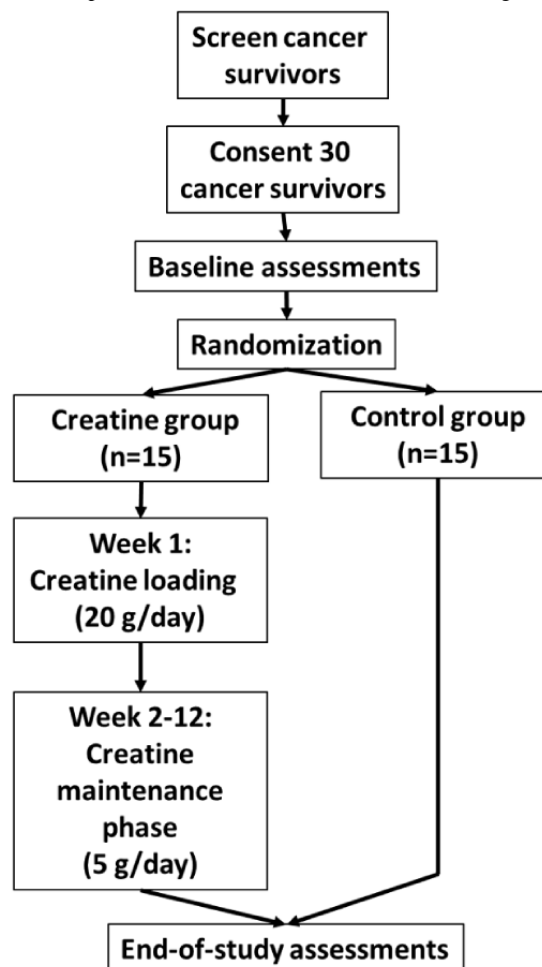
Table 1. Study schedule of events.

Event	Screen day (−28 to −7 days)	Baseline assessments (−7 to −2 days)		Study week			12-week end-of-study assessments (>2 days and <7 days after the last exercise session)	
		Visit A	Visit B	Week 2	Week 5	Week 9	Visit A	Visit B
Phone screen	✓							
Physical exam	✓						✓	
Medical history	✓			✓	✓	✓	✓	
Medication history	✓			✓	✓	✓	✓	
Clinical labs	✓			✓			✓	
Electrocardiography	✓			✓				✓
Vital signs	✓						✓	
Height	✓							
Weight	✓						✓	
Body circumference	✓						✓	
Waist to hip ratio	✓						✓	
Mood disorder questionnaire								
Pregnancy test		✓					✓	
Handgrip dynamometry		✓					✓	
Isometric leg strength		✓					✓	
Dual x-ray absorptiometry		✓					✓	
6-minute walk test		✓					✓	
Survey completion		✓					✓	
Magnetic resonance imaging and magnetic resonance spectroscopy			✓					✓
1-repetition and 10-repetition maximum testing			✓					✓
Exercise familiarization			✓					
Dispense creatine (20 g/day)			✓					
Dispense Creatine (5 g/day)				✓	✓	✓		

Methods

Ethical Approval

This trial has been approved by the institutional review board at the University of Texas Health Science Center at San Antonio and the protocol review committee at the National Cancer Center Institute Mays Cancer Center at the University of Texas Health Science Center at San Antonio (2019-610H). All participants who meet the inclusion criteria will be eligible for participation. Any deviations from the protocol, breaches of confidentiality, and reportable adverse events will be reported to the institutional review board and Data Safety Monitoring Board at the Mays Cancer Center. The study is registered with ClinicalTrials.gov (trial number: NCT04207359).

Study Setting

The study will enroll breast cancer survivors from San Antonio, Texas, and the surrounding community. The majority of the patients who will be enrolled in this study will be patients of the Mays Cancer Center at the University of Texas Health Science Center at San Antonio—a National Cancer Institute–designated cancer center. An interprofessional team of exercise physiologists, medical oncologists, nutritionists, mental health professionals, personal trainers, research coordinators, and research assistants will implement the various aspects of this study.

Study Population

The study will enroll 30 patients with breast cancer who have completed chemotherapy within 6 months prior to consenting to this study. The recruitment methods include media advertisements, community events, and queries of institutional medical records for potentially eligible subjects. The inclusion criteria are the following: (1) an age of 18 to 75 years; (2) a diagnosis of breast cancer and the recent (within 6 months) completion of chemotherapy; (3) the willingness to attend 3 exercise sessions per week; (4) the ability to take oral medications; (5) the willingness and ability to provide consent for participating in the study; and (6) a serum creatinine level

of ≤1.5 times the upper limit of normal or an estimated glomerular filtration rate of ≥30 mL/min/1.73 m^2, as determined by the Chronic Kidney Disease Epidemiology Collaboration equation. The exclusion criteria are as follows: (1) physical indications that performing exercise may be limited or contraindicated; (2) poorly controlled hypertension (resting systolic blood pressure: >160 mm Hg; resting diastolic blood pressure: >95 mm Hg); (3) current tobacco use (within 6 months); (4) anabolic steroid use; (5) a pitting edema grade of 2+; (6) patients who are currently undergoing medical treatment for cancer (ie, currently undergoing chemotherapy; radiation therapy is allowed); (7) a history of moderate-severe heart disease (New York Heart Classification of >grade II) or pulmonary disease (dyspnea on exertion upon climbing ≤1 flight of stairs and abnormal breath sounds on auscultation); (8) pregnant patients or patients who are planning to become pregnant during the study; (9) recent (within 1 month) or anticipated treatment with corticosteroids (except those for short-term use during the time of chemotherapy) or other appetite stimulants; (10) bipolar disorder; (11) creatine supplementation within the past 30 days; and (12) a change in supplement use within the past 14 days.

Allocation

Patients who are eligible to participate in the study will be allocated to either the creatine and exercise group or the exercise alone control group (1:1). Randomization will be performed through the study's REDCap (Research Electronic Data Capture; Vanderbilt University) database. We will use randomized blocks to conceal the group allocation results from the patients, recruitment staff, and assessment staff, and concealment will be maintained until the patients complete the baseline assessments. The research pharmacy at the Mays Cancer Center will conceal the randomization and will direct the research team to assign study participants to specific groups. A sample of 15 breast cancer survivors will be enrolled in each group with the goal of having 12 completers in each group. Due to the nature of the study, the principal investigator and study participants will not be blinded. However, to alleviate any issues with assessment fidelity, the research assistant who will be performing the outcome assessments will not be aware of the groups to which participants are randomized. Further, the statistician who will be supporting the analyses in the study will be blinded as well.

Exercise Intervention

All participants will engage in 3 center-based exercise sessions each week for 12 weeks. Each session will last roughly 1 hour and include a 10-minute warm-up and a 50-minute stimulus phase. Exercise sessions will be held on nonconsecutive days to allow for adequate rest and recovery. The prescription will include 2 or 3 sets of 6 exercises, which will be performed at a 10-repetition maximum intensity (ie, participants will be able to perform only 8 to 12 repetitions per set), as per the American College of Sports Medicine's guidelines for exercise testing and prescription [29] and the consensus statement on exercise guidelines for cancer survivors [30]. Each session will consist of the following exercises, which will be done in the following order: chest press, leg press, seated row, shoulder press, leg extension, and leg curl. The resistance load will be set at 70% of the measured or estimated 1-repetition maximum. If participants cannot perform an exercise with this resistance load, the load will be reduced to allow them to complete the prescribed repetitions for each set. Participants will complete 2 sets of each exercise in week 1. This will allow participants to familiarize themselves with the resistance load and will minimize the risk of injury for novice participants. Starting in week 2, participants will transition to performing 3 sets of each exercise. The load will be increased when a participant is able to perform 12 repetitions in 2 of 3 sets for an exercise. Participants' heart rates will be monitored continuously during exercise sessions. Self-reported perceived exertion will also be recorded periodically during exercise sessions [31], and this information will be used to track the subjective experiences of participants and interpret adherence data.

Creatine Dosing Protocol

Participants who are randomized to receive creatine (experimental group) will be initially dosed at 20 g per day for 7 days to boost the availability of creatine systemically [32]. Thereafter, the dose will be reduced to 5 g per day for maintenance throughout the duration of the 12-week protocol. This dosing protocol is based on the traditional dosing protocol for healthy individuals, which includes a loading phase (5 g of creatine taken 4 times per day) that is followed by a low-dose maintenance period (5 g of creatine per day) for maintaining creatine stores [12]. The individuals in this group will receive creatine in powder form at 4 different schedules based on their progress throughout the protocol. Each bottle of creatine will contain a 5-mg dosing spoon. Bottle 1 will be provided at the start of the study, and an equivalent dose for the loading phase will be assigned in week 1 of the study. In week 2, participants will return to the clinic and be provided with 21 days' worth of creatine doses (5 g/day). At weeks 5 and 9, participants will again return to the clinic and be given 28 days' worth of creatine doses (5 g/day). Bottles will be exchanged at these scheduled intervals, and dosing adherence will be determined by measuring the amount of creatine that remains in the bottles. For weeks 2 to 12, participants will also be asked to take the creatine at approximately the same time of the day and enter the time of dosing in a dosing diary. The individuals in this group will have safety labs drawn after the loading phase to ensure normal kidney function, and electrocardiography will be performed to rule out any abnormalities. Participants will be removed from the creatine group if the lab results show serum creatinine levels of >2 times the upper limit of normal or estimated glomerular filtration rates of <30 mL/min/1.73 m^2. These participants will complete the remaining exercise interventions.

Study Procedures

Telephone Screening

Potential participants will undergo telephone screening to rule out clear, excluding medical conditions prior to in-person screening. Individuals who are known to meet no clear exclusionary criteria will be invited to an initial screening visit.

Screening Visit

At the screening visit, participants will read and sign the informed consent form. Once consent is provided, a complete medical history and physical exam will be performed to ensure that the participants meet the inclusion criteria for the study. This will include measurements of vital signs, height, and body weight. Blood will be collected following an overnight fast for clinical lab tests, which will include renal function testing, comprehensive metabolic panels, and lipid and complete blood count tests. Resting electrocardiograms will be acquired and evaluated by a clinician to confirm a healthy heart rate and rhythm. Questions regarding the intent to become pregnant will be asked. A mood disorder questionnaire will be completed by participants and evaluated by study staff to assess for bipolar mood disorder. Subjects who meet the study eligibility criteria will be scheduled for study assessments.

Outcome Assessments

Assessments will be performed at baseline and at the end of the study (Table 2).

Table 2. Study assessments and methods.

Assessment	Method
Renal function testing, metabolic panels, and lipid and complete blood count tests	Lab test
Muscle strength (power and torque)	Dynamometry
Muscle strength	1-repetition maximum and 10-repetition maximum training
Body composition and bone density	Dual x-ray absorptiometry
Muscle cross-sectional area	Magnetic resonance imaging
Muscle creatine, phosphocreatine, and adenosine triphosphate	Magnetic resonance spectroscopy
Physical function	6-minute walk test
Quality of life	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-BR23

Body Composition

Body composition (fat mass, muscle mass, and bone) will be measured via dual x-ray absorptiometry. By using dual x-ray absorptiometry scans, we will measure whole-body and regional adipose and lean mass [33] as well as bone mineral density.

Strength and Physical Function

A 1-repetition maximum test will be performed to evaluate the maximum amount of force that can be generated through a full range of motion for a particular body region [34]. This will be directly tested for chest presses and leg presses and estimated (via 10-repetition maximum testing) for shoulder presses, leg extensions, and leg curls. Isometric knee extensor strength will be assessed in the right leg of each participant (unless contraindicated) by using a Biodex dynamometer (Biodex Medical Systems). The isometric maximum voluntary contraction force will be measured at approximately 60° knee flexion [35]. The average values from 3 attempts and percent variance will be recorded. Dominant isometric handgrip strength will also be tested by using a handgrip dynamometer (Jamar Plus+ Digital Hand Dynamometer; Jamar Plus+) [36]. Participants' 6-minute walk distances will be assessed to measure endurance function by using a standardized protocol [37].

Patient-Reported Outcomes

Study participants will complete the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 (version 3) quality of life survey and EORTC QLQ-BR23 survey for breast cancer survivors [38,39]. The EORTC QLQ-C30 is a 30-item measure of health-related quality of life. It includes 6 functional scales (physical, role, emotional, social, cognitive, and global quality of life scales), 3 symptom scales (fatigue, pain, and nausea and vomiting scales), and 6 single items (dyspnea, sleep disturbance, appetite, diarrhea, constipation, and financial difficulties). The EORTC-QLQ-BR23 is a 23-item measure of the symptoms and problems experienced by breast cancer survivors.

Muscle Cross-sectional Area and In Vivo Assessments

Magnetic resonance imaging will be used to measure the right midthigh muscle cross-sectional area (unless contraindicated) by using a whole body 3.0 T magnetic resonance imaging scanner (TIM Trio; Siemens AG). At the same time, intramuscular creatine, phosphocreatine, and ATP content will be assessed in vivo by conducting magnetic resonance spectroscopy (MRS), as previously described [40,41]. A phosphorus-31/hydrogen-1 dual-tuned, rigid, arc-shaped surface coil (RAPID Biomedical GmbH) will be positioned under the vastus lateralis. The vastus lateralis muscle was chosen for in vivo analysis because of the superficial positioning of the muscle and because it is the largest muscle in the quadriceps muscle group, which is the largest and strongest muscle group in the body. Lower extremity muscle weakness is also associated with long-term fatigue in breast cancer survivors [3]; thus, in vivo measurements are warranted for this muscle. An external reference 6-mL plastic vial with an 850mM concentration of methylenediphosphonic acid will be fixed to the center of the coil. Methylenediphosphonic acid was chosen due to its resonance frequency of around 22 parts per million downfield from phosphocreatine; this does not overlap with any relevant metabolite peaks. After a subject is scanned, a 15-cm–diameter, 4-L, plastic, cylindrical leg phantom containing 35mM

phosphoric acid will be placed on the coil and scanned by using the same MRS parameters and slab positions, so that the data can be collected from the same area within the radio frequency excitation field of the coil. A slice-selective phosphorus-31 MRS slab sequence (excitation pulse repetition time=10 seconds; time to echo=2.3 seconds; number of signals averaged=16; slice thickness=25 mm; receiver bandwidth=3000 Hz) will be performed for the quadriceps muscles of subjects and for the previously described leg phantom. Raw spectral data will be analyzed with Java Magnetic Resonance User Interface software [42], and the processing steps will include apodization to 5 Hz and Fourier transformation and phase correction. For spectrum quantification, the AMARES (Advanced Method for Accurate, Robust, and Efficient Spectral Fitting) algorithm [43] will be used.

Capturing and Monitoring Adherence

Adherence to creatine supplementation will be assessed by measuring the quantity of creatine that is left in the returned bottles, as described in the *Creatine Dosing Protocol* section. Individuals will not be withdrawn from the study for noncompliance with the creatine dosing regimen. The dosing quantity (number of scoops) and the dosing time will be documented in a dosing diary. Each exercise session will be documented, and information regarding session duration time as well as exercise mode and intensity during each training session will be documented. Participants will be encouraged to adhere to the protocol to the best of their ability. Participants will be withdrawn if more than 33% (12/36) of exercise sessions are missed.

Monitoring Adverse Events

Adverse events will be assessed during each interaction with a participant (ie, 3 times per week). Before and after each exercise session, participants will be asked about how they are feeling. If the answer is anything other than "feeling fine," the participant will be queried about the date and time of the onset of an adverse event, self-perceived severity, and any self-administered treatments. Upon the conclusion of the intervention, each adverse event will be graded by medical professionals based on severity, the event's relationship to the study intervention, the actions taken by the study personnel and participants, adverse event outcomes, whether the event was expected, and whether the event was serious. We will use the Common Terminology Criteria for Adverse Events version 5.0 [44] to grade the adverse events.

Data Management

Each participant will be assigned a unique study code. Data will be saved and stored by using the REDCap electronic data management system. Surveys will be completed electronically and linked to the participants' electronic data files to limit the incidence of transcription errors. Patients' charts will be kept inside a locked cabinet that is located inside the clinical research space, which is directed by DIP.

Statistical Analysis

The proposed analysis of 30 participants is based on a feasibility assessment [45]. Based on a preponderance of published feasibility and pilot studies, a minimum sample size of 15 participants per group was chosen to complete the study and estimate parameters for future studies [46,47].

Data on recruitment, adherence, and attrition rates will also be collected. Participants that withdraw from the study or are withdrawn for safety reasons will not be replaced.

Statistical analyses will be performed by using IBM SPSS 19.0 software (IBM Corporation). Descriptive statistics will be used to summarize the data. The primary analysis will be an intent-to-treat analysis, which will be conducted by using a 2-sided, stratified log-rank test. Cox proportional hazard regression models will be used to estimate hazard ratios with 95% CIs to quantify the effect of the intervention after adjusting for stratification, age, and BMI. We will also conduct secondary analyses for nonadherence, the rate of perceived exertion, and the number of exercise sessions completed. Pearson product moment correlation analyses will be used to measure associations among biomarkers of body composition, physical function, and quality of life measures. A *P* value of <.05 will be considered statistically significant, and all statistical tests will be 2-tailed. The results of our study will be used to calculate power and determine sample sizes for future research in this field.

Results

As of October 2021, a total of 19 patients have been screened, 12 have consented, and 9 have enrolled into the study. No adverse events have been reported in the creatine arm of the study. Muscle soreness and tingling associated with chemotherapy-related peripheral neuropathy have been reported as adverse events. No unexpected adverse events have been reported. Enrollment is planned to be completed by summer 2022.

Discussion

Our project will determine if creatine—a naturally occurring substance in the body—that is consumed as a supplement can be used to improve the adaptation of exercise training and accelerate the gain of muscle mass, strength, and lean body mass. Individuals with cancer are exposed to a variety of factors that impact their ability to live active lifestyles. Some of these factors are tumor related [48], while others are related to cancer treatment [49]. The loss of muscle mass and function greatly impacts a breast cancer survivor's quality of life [50]. The prevalence of muscle loss in individuals with cancer can range from 11% to 74% [51-56]. Exercise has been shown to combat this decline in muscle mass [56]. Exercise programs are capable of attenuating many of the deleterious effects of muscle loss [56]. Commercially available agents, such as creatine, have the potential to accelerate exercise adaptations and increase muscle mass, strength, and lean body mass [57,58].

Only 4 studies have been published to date on the effects of creatine supplementation in cancer survivors [22-25], and only 1 of the 4 studies involves creatine dosing in combination with an exercise program. In the combination study, which was conducted by Lønbro et al [22] in 2013, a total of 30 patients with head and neck cancer who were treated with radiotherapy

were supplemented with 5 g of creatine per day. The investigators reported greater improvements in lean body mass for creatine-supplemented participants compared to those reported for participants who took placebos [22]. A limitation to the study by Lønbro and colleagues [22] was that they did not use the suggested dosing regimen (20 g of creatine per day) at the start of the study to load intramuscular creatine concentrations. Research has demonstrated that this loading protocol can result in increased intramuscular creatine stores (ie, a 10% to 40% increase in muscular creatine and phosphocreatine stores). Using a lower dose will result in a gradual increase. Our study will be the first to investigate the effects of creatine supplementation in combination with exercise by using the recommended dosing protocol.

There is strong evidence that suggests that creatine supplementation can promote the overexpression of genes and proteins related to muscle hypertrophy [59] and satellite cell activation [60] in healthy subjects who participate in an exercise program. The growth-promoting potential of creatine may be useful in situations where anabolic activity is suppressed, as is the case with patients with prostate cancer on androgen deprivation therapy [61]. Therefore, we hypothesize that a positive impact of our study will be a significant improvement in intramuscular stores of creatine that will result in greater improvements in muscle strength, physical performance, and lean body mass compared to those improvements in the control group.

Acknowledgments

Authors' Contributions

DIP and AG wrote the initial draft of the manuscript. All other authors reviewed and edited the manuscript. All authors approved this article for publication.

Conflicts of Interest

None declared.

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Abbreviations

AMARES: Advanced Method for Accurate, Robust, and Efficient Spectral Fitting
ATP: adenosine triphosphate
EORTC QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
MRS: magnetic resonance spectroscopy
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Protocol

Effectiveness of Individual Feedback and Coaching on Shared Decision-making Consultations in Oncology Care: Protocol for a Randomized Clinical Trial

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Abstract

Background: Shared decision-making (SDM) is particularly important in oncology as many treatments involve serious side effects, and treatment decisions involve a trade-off between benefits and risks. However, the implementation of SDM in oncology care is challenging, and clinicians state that it is difficult to apply SDM in their actual workplace. Training clinicians is known to be an effective means of improving SDM but is considered time consuming.

Objective: This study aims to address the effectiveness of an individual SDM training program using the concept of deliberate practice.

Methods: This multicenter, single-blinded randomized clinical trial will be performed at 12 Dutch hospitals. Clinicians involved in decisions with oncology patients will be invited to participate in the study and allocated to the control or intervention group. All clinicians will record 3 decision-making processes with 3 different oncology patients. Clinicians in the intervention group will receive the following SDM intervention: completing e-learning, reflecting on feedback reports, performing a self-assessment and defining 1 to 3 personal learning questions, and participating in face-to-face coaching. Clinicians in the control group will not receive the SDM intervention until the end of the study. The primary outcome will be the extent to which clinicians involve their patients in the decision-making process, as scored using the Observing Patient Involvement–5 instrument. As secondary outcomes, patients will rate their perceived involvement in decision-making, and the duration of the consultations will be registered. All participating clinicians and their patients will receive information about the study and complete an informed consent form beforehand.

Results: This trial was retrospectively registered on August 03, 2021. Approval for the study was obtained from the ethical review board (medical research ethics committee Delft and Leiden, the Netherlands [N20.170]). Recruitment and data collection procedures are ongoing and are expected to be completed by July 2022; we plan to complete data analyses by December 2022. As of February 2022, a total of 12 hospitals have been recruited to participate in the study, and 30 clinicians have started the SDM training program.

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Conclusions: This theory-based and blended approach will increase our knowledge of effective and feasible training methods for clinicians in the field of SDM. The intervention will be tailored to the context of individual clinicians and will target the knowledge, attitude, and skills of clinicians. The patients will also be involved in the design and implementation of the study.

KEYWORDS

decision-making; shared; education; professional; feedback learning; coaching; medical consultation; medical oncology; palliative care

Introduction

Background

Shared decision-making (SDM) has been promoted to support patients in making informed decisions that best fit their personal preferences, circumstances, and concerns [1,2]. This is particularly important in oncology as many treatments involve serious side effects, and treatment decisions involve a trade-off between benefits and risks [3,4]. Approximately 110,000 Dutch patients are diagnosed with cancer each year [5]. Surgery, radiation, and systemic treatment options are available for most patients with cancer. The made treatment decisions determine crucial aspects of the lives of all patients and their families. Being diagnosed with cancer brings emotional stress, which affects patients' information recall and the decision-making process [6-8].

However, SDM implementation in oncology is challenging [9-12]. There is a relatively high level of uncertainty in cancer care regarding the treatment benefits and risks [10,12,13]. *Fighting* cancer is paramount in the focus of both clinicians and patients, which may impede the process of considering multiple treatment options and weighing their short- and long-term consequences [14-16]. Moreover, different clinicians within a team must coordinate the decision-making process over an extended period and for several decisions, which makes it difficult to guarantee continuity in the decision-making process [4]. Interventions tailored to specific local contexts have been proposed to stimulate the integration of SDM in usual care [17-21].

In addition, clinicians underline the importance of communication with their patients but feel that it is difficult to apply SDM in their actual workplace and believe that applying SDM does not differ much from their current practice [22-24]. Training clinicians as part of the implementation of SDM is generally seen as vital to overcome these hurdles [22,25-29]. Training involves theory and skills but is more effective when it also accounts for peer pressure, individual attitudes, and learning objectives [30]. It has been suggested that elements such as reflection and real time feedback be added to a clinician's actual SDM performance [31]. Recent efforts that incorporate feedback from observations of consultations to improve SDM competencies are promising [23,29,32].

SDM behavior is complex as it comprises interacting elements that are also influenced by contextual factors [32-34]. Medical professionals are expected to continuously improve their knowledge, skills, and behaviors, which requires the development and use of reflective practice skills [35,36]. Regarding medical performance, it has been stated that additional experience will not improve once it reaches the level of automaticity and effortless execution [37]. Deliberate practice involves the provision of immediate feedback, time for problem-solving and evaluation, and opportunities for repeated performance to refine behavior [37,38]. As deliberate practice supports teaching that is more focused on the motivation and self-directed learning of the clinician, coaching is being increasingly recognized as a method of enhancing technical and nontechnical clinical performance [39-42]. Effective coaching on complex communication skills, including those involved in SDM, requires direct observation or review of audio- or video-recorded health care encounters, followed by constructive feedback from the coach and the processing of this feedback into developmental actions by the coachee [43,44]. As training clinicians—face to face, individually, or in a team—is time consuming and challenging for a busy health care team [26,45], training approaches that improve SDM behaviors should be both effective and feasible. The effects of deliberate practice have not been evaluated in the design of effective SDM education but coincide with clinicians' own views that feedback and reflection, tailored to their own learning needs and firmly embedded in the daily working context, are considered vital to effectively learn communication skills [46].

Objective

The aim of this randomized clinical trial is to examine whether an individual SDM training program for oncology clinicians grounded in the theory of deliberate practice [37], as compared with their standard clinical practice, improves SDM behavior. The program comprises audiotaping the consultation or consultations of a single patient and conducting an SDM e-learning program containing both theory and a role-play example, followed by self-assessments, individual feedback reports, and coaching facilitated by an individual action-planning template.

Methods

Trial Design

This multicenter, single-blinded randomized clinical trial was designed and will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines [47]. The trial addresses the effect of SDM interventions in real-life clinician-patient consultations on the extent to which clinicians

involve their patients in the decision-making process. The design is unpaired, meaning that patients are only audiotaped once, either before or after the intervention. In the control group, the clinicians will not receive the SDM intervention until the trial period has finished. The trial will include different oncology clinicians, diagnoses, hospitals, and decisions to investigate applications in a range of oncological diagnoses, including patients in palliative care.

Study Conduct

When joining the study, clinicians will complete a short questionnaire asking about their number of years of experience, former participation in SDM skills training (yes or no) during medical school or as part of continuous medical education, residency, profession, age, and gender. The diagnosis, gender, and age of the patients will be recorded by the clinician to gather the basic demographic data of the study sample.

A measurement involves recording ≥1 consultation relevant to a decision-making process of 1 patient only, with a questionnaire that measures patients' perceived involvement in the decision-making process. The physicians and patients will be aware that consultations are being recorded. Each clinician will record the decision-making process for 3 different patients. By recording 2 consultations after the SDM intervention, with a time interval of 3 to 4 weeks between the recordings, the effectiveness of the SDM intervention for clinicians can be measured over time. The duration of the consultations and coaching sessions will be noted by the researcher (HvV) directly from the recordings. Clinicians will be instructed not to participate in educational activities related to patient-centered communication during the study. In addition, clinicians in the intervention group will be asked not to discuss the training contents or study-related information with participants in the control group. Once the final consultation is recorded, clinicians in the control group will receive the equivalent communication training. The period between each measurement will be 3 to 4 weeks, summing up to a total participation of approximately 8 weeks per clinician.

Participants

A total of 12 hospitals in the Netherlands will be included in this study (n=3, 25% universities; n=5, 42% general teaching; and n=4, 33% district hospitals). The recruitment of consecutive clinicians, who will discuss treatment decisions with their patients, will take place from April 2021 to July 2022.

All clinicians from the 12 hospitals involved in the decision-making process with patients of oncology regarding treatments will be invited to participate in the study. Clinicians in training (residents) are also eligible as, in the Dutch situation, they work under supervision but communicate with patients independently. Clinicians who have already received individual feedback on consultations or participated in SDM training within the past 3 years will be excluded. The inclusion criterion is that clinicians should be conducting consultations in which a decision is to be made with a patient who is capable and willing to participate. In addition, choices may relate not only directly to the final treatment decisions but also to other aspects of the care process. Consultations with patients who are palliatively

treated with no prospect of cure, for whom decisions are to be made regarding the quality of life, are also eligible.

Intervention

Overview

To clarify what SDM entails when applied in daily practice, we will invite clinicians to reflect on their own communication behavior during ≥1 consultation in which a treatment decision is made in relation to the following four steps for applying SDM: (1) creating option awareness, (2) discussing the options and their pros and cons, (3) exploring patients' values, and (4) agreeing on a decision that fits best with the patients' personal preferences [48]. All participants receive a *crib sheet*, a pocket-sized card to be used during or in between consultations that shows the 4 SDM steps with example phrases. These 4 steps are also key elements in the educational components of our intervention.

To support the adoption of SDM behavior by clinicians in daily practice, we will use the following four implementation levels of the Meetinstrument Determinanten van Innovaties model and their change determinants for our implementation approach [21]: (1) innovation (the implementation of SDM), (2) users of the innovation (clinicians and patients), (3) organizational context, and (4) sociopolitical context. To take the social context into account, oncology clinicians will be asked to participate as teams to enhance implementation success. By asking for a fee for participation in the training, we also ensure financial commitment from the hospitals to increase legitimacy and adherence to the trial.

Next, we will use the principles of deliberate practice as the basis for the educational approach. The best training situations focus on activities of short duration with opportunities for immediate feedback, reflection, and corrections [37]. In addition, additional reinforcing principles of medical coaching and action learning have been added [49-55].

The full SDM intervention takes <2.5 hours and comprises 4 parts, as described in the following sections.

e-Learning (45 Minutes)

An e-learning program was developed to comprehensively explain the principles and theoretical background of SDM. It addresses knowledge (ie, definition, rationale, effect, and the 4 steps for applying SDM); attitude (ie, reported barriers, own beliefs, and providing evidence on frequent misconceptions about SDM) [52]; and, to a lesser extent, self-efficacy illustrated with a video example of a consultation following the 4 steps of SDM. In e-learning, information is given about patients' perspectives on SDM based on internet polls among (former) patients. A total of 7 questions will be asked during the 45-minute e-learning program to stimulate reflection and memory. e-Learning was used and evaluated in a former implementation project on breast cancer [23,32]. The completion of basic SDM e-learning will be mandatory. Additional e-learning may be completed on a voluntary basis.

Reflection on Feedback Report (15 Minutes)

Participants will receive a personal feedback report from a communication researcher based on the Observing Patient Involvement–5 (OPTION-5) scores of their own consultation or consultations recording of a decision process with a patient [30]. This individual report will contain a score (0-4) per OPTION-5 item, as well as illustrative quotes and behaviors during the encounter that contributed most to a score and comprises 1 to 2 pages of ≥1 consultation per patient. The report was tested in 11 teams comprising patients with breast cancer during former implementation projects [23,32]. The direct observation of clinical encounters followed by structured feedback and coaching is educationally valuable [30] and seems promising for improving SDM behaviors [29,56,57]. By recording an actual clinical consultation in which a decision with a patient is made, feedback can be provided, and the recording can be stopped at critical points to reflect on and discuss appropriate goals with the coach. We put emphasis on quotes and nonjudgmental feedback rather than using a summative assessment form, as clinicians might feel this may reduce communication skills to behavioral components and may perceive this as impeding the improvement of their communication skills [46].

Self-assessment and Defining 1 to 3 Personal Learning Questions (30 to 45 Minutes)

This feedback will be aligned with the learner's ambition by giving clinicians a short version of the OPTION-5 checklist to complete a self-assessment of their recording. Next, we strive to provide feedback as individualized as possible and as close to their clinical reality by using quotes and linking the quotes to a practical 4-step model that can be used in the consultation. In addition, clinicians will then be asked to write down 1 to 3 learning questions, which will help reflect on their own performance. In addition, defining a personal ambition stimulates intrinsic behavioral changes. Participants will use e-learning, self-assessment, and personal feedback reports to reflect on what would help them improve the adoption of SDM in their daily practice the most. Writing down learning questions is the first part of the action-planning template, which is provided to serve as a checklist for the coaching session, self-reflection, and follow-up of planned actions.

Face-to-face Coaching: 15 to 30 Minutes

Clinicians will discuss the feedback with an experienced communication coach (HvV, Maaike Schuurman, or Esther van Weele) using both the participants' learning question or questions and the feedback report. To support reflexive and action learning, all participants will be provided with an action-planning template [50]. A model for effective coaching [40] will be used that involves four steps: (1) establishing principles of the relationship, (2) conducting an assessment, (3) developing and implementing an action plan, and (4) assessing the results of action plans and revising them accordingly. After the coaching session, each clinician will complete the action-planning template to force them to reflect on their SDM behavior, consider goals, and decide which strategies and skills will help them attain those goals. The coaching model is explained in Table 1, and the study design is presented in Figure 1. A professor of clinical medical education (PB) was consulted to finalize the form of coaching. In addition, an evaluation of the coaching will take place after 3 and 10 coaching sessions. After the coaching, the following characteristics of the coaching session will be noted: the content of the session; action planning; duration of the session; whether the clinicians prepared the learning objectives, relistened their own consultation, and read the feedback report beforehand; and the number of e-learnings completed.

Table 1. Elements and working constructs of effective coaching.

Element for effective coaching [40]	Working construct	Translation to our coaching approach [39,43,53,54]
Establishing principles of the relationship	Establish goals and parameters of the relationship, as well as ethical considerations, including confidentiality and boundary issues	• Express roles: the learner sets goals and designs the actions that help to apply SDM[a]; the coach makes suggestions and encourages the learner to define actions to realize ambitions • Downplay the coaches' role: position the coach as a learner, not an expert, to establish a nonhierarchical relationship that contributes to creating a safe space, as well as to coconstruct meaning and knowledge rather than to dictate it; emphasize that interdependence is the basis of valuable interaction • Facilitate honest discussion about strengths and challenges regarding SDM; help clinicians shift their focus from performance to learning • Make room for discussing areas for improvement of applying SDM in daily practice • Ask about the positive consequences the learner expects to accomplish with applying new SDM behavior
Conducting an assessment: self-assessment and assessment by a communication coach	To facilitate a feedback process to begin self-monitoring and encourage learners to gain reflective skills to help them set goals for their program through personal (to foster discovering the students' learning or interpersonal management style) and systemic assessments (assessments provided by the learner's program)	• In general, active and appreciative listening and asking questions; stimulate reflection: capable of being introspective and learning from yourself • Ask about the importance of SDM for the learners' professional role and development • Provide written feedback, after permission, of audio-recorded consultation or consultations of the learner with a patient in which a decision is made • A self-assessment is performed by listening back to their own consultation and using a shortened OPTION-5[b] measurement tool • Ask the learner to draw up 1 to 3 personal learning questions for the coaching session based on personal ambition and feedback • Review the written feedback that was provided together and whether it was recognizable to promote self-reflection and goal setting as the foundation of self-regulated learning [43] • Discuss the theory of SDM: what does it intend? What insights and questions come from the e-learning? • Use the 4-step model as a mirror for reflection on feedback and the goals • Use practical examples from best practices, including prompts, of potential areas of struggle to help learners identify challenges
Developing and implementing an action plan	This step determines new and revised actions that will lead to goal attainment; the learner reflects on what is working and what is not working, relate these to their learning style, and identifies learning opportunities that build knowledge and skills or initiates actions that demonstrate the learner's progress toward competence	• Focus discussion to areas of dilemmas and best cases to create action ideas; ask the learner what they need to accomplish their expressed ambitions regarding SDM • If clinicians express the wish to gain knowledge about SDM (ie, evidence for the use of teach-back, decision aids, background information about SDM measurement tools, or theory about elicitation values and preferences), we will provide handy cards, decision tools, support (ie, decision tools and tips to apply SDM as a team), or written information to read • Facilitate the transition from self-assessment and feedback to intervention: collaboratively crafting an action plan to implement appropriate intervention strategies [50,51] • Encourage the learner set 1 to 3 goals to be attempted in the next consultation and establish a short action-planning template • Ask questions to make goals ISMART[c] • Ask the learner about possible barriers to or facilitators of achieving their expressed goals and discuss possible ways of coping with them to increase clinicians' level of confidence in achieving the planned actions and coping with the feelings of failure
Assessing the results of action plans and revising accordingly	The coach and the learner review and evaluate the learners' progression according to the action plan and whether features of the plan should be revised	• The action-planning template ends with identifying at least two goals for their clinical practice over the ensuing weeks • After the coaching session, clinicians will receive feedback on their aspired goals, integrated as part of the feedback on their consultation • Evaluate the session and ask if there are any issues left to discuss • If a next meeting is desired, plan the date and agenda for the next meeting • Finally, residents will complete a brief evaluation, with Likert scale response options, that addresses the acceptability and usefulness of coaching

[a]SDM: shared decision-making.

[b]OPTION-5: Observing Patient Involvement–5.

[c]ISMART: important, specific, measurable, accountable, realistic, and timeline.

Figure 1. Design of the study.
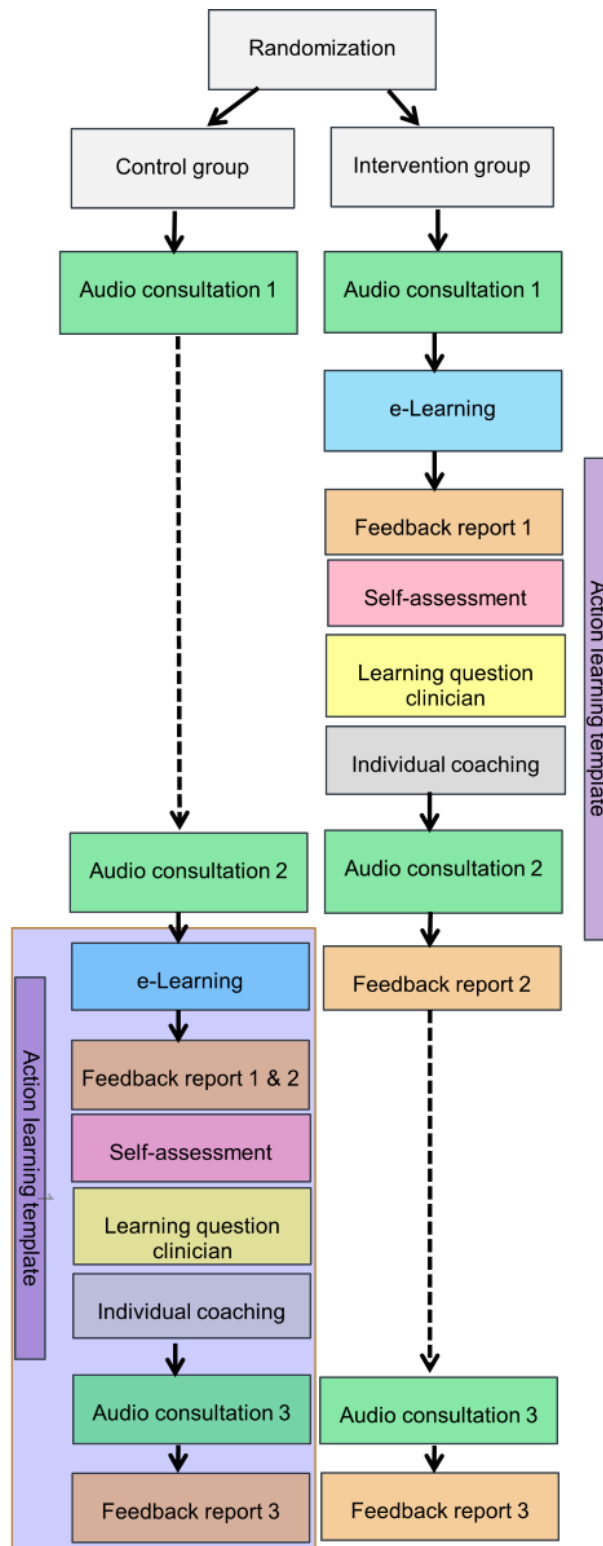
Comparator

The time schedule for participants randomized to the control group is shown in Figure 1. They will first be asked to complete the recording of the decision-making process of 2 different patients before they are offered the intervention (including recording a third decision-making process). This will enable a comparison of their SDM behavior with participants who are exposed to the intervention. By offering the intervention to participants in the control group after the trial period, we will ensure that all participants in this trial have the opportunity to develop themselves in the field of SDM. To keep similar trial circumstances, the interval between these 3 recordings (3-4 weeks) will be similar to that of the intervention group.

Outcomes

The primary outcome is the OPTION-5 instrument to rate the clinicians' behavior in the decision-making process objectively,

which will be performed by 2 of the 3 researchers (HvV and Maaike Schuurman and Esther van Weele) independently [30]. Each of the 5 items will be rated on a scale ranging from 0 (no effort made) to 4 (exemplary effort made).

As secondary outcomes, we will use subjective measures of SDM scored by the patients: the iSHARE, Control Preferences Scale (CPS), and the SDM Questionnaire–9 (SDM-Q-9) questionnaires.

The 15-item iSHARE questionnaire measures the perceived level of SDM during medical consultation or consultations; it was recently developed and has shown adequate content validity and comprehensibility [55]. It covers the entire SDM process rather than a single consultation and involves both clinician and patient behaviors. It is especially meant for the oncology setting, as definitions of SDM differ between health care settings [58]. The CPS has proven to be a clinically relevant, easily administered, valid, and reliable measure of preferred or experienced roles in decision-making among people with life-threatening illnesses [59]. The CPS comprises 1 question with 5 possible statements indicating the role of the clinician and patient in the decision-making process. The SDM-Q-9 comprises 9 statements. For each statement, patients rate the extent to which they *completely disagree* (0) to *completely agree* (5) on a 6-point Likert-type scale. The scores are added, multiplied by 20, and divided by 9 to provide a percentage of the maximum score, ranging from 0 (no SDM) to 100 (maximum level of SDM). If needed, a maximum of 2 missing items will be imputed with the mean of the items that are scored [60]. The duration and number of consultations are registered for each physician directly from the audiotaped consultation or consultations.

Sample Size

The primary outcome of this trial will be the extent to which clinicians involve their patients in the decision-making process, as scored using the OPTION-5 instrument [30,61]. A ≥10-point improvement in the OPTION-5 score is considered clinically relevant and significant, given the relatively limited time investment of the participants. For instance, a >10-point OPTION-5 score indicates 2 out of 5 items improving from moderate effort (2 points) to skilled effort (3 points) or 1 item improving from minimal effort (1 point) to skilled effort (3 points).

A preintervention mean score of 38 is assumed for our sample, which was measured in a former implementation project involving 6 outpatient breast cancer teams [32]. This is a high baseline score compared with other studies in general [56] and for oncology [9,11,57]. A total sample size in a 2-sided Z test for 2 means of 72 patients will be calculated based on an increase in the OPTION-5 score from 38 before implementation to 48 after implementation, with an SD of 13 in both groups, achieving a 90.38% power at the 5% significance level [13,32,56]. We will expand the sample size to 100 clinicians to account for possible failed recordings and dropouts of clinicians. A subanalysis will be performed to evaluate whether the results for palliative decisions, that is, patients who are palliatively treated (both tumor targeted and non–tumor targeted), are similar to those for the group with curative treatment intentions.

Randomization and Blinding

Randomization (Figure 1) will be conducted by allocating each clinician agreeing to participate in the study to either the intervention arm or the control arm (1:1) based on randomly mixed block sizes (2, 4, or 6) using Castor EDC (Castor Company) [62]. This type of randomization is common in multicenter studies that include approximately 100 participants to reduce the predictability of allocation [63]. All patients and raters will be blinded, whereas clinicians cannot be blinded to their allocation. The allocation sequence, enrollment, and assignment of participants to interventions will be conducted by a coordinator (LP) not involved in rating consultations and coaching of the participants.

Statistical Methods

All raters will use the OPTION-5 coding scheme, which has been refined for patients of oncology and vascular surgery [61,64]. The manual will be adjusted to be relevant to the oncology setting to increase raters' agreement in scoring the audio recordings. All audio recordings will be scored independently by 2 raters blinded to the intervention using the OPTION-5 instrument. After the first 10 audio recordings, these scores will be compared, and the coding rules will be discussed to reach an agreement over the final score. Moreover, the personal feedback and coaching sessions with the first 10 clinicians will be discussed by the project team in which patients are involved, and the unweighted Cohen κ values will be calculated as a measure of the interrater agreement [65]. The OPTION-5 score will be converted from a 0- to 20-point scale into a 0% to 100% scale.

Descriptive statistics will be presented as percentages or means with SDs. Differences will be expressed as mean differences with 95% CIs. The Pearson chi-square statistic will be used to analyze the differences between categorical variables at $P<.05$. We will check whether previous training in communication skills, professional background, disease, duration of the consultation or consultations, hospital, age, and number of consultations are equally distributed between the study arms. If they are not equally distributed, they will be included in the regression model for the OPTION-5 score. We will also perform a subanalysis for palliative decisions to evaluate whether the effectiveness of the SDM intervention for these consultations is comparable with that for the entire group. Statistical analyses will be performed using SPSS Statistics (version 25; IBM Corporation).

Patient Involvement

To guarantee that the patient's perspective is sufficiently included in the design of the SDM intervention, 2 patient representatives (Maaike Schuurman and Ella Visserman) and 1 (former) patient with breast cancer (Lisanne de Groot) have been involved in the study. The 2 patient representatives have been involved from the start of setting up the research project (including determining research questions and outcome measures) as part of the research team in recruiting clinicians for the study and are also committed to disseminating the study results and methodology in oncology care. A patient representative (Maaike Schuurman) is involved as a researcher

in rating consultations with the OPTION-5 instrument and providing coaching to clinicians (Maaike Schuurman), and all three (Maaike Schuurman, Ella Visserman, and Lisanne de Groot) will give feedback on specific parts of the training program, such as the content of the coaching sessions and feedback reports.

Ethics Approval and Informed Consent

All participating clinicians will receive information about the study and will be asked to give verbal consent for participation in the study: providing contact details, selecting a patient, and recording a consultation will be considered as their verbal consent. Their patients will complete a written consent form as consultations will be audio recorded, and patient characteristics will be collected. Non–Dutch-speaking patients will be excluded unless they are accompanied by a person who speaks Dutch sufficiently. Approval for the study has been obtained from the medical ethics review board of Leiden Den Haag Delft, located at Leiden University Medical Center, the Netherlands (reference N20.170/ML/ml). Each participating hospital provided local approval for this study.

Data Management

All sensitive data will be stored in encrypted password-protected databases (EUR Document Vault and Codific Document Vault [to save audio recordings during the study period]). Data will be entered by the study coordinator (LJP).

Results

Ethical approval for the study was obtained in December 2020, and thereafter, until December 2021, each of the 12 participating hospitals obtained local approval for this study. The first clinician started with the individual SDM training program in May 2021. As of February 2022, we enrolled 30 clinicians, of whom 5 (17%) have completed the training program. The pace of participant inclusion in the study is increasing; therefore, study recruitment is planned to be finalized around July 2022. We plan to complete data analyses by December 2022.

A mixed cofunding was obtained from the participating clinicians themselves (voluntary contribution), from the Dutch OncoZon-Citrienfonds (a professional oncology network), CZ Health Care Insurer, and DSW-Phoenix Health Care Insurer.

The study results will be disseminated to partnering organizations, study participants, and organizations involved in the development of clinician education. The findings will be submitted to a peer-reviewed journal and presented at academic conferences.

Discussion

Principal Findings

We hypothesize that clinicians exposed to this intervention are more likely to adopt SDM behavior than clinicians who do not, resulting in decisions that better match the preferences and values of oncology patients. We expect that clinicians in the intervention group will increase their observed level of SDM after each part of the intervention. We also believe that the effect

of the training program will be at least as large as the average increase that other interventions have shown [56]. Another possible effect is that patients may perceive greater involvement in the decision-making process and thereby experience a higher level of autonomy.

Comparison With Prior Work

We have previously worked on designing effective interventions, including training, to help clinicians adopt SDM in daily practice [23,31,32]. The theory-based and blended approach builds on previous research and includes different types of clinicians, diagnoses, hospitals, and oncology decisions to stimulate generalizability [29]. This approach is grounded in the theory of deliberate practice [37]. Moreover, patient involvement is guaranteed in the design and implementation of this study. Therefore, the study is perceived to have global value and should engender considerable interest in the academic and clinical education fields.

Strengths and Limitations

A strength of our approach is that it will be tailored to the context of individual clinicians and that it targets attitudes, knowledge, and skills of clinicians. The possible limitation of this protocol could be that participating clinicians may already have an inclination toward SDM, which can lead to selection bias. Therefore, we will try to invite clinical teams rather than individuals to participate in this study to include a group of clinicians with a wide range of SDM interests and skills. Another limitation is that the clinicians cannot be blinded to the intervention. This might encourage them to practice SDM apart from the intervention itself.

Future Directions

This trial takes the next step in the pursuit of developing effective training methods for clinicians in the field of SDM. It will increase our knowledge about how effective and feasible the direct observation of audio-recorded health care encounters, followed by constructive feedback from a coach, can be. Principles of deliberate practice are used as the basis for the educational approach, which enables effective learning [37], and the intervention is substantiated by implementation theory (Meetinstrument Determinanten van Innovaties model) and a 4-step model for applying SDM during clinical consultations [21,48].

Our intervention incorporates important elements from the theory of deliberate practice, such as having a well-defined goal, motivation to improve, and providing feedback on real-life situations [37]. Nevertheless, in our delineated intervention, it is difficult to meet the hallmark of providing opportunities for repetition and gradual refinement of performance over time. Therefore, future studies should address this challenge.

Conclusions

For most patients with cancer, multiple treatment options exist, and SDM is crucial to support them in making informed decisions that best fit their personal preferences. Clinicians play an important role in enhancing SDM implementation; however, SDM implementation remains challenging. This study will examine the effectiveness of an individual SDM training

program for physicians. The results of this study will be disseminated through publication in an open-access journal to enable the uptake of this deliberate practice study in other fields of interest and through presentations. In the Netherlands, patient organizations, professional bodies, and health care insurers are involved in the project and are committed to using valuable results for daily practice. Although our educational intervention is a mixed set of interventions with several elements over a 10-week period, it is relatively short and labor intensive, with one-on-one feedback and coaching. For implementation, it is important to take this into account and continue to look for interventions that are applicable in daily (oncological) care as well as support a continuous learning process for clinicians.

Acknowledgments

Authors' Contributions

The authors contributed to the work in accordance with the recommendations of the International Committee of Medical Journal Editors. All authors provided feedback on the concept of the work and the acquisition, analysis, and interpretation of data. HvV coordinated the design and preparation of this trial and drafted the protocol with primary support from LJP, FES, DTU, AMS, PLPB, and GV. HvV, LJP, DTU, and CGJMH were involved in the acquisition of funding and the recruitment of clinicians. HvV, LJP, and PLPB were involved in preparing the coaching interventions. All authors contributed to the final version of the manuscript and agreed to be accountable for all aspects of this work.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CPS: Control Preferences Scale
OPTION-5: Observing Patient Involvement–5
SDM: shared decision-making
SDM-Q-9: Shared Decision-Making Questionnaire–9

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Protocol

Comparing the New Interdisciplinary Health in Work Intervention With Conventional Monodisciplinary Welfare Interventions at Norwegian Workplaces: Protocol for a Pragmatic Cluster Randomized Trial

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Abstract

Background: Musculoskeletal and mental health complaints are the dominant diagnostic categories in long-term sick leave and disability pensions in Norway. Continuing to work despite health complaints is often beneficial, and a good work environment can improve work inclusion for people affected. In 2001, the Norwegian Labour and Welfare Administration began to offer *inclusive work measures* to improve the psychosocial work environment and work inclusion of people with health complaints. In 2018, the Norwegian Labour and Welfare Administration and specialist health services started offering the new collaborative *Health in work* program. Its workplace intervention presents health and welfare information that may improve employees' coping ability regarding common health complaints. It encourages understanding of coworkers' health complaints and appropriate work adjustments to increase work participation.

Objective: This protocol presents an ongoing, 2-arm, pragmatic cluster-randomized trial. Its aim is to compare the effect of monodisciplinary *inclusive work measures* (treatment as usual) and interdisciplinary *Health in work* in terms of changes in overall sickness absence, health care use, health-related quality of life, and costs. The secondary objectives are to compare changes in individual sickness absence, psychosocial work environment, job and life satisfaction, health, and health anxiety at both the individual and group levels.

Methods: Data will be collected from national registers, trial-specific registrations, and questionnaires. Effects will be explored using difference-in-difference analysis and regression modeling. Multilevel analysis will visualize any cluster effects using intraclass correlation coefficients.

Results: Inclusion was completed in July 2021 with 97 workplaces and 1383 individual consents. Data collection will be completed with the last questionnaires to be sent out in July 2023.

Conclusions: This trial will contribute to filling knowledge gaps regarding the effectiveness and costs of workplace interventions, thereby benefiting health and welfare services, political decision makers, and the public and business sectors. The findings will be disseminated in reports, peer-reviewed journals, and conferences.

Trial Registration: ClinicalTrials.gov NCT04000035; https://clinicaltrials.gov/ct2/show/NCT04000035

International Registered Report Identifier (IRRID): DERR1-10.2196/36166

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KEYWORDS

sickness absence; work environment; work environment intervention; health related quality of life; cluster randomized trial; cost-effectiveness-analysis; cost-benefit-analysis; health in work

Introduction

Sickness Absence in Norway

Musculoskeletal and mental health complaints are the dominant diagnostic categories in long-term sickness absence and disability pensions in Norway [1-4]. Many of these complaints can be described as subjective health complaints with high prevalence in the general population [5-7]. Preventing subjective health complaints is difficult, but improving the person's perception of the complaints as well as related coping mechanisms seems to have a positive impact in terms of sickness absence [8]. In fact, work-focused cognitive behavioral therapy and brief workplace interventions have been shown to reduce sickness absence [9-11]. Workplace interventions that presented reassuring information about low back pain based on the "non-injury-model" introduced by Aage Indahl [12] were shown to increase work participation [9,13], improve self-rated work ability, and reduce experienced complaints without changing the prevalence of low back pain [13].

For people with common health complaints, especially regarding mental health, work options often seem more beneficial than being on sick leave [14]. A Norwegian report showed that the general work environment seems to play a key role in deciding whether to go on sick leave or master one's back pain at work [15]. Thus, workplace interventions that include both health information and workplace processes that can create a flexible and inclusive work environment seem beneficial.

To address the comparatively high rate of sickness absence in Norway [16], the government, employer-organizations, and employee-organizations signed the first Inclusive Work Agreement (Intensjonsavtale om et mer inkluderende arbeidsliv; IA-avtalen) in 2001, with the latest update in 2018 [17].

Measures for Work Inclusion and Participation

To support workplaces in achieving the Inclusive Work Agreement goals of more inclusive work environments and reduced sickness absence, the Norwegian Labour and Welfare Administration (NAV) established NAV work centers (NWCs NAV Arbeidslivsenter) in every county [17,18]. Although NWCs offer a variety of monodisciplinary *inclusive work measure* (IWM) interventions both standardized and customized, the goal of the Inclusive Work Agreement of reducing sickness absence by 20% was not reached in the public sector [19-21], revealing a need for more effect-focused studies of IWM interventions [15].

Background of the Health in Work Program

In 2018, the collaboration between NAV and specialist health services began to offer a new interdisciplinary program called *HelseIArbeid*, or *Health in work* (HIW) [22]. The program is one of the policy instruments in the latest Inclusive Work Agreement [17] and has elements of both IWM and "raskere tilbake," a quick-access outpatient service intended to reduce sick leave by cutting wait times, which was in effect during 2007-2018. Thus, the HIW program has 2 main parts. The *individual measure* is an outpatient service where individuals can obtain quick access to an interdisciplinary assessment of common musculoskeletal, mental health complaints, or both, with a focus on how to better cope with these complaints to continue to engage in work and leisure activities. The second part is called the *company measure*, an interdisciplinary workplace intervention consisting of workplace processes regarding work environment as well as structured evidence-based health information about musculoskeletal and mental health complaints in general work contexts and related to the specific workplace [22]. Personnel from NWCs and specialist health services work in collaboration to deliver the intervention. This trial investigates the *company measure*, hereafter referred to as the HIW intervention. This trial is registered in ClinicalTrials.gov (NCT04000035).

The intersectoral and interdisciplinary collaboration between NAV and specialist health services, which is the core of the HIW intervention, is based on experiences from an earlier program called *iBedrift,* or *atWork*. The original *atWork* program started in some of Norway's southern counties [8]. Its workplace interventions focused mainly on health information provided by health personnel. The *atWork* program further evolved in Troms County, where it was adapted into the interdisciplinary *atWork Troms* program, which was in effect during 2009-2017. The *atWork Troms* workplace interventions consisted of health information about musculoskeletal and common mental health complaints provided by health personnel combined with work processes outlined in the Inclusive Work Agreement guided and facilitated by NWC personnel. The recommendation for national implementation of the HIW intervention studied in this trial is closely related to the *atWork Troms* program [22].

Rationale of the Trial

An evaluation of the Inclusive Work Agreement for the 2014-2018 period concluded that there was a lack of studies on workplace processes [15], including those presented in IWM interventions. Participants gave good feedback regarding the collaboration between health and NAV personnel in *atWork Troms* interventions, but no scientific evaluation of these interventions had been done. We know that certain parts of such interventions, such as providing health information at the workplace, can reduce sickness absence, increase self-rated work ability, and reduce physical and mental health complaints [8,23]. However, knowledge is still lacking about the effects and economic aspects of interventions integrating health information with workplace process assignments from NAV.

IWM interventions are customized according to the company's needs and requests; thus, they can range from comprehensive interventions to simple ones that require little or no time or resources. In contrast, owing to their interdisciplinary nature and the required participation of all employees, HIW interventions are resource-demanding. It is unknown whether the costs of HIW interventions outweigh those related to sick

leave and lost quality of life. Cost-effectiveness and cost-benefit analyses will provide an indication as to whether HIW is reasonable from a health and socioeconomic standpoint. Analyses of changes in outcomes related to health and the work environment will provide further information about the effect of HIW interventions.

Data on how the HIW intervention is perceived by both participants and intervention personnel will be gathered in the qualitative part of the overall mixed methods project, which is not described in this paper. The combination of qualitative and quantitative research methods will provide a more comprehensive picture of HIW interventions and may provide evidence of potential improvements to these interventions. The Norwegian Directorate of Health and NAV highlighted the need for knowledge about the effect of measures that combine the perspective of health and work [24] and encouraged quantitative and qualitative research to optimize the implementation and content of the *Health in work* program [22]. Therefore, this trial is an important contribution in the field and relevant for political decision makers, NAV, health services, and public and private workplaces.

Specific Objectives

The main objective of this trial is to compare the effects of monodisciplinary IWM (treatment as usual) and interdisciplinary HIW interventions in terms of changes in overall sickness absence, health care use, health-related quality of life, and costs. The secondary objectives are to compare changes in individual sickness absence, psychosocial work environment, job and life satisfaction, health, and health anxiety at both the individual and group levels. Comparisons will be conducted both within and between trial arms.

Methods

Trial Design and Setting

This protocol presents a pragmatic, cluster-randomized, multicenter superiority trial with 2 parallel arms and a 1:1 allocation ratio. HIW and IWM interventions are to be carried out at workplaces throughout the county of Troms and Finnmark, Norway's northernmost county, which covers an area of approximately 750,000 km^2 and has a population of approximately 243,000 people. Workplaces in both urban and rural areas are included.

As both IWM and HIW interventions are aimed at all employees within a workplace, randomization must be conducted at the workplace level rather than at the level of individual employees.

Eligibility and Exclusion Criteria for Clusters (Workplaces) and Individual Participants

To be eligible for inclusion, workplaces must have a minimum of 8 employees and have accessible data on sickness absence

(both self- and physician-certified) for the 2 years before allocation. Individual participants must speak Norwegian, be aged 18-70 years, and be employed ≥20% in the participating workplaces to be included in the trial. Workplaces that are experiencing profound reorganization (ie, >20% change in workplace staff during the research period) are excluded.

Interventions

HIW Intervention

Personnel from the NWCs and specialist health services work in collaboration to provide HIW interventions according to a standardized protocol. An initial meeting is held to define the workplace's goals and plan the course of the intervention, followed by three 1.5-hour sessions over a 12-month period. During these sessions, health personnel present structured health information about musculoskeletal, pain, and mental disorders, and NAV personnel put this information in the context of work and the specific workplace. Between sessions, group-based workplace process exercises are carried out. During these exercises, challenges related to session content as well as topics around the work environment and work inclusion should be addressed.

In more detail, the first session aims to use health information on common neck and back complaints to increase workers' ability to cope with them as individuals and collectively. It also presents tasks that foster reflection and dialogue on factors that promote the health and inclusion of workers with musculoskeletal complaints in the workplace. The second session aims to communicate health information regarding pain to increase workers' ability to cope with it individually and collectively. The third session is similar to the first but with content related to common mental health complaints.

Both the sessions and the group exercises between the sessions should involve all workplace staff (management and employees). The group exercises should be active meetings that take place without the involvement of intervention personnel. Finally, at the end of the 3 sessions, an evaluation meeting is held to discuss possible further follow-up.

IWM Intervention (Treatment as Usual)

IWM consists of conventional welfare interventions given over a 12-month period by NWC personnel only. The interventions focus mainly on work inclusion and psychosocial work environment. There are several types of interventions available, some of which are presented in Figure 1. The choice of delivery is customized to the individual workplace; thus, treatment as usual varies according to the workplace's demands. An evaluation meeting discussing possible further follow-up is optional.

A flowchart of intervention content and the study process is shown in Figure 1.

Figure 1. Schematic overview of activities in the *Health in work* (HIW) and *inclusive work measure* (treatment as usual) interventions. IWM: inclusive work measure; NAV: Norwegian Labour and Welfare Administration.
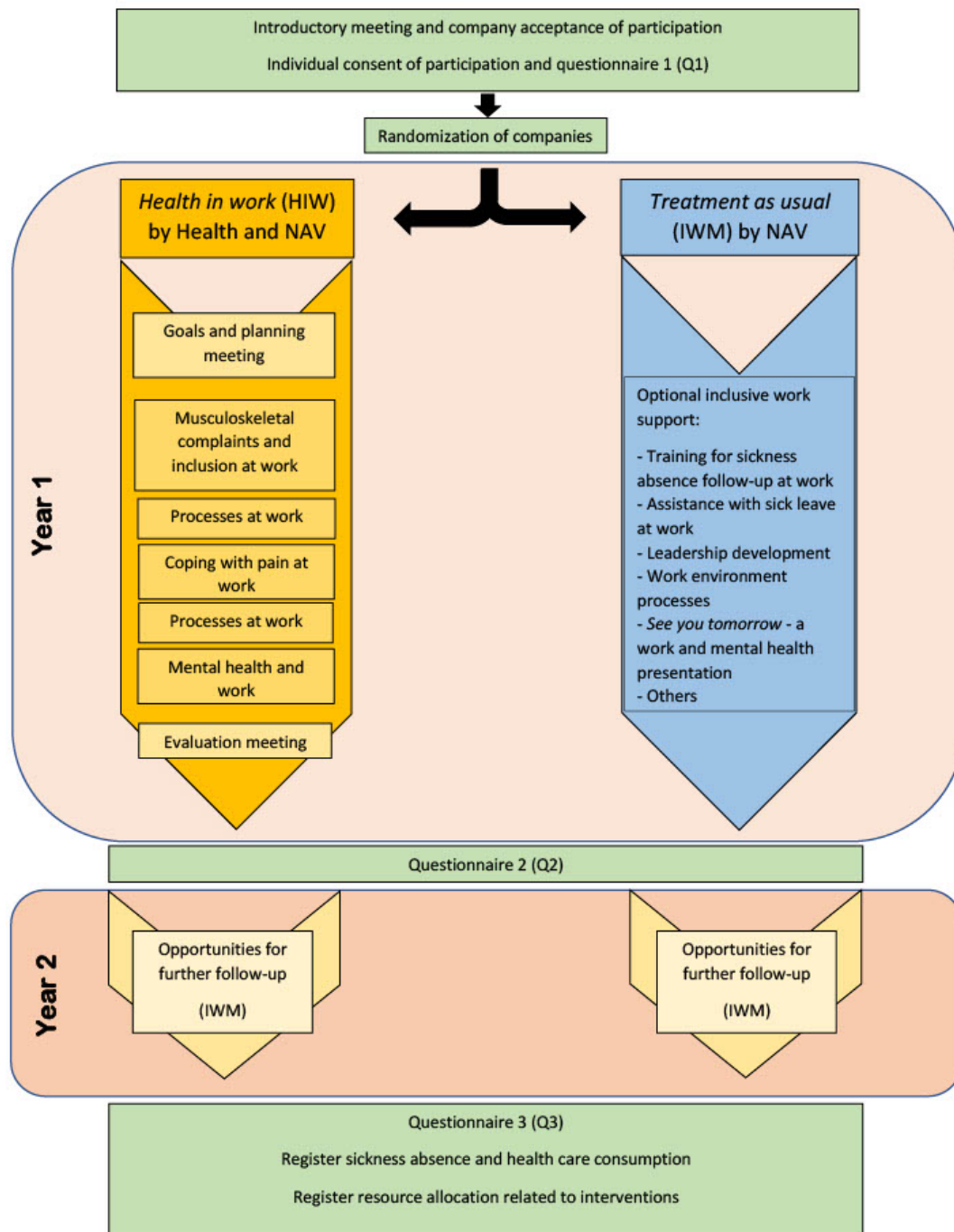
Intervention Personnel

Health personnel comprise employees from specialist health services from the University Hospital of North Norway (UNN), Finnmark Hospital in Kirkenes, or the Rehabilitation Center Finnmark in Alta. They work in the field of rehabilitation medicine; for example, as physiotherapists, medical doctors, or occupational therapists. NAV personnel are from NWCs located at multiple sites in the county of Troms and Finnmark. They are experienced in Inclusive Work Agreement processes and have different backgrounds (eg, teaching, management, human resources, and nursing). Many have previously delivered *atWork Troms* interventions. NWC personnel deliver both HIW and IWM interventions according to their portfolio. All intervention personnel undergo in-house training according to protocol,

including observation of experienced personnel, literature, and courses.

Adherence to the Trial Protocol and Concomitant Activities

Participating NWC personnel, health personnel, and workplaces are to register and report on activity and time spent on either HIW or IWM each quarter. The research team sends reminders about these reports as a means of improving adherence.

Participating workplaces in both groups are allowed to implement other workplace measures (eg, measures from occupational health services or from NAV). The pragmatic design does not restrict the type or number of other workplace measures except for the HIW intervention, which is exclusively reserved for the HIW group. The content and extent of the applied measures have to be reported to the research group. Individual employees have no study-specific restrictions.

Recruitment

The main role of NWCs is to support workplaces that wish to address the development and maintenance of a good work environment independent of their level of sickness absence. Workplaces can contact NWCs, but NWCs also reach out to workplaces. NWC personnel have good knowledge of and contact with workplaces in the region. Through this contact, workplaces from the county of Troms and Finnmark were recruited for the trial. They were informed about the ongoing trial and the fact that they may be allocated to either the HIW or IWM intervention in an introductory meeting with employers and union representatives. After initial slow recruitment, an additional meeting with detailed information solely on the trial and its implications given by one of the research group members (mainly CLT, occasionally NF or ACH) was added to increase participation.

Timeline

Upon agreement to participate in the trial, all employees and management at the workplaces received the following by email from their employer: information about the trial, a PDF file with the individual informed consent form, and a link to questionnaire 1. Completed paper forms with individual informed consent were collected for 2 weeks, and then the random allocation was executed. Intervention periods were scheduled to be 12 months for both trial arms. Questionnaires 2 and 3 were to be completed 12 months and 24 months after allocation, respectively. Owing to the global pandemic, the trial was halted between mid-March 2020 and September 2020, and activities were reduced at several time points. Therefore, the intervention period and time points for questionnaires 2 and 3 were adjusted for workplaces included before April 2020 and in fall 2020, whereas workplaces included in 2021 were expected to follow the usual timeline. A flowchart of the study process is shown in Figure 1, and the timeline is shown in Figure 2.

Figure 2. Timeline for enrollment, intervention, and assessment. GJS: Global Job Satisfaction; HIW: *Health in work*; IWM: inclusive work measure; KUHR: Norway Control and Payment of Health Reimbursement; NDSS–16: Nondirective and Directive Support Survey; NPR: Norwegian Patient Register; SHC: subjective health complaints; SWLS: Satisfaction With Life Scale.

	Prestudy Period	Study Period			
		Enrollment	Allocation	After allocation	
Time point	-T2 24 months Prior	-T1 2 weeks Prior	T0	T1 12 months (later depending on the development of the pandemic)	T2 24 months (later depending on the development of the pandemic)
ENROLLMENT		x			
Eligibility screen		x			
Informed consent		x			
INTERVENTIONS					
HIW					
IWM					
ASSESSMENTS:					
Questionnaire		x		x	x
- Health-related quality of life (EQ-5D)		x		x	x
- Work environment (Demand-Control-Support, NDSS-16, GJS)		x		x	x
- Health (SHC, Whiteley-7 index)		x		x	x
- Satisfaction with life (SWLS)		x		x	x
- Demographics (age, height, weight, education, income, marital status, social networks, alcohol consumption, smoking, physical activity, and medication)		x		x	x
- Use of health services in the past 12 months		x		x	x
- Adaption measures at participant's workplace		x		x	x
- Self-reported sickness absence in the past 3 months		x		x	x
Sick leave data: workplace					
Working hours and direct costs: intervention staff					
Working hours and direct costs: workplaces					
Sick leave data: individual register					
Healthcare utilization individual register (KUHR, NPR)					

Assignment of Intervention

The randomization sequence was created using a computer-generated random number list [25] with a 1:1 allocation using random block sizes of 16 to 20. On the basis of this allocation, a sheet of paper was marked with either *HELSEIARBEID* (HIW) or *KTRIAARBEID* (IWM). The paper was then folded and placed in a sequentially numbered opaque envelope, and the envelope was sealed (allocation envelope). In this manner, a total of 104 allocation envelopes were produced. In November 2020, owing to an unexpectedly high number of retractions after initial recruitment but before inclusion in the trial, another 50 allocation envelopes were

produced. Sequence generation and allocation concealment were performed independently by co–principal investigator (PI) ACH, who was not involved in the recruitment or allocation of workplaces. A list of the envelope numbers and the intervention they contained was locked away in a file cabinet at UNN, to which none of the personnel (research, NAV, or HIW personnel) has access. The workplaces were consecutively numbered as they agreed to participate in the trial during recruitment. Final inclusion was not completed until informed consent forms were received from the respective workplaces. The corresponding numbered allocation envelope was then opened by the PI, NF, together with a research assistant. The workplace was notified of the intervention to which it had been allocated, as was the

supervisor of the relevant NWC. The workplace identifier was noted on the allocation envelope and locked away in a file cabinet. Blinding beyond allocation was not relevant for obvious reasons.

Data Collection and Management

Trial questionnaires are electronic and administered by REDCap (Research Electronic Data Capture; Vanderbilt University) tools. Completed questionnaires are double-checked manually with informed consent forms to guarantee that only the data of those who have provided consent are used. Informed consent forms contain three sections to obtain separate consent for each of the following: use of questionnaire data, linkage to register data, and linkage to data from Tromsø 7, if applicable (Multimedia Appendix 1).

When answering questionnaire 1 at enrollment, participants registered their email address, to which links for later questionnaires will be mailed. Questionnaires 2 and 3 are completed at 12 and 24 months after allocation, respectively, or as appropriate owing to pandemic-related delays.

Questionnaires 1-3 all have the same questions on health-related quality of life, symptoms, work environment, and individual self-certified sickness absence. Validated questions were used when possible (see *Evaluation Outcomes* and Figure 2). Individual physician-certified sickness absence and health care use data are collected through register data for the period from 24 months before allocation to 24 months after allocation.

During the intervention period, workplaces report the time used for intervention activities on a quarterly basis. The sickness absence rate at the unit level is reported for the periods 24 months before allocation to allocation, the intervention period, and 12-24 months after allocation. Intervention staff registers the time spent on the preparation and execution of the intervention.

Workplaces that withdraw from the interventions before completing the intervention period are asked to continue to report their sickness absence data, and the individual participants are encouraged to answer all questionnaires, enabling intention-to-treat (ITT) analysis.

Data are stored on a secure research server at UNN with restricted access, which will also be used for data analysis. The personal national identification number will be used to collect register data according to consent. Data access is restricted to the project research group.

Study-specific personal identifiers will be used for all data storage, linkage, and analysis. The key list of identifiers is kept separate from the remaining data; access is restricted to PI NF and co-PI ACH.

Ethics Approval

This research will be carried out in compliance with the Helsinki Declaration of 1975 as revised in 2000 [26]. Personal confidentiality is guaranteed. Written informed consent forms will be collected from each participant. The consent forms emphasize the right to withdraw from the trial at any time without explanation according to the consent form template

created by the Norwegian Regional Committee for Medical and Health Research Ethics (REC). Information about the trial is given orally in an information meeting as well as in written form, with the opportunity to ask questions via telephone or email.

This trial protocol has been approved by the REC (ID 15680) and is registered at ClinicalTrials.gov (NCT04000035). Possible substantial protocol modifications must be approved by the steering committee and the REC and will be registered in ClinicalTrials.gov. The participant-level data set will not be available for public access owing to General Data Protection Regulations. Metadata and statistical codes beyond those reported in publications will be available upon reasonable request.

Statistical Analysis

Power Calculation

The calculation of the sample size for the number of workplaces is pragmatic and based on Odeen et al [8]. ITT sickness absence will be collected at the unit level, and a 10% reduction from 6.6% (mean certified sickness absence in Troms) to 5.9% (SD 2.5%) will be considered significant in both a clinical and societal context. Odeen et al [8] demonstrated a statistically significant 11% difference in rate ratios at the unit level, with 42 and 48 units in the 2 arms. We consider actual units for inclusion as comparable and, therefore, plan to include 50 workplaces in each arm in line with the study by Johnsen [23] on workplace interventions in kindergartens.

At the individual level, the necessary sample size to detect a clinically significant difference within the arms was calculated according to the hypothetical use of the patient activation measure. A clinically significant difference in patient activation measure between the arms can be set at $D=5$ [27]. On the basis of this, and using a quantitative method where $f(a=0.05, b=0.20)=10.5$, we can calculate the necessary sample size for the trial arms: 182 ($n = 2[SD/D]^2 \times f[a,b]$) individuals in each arm if the SD is 17, strength (b) is 80%, and significance level (a) is 5%. Therefore, we need to include a total of 364 participants in the trial. To take into account the lack of independence between workers in clusters, this number should be corrected by *the variance inflation factor* $1 + (n - 1)\rho$, where n is the average cluster size and ρ is the intracluster correlation coefficient for the particular outcome [28]. With the value of n being 4, the inflation factor equals 1.3 when P equals .10; thus, each trial arm should include 240 individuals. This indicates that, with a 50% response rate and a mean workplace size of 20 employees, we will have the power to perform gender-stratified analyses with 50 workplaces in each study arm.

Analysis of Data

Difference-in-difference analyses will be used to address any differences in sickness absence, health care refunds, and health-related quality of life between the trial arms at the unit level. Cost-effectiveness and cost-benefit analyses will compare the trial arms in terms of incremental costs based on direct and indirect costs related to interventions throughout the intervention period.

At the individual level, outcomes will be analyzed based on changes from enrollment. Moreover, 2-tailed *t* tests or Mann-Whitney *U* tests and chi-square tests will be used when appropriate. A generalized linear mixed effects Poisson model will be used to investigate possible differences in percentage of sick leave between the 2 trial arms. A multivariable, multilevel logistic, ordered logistic, and linear regression allowing for clustering at the unit level will be used according to the outcome measure (OM) analyzed. To consider changes owing to the pandemic-related temporary halt of the study, other statistical methods such as stratification will be relevant.

We will use 2-sided *P* values with $\alpha < .05$ level of significance for all tests.

The analysis will be according to ITT regardless of protocol adherence.

Results will be reported in line with CONSORT (Consolidated Standards of Reporting Trials) guidelines.

Evaluation Outcomes

The *Health in work* program and the Inclusive Work Agreement have several complex, nongraded aims, which focus on improved work environment, sustainable job participation, and prevention and reduction of sickness absence. The *Health in work* program especially pinpoints work participation as an aspect that contributes to better health. However, it is not known to what extent the systematic intersectoral collaboration between NAV and specialist health services in HIW interventions is an effective use of resources. Therefore, it is impossible to define a single primary OM for this trial and, thus, the four primary OMs are as follows: (1) change in overall sickness absence rates (self- and physician-certified) at the workplace (unit level) in percentage of planned workdays for the period 24 months before allocation compared with the period 12-24 months after allocation (OM 1); (2) change in health care use, assessed using data from the National Register of Control and Health Service Refunds (The Norwegian Directorate of Health) and the Norwegian Patient Register (The Norwegian Directorate of Health), for the period 24 months before allocation compared with the period 12-24 months after allocation (OM 2); (3) change in health-related quality of life, measured using the EQ-5D-5L and EQ VAS for the period from enrollment to 24 months after allocation (OM 3); for OMs 1-3, changes within and between trial arms will be analyzed); and (4) health economic analyses comprising cost-effectiveness analyses based on OM 3 and cost-benefit analyses based on OMs 1 and 2 comparing the trial arms in terms of incremental costs based on direct and indirect costs related to the interventions throughout the intervention period (OM 4).

Secondary OMs focus on health complaints, anxiety, and different aspects of work and work environment and comprise the following: change in physician-certified mean sickness absence rates (individual level) based on data from the Norwegian National Register of Sickness Absence (NAV sykefraværsregister) for the period 24 months before allocation compared with the period 12-24 months after allocation (OM 5); change in self-certified sickness absence rates (individual level; OM 6); change in psychosocial work environment, assessed using the Demand–Control–Support Questionnaire score (OM 7); change in social support from colleagues, assessed using the Nondirective and Directive Support Survey score (OM 8); change in job satisfaction, assessed using the Global Job Satisfaction score (OM 9); change in subjective health complaints, assessed using the subjective health complaints score (OM 10); change in health anxiety, assessed using the Whiteley index score (OM 11); and change in satisfaction with life, assessed using the Satisfaction With Life Scale score (OM 12).

OMs 6-12 are based on data from the trial questionnaires. Changes within and between trial arms will be analyzed for the following periods: enrollment to 12 months after allocation and enrollment to 24 months after allocation for each OM and 12 to 24 months when relevant.

For in-depth details regarding OMs, see ClinicalTrials.gov.

The trial questionnaire collects information on background variables (ie, type of employment, height, weight, education, income, smoking habits, alcohol consumption, and physical activity) as well as self-reported sickness absence and health care use. Several sections of the trial questionnaire are the same as those in the seventh and latest survey of the Tromsø Study (Tromsø 7), which took place in 2015-2016. For trial participants who also participated in Tromsø 7 and provided explicit consent, trial data will be linked to Tromsø 7 data to obtain an impression of natural intraindividual variation over time.

For all analyses, the possible impact of the COVID-19 pandemic will be addressed.

Patient and Public Involvement

Patients and the public have been involved in the design of and recruitment for the study by representatives of employer and employee organizations both in the preparation phase and in the steering committee. They will be further involved in dissemination activities to ensure that information is clearly given and easy to understand for our different audiences.

Steering Committee and Reference Group

The overarching mixed methods project has a steering committee with members from a Labour Union (Landsorganisasjonen i Norge [LO]) and an employer union (The Confederation of Norwegian Enterprises [NHO]) as well as funders and sponsors NAV research and development fund, UNN, UiT The Arctic University of Norway, and NWCs). The committee is chaired by NAV Troms and Finnmark, which is guiding the practical execution of the interventions. A reference group comprising representatives from the research group, NAV research and development fund, and intervention participants as well as researchers from *Stiftelsen for industriell og teknisk forskning* (SINTEF) and the University of South-Eastern Norway advises on scientific questions.

Results

Inclusion began in June 2019 and was completed in July 2021, resulting in 97 included workplaces and 1383 individual consents. Recruitment of workplaces was difficult. Of the 146 recruited workplaces that had initially agreed to participate,

only 97 (66.4%) finally consented to inclusion, whereof 46% (45/97) were allocated to HIW and 54% (52/97) were allocated to IWM. Reasons given for retraction were both pandemic-related and organizational challenges that would have made it difficult for the workplaces to satisfy the study requirements.

Questionnaire 1 was answered by 962 participants, yielding a response rate of 69.6% (962/1383). Although the time point for questionnaire 2 has been reached for only a part of the participants, none have received questionnaire 3 as of February 20, 2022. Data collection will be completed with the last questionnaires to be sent out in July 2023. Results on intervention-related difference-in-difference regarding self-rated health measures, sickness absence, and health care use are expected to be published from autumn 2023 onward.

Discussion

Preliminary Principal Findings

This trial will examine different aspects of workplace interventions and specifically compare the new interdisciplinary HIW program with usual monodisciplinary IWM in terms of health care use, health-related quality of life, and costs. As secondary objectives, it will also compare changes in individual sickness absence, psychosocial work environment, job and life satisfaction, health, and health anxiety at both the individual and group levels.

Although the number of finally enrolled workplaces was slightly below our desired target of 100 workplaces, individual participant numbers were well above the anticipated goal of 1000 enrolled participants. Despite computer-generated randomization, the distribution to the 2 intervention groups was slightly skewed toward the IWM group but not significantly different.

To date, the response rate for our questionnaire can be considered good, being 69.6% (962/1383), but response rates for questionnaires 2 and 3 will likely be lower. Incentives have proven to increase participation rate in follow-up questionnaires in randomized controlled trials [29]. We are already applying incentives in the form of gift certificates for 750 Norwegian kroners (US $84.31), which are randomly drawn from every 50 questionnaires received since the start of the study. Information about this was provided in the original email before questionnaire 1 and is included in emails for follow-up questionnaires 2 and 3.

Strengths and Limitations

Our trial is the first large-scale scientific evaluation of the *Health in work* program, which has thus far not been scientifically evaluated. The pragmatic design will reflect the effects that can be achieved by the 2 interventions in real life. The combined use of questionnaires and register data is a strength that could ameliorate the negative impact that a possible low response rate to follow-up questionnaires would have on representativeness.

A major strength is the trial design, with random allocation to one of the 2 intervention groups. As allocation was conducted by persons not involved in the production of allocation envelopes and only after individual consent forms were received, we have ameliorated the chances of selection bias (ie, the selective enrollment into the trial based on likelihood of the next treatment allocation). In addition, during the recruitment period, NWCs offered HIW only to workplaces participating in the trial (with a 50% chance of receiving HIW or IWM). IWM support was administered independent of trial participation. However, this could also have introduced a bias in that workplaces that wanted to receive HIW but were allocated to IWM will be less motivated for IWM activities or answering questionnaires. Attention will have to be given to possible differences in response rates of follow-up questionnaires in the HIW and IWM groups.

A potential limitation is that there might occur cross-contamination between trial arms, between nearby workplaces, and because of personnel serving both HIW and IWM interventions. In addition, generalizability could be influenced by regional workplace culture and characteristics, such as the experience of executing staff from NAV and specialist health care services.

Dissemination Plan

Trial results will be disseminated to participants, researchers, health personnel, authorities, and others interested through scientific conferences, publications, reports, and public dissemination measures. There are no publication restrictions, and the results will be disseminated regardless of the magnitude or direction of the effect. Authorship eligibility is determined according to the International Committee of Medical Journal Editors criteria for manuscripts submitted for publication. There is no intended use of professional writers.

Data presentation will be performed in a way that ensures confidentiality for individual or workplace-specific data.

Authors' Contributions

NF, consultant physician at the Norwegian Labour and Welfare Administration and Associate Professor at UiT The Arctic University of Norway, is the principal investigator of the overall mixed methods study. ACH, researcher at UiT and consultant

physician at the University Hospital of North Norway, is the co–principal investigator of the randomized controlled trial. CLT is a PhD student in health economics at UiT and a quality advisor at University Hospital of North Norway. NF conceived the study. NF and CLT provided statistical and practical expertise for the trial design and planned the study together with ACH. NF and ACH have administrative responsibility, and NF and CLT assisted implementation. ACH wrote and revised the manuscript with support from NF and CLT. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Conflicts of Interest

NF, CLT, and ACH are receiving salaries from the Norwegian Labour and Welfare Administration, the University Hospital of North Norway, and UiT The Arctic University of Norway, respectively, and, therefore, have a possible conflict of interest. However, neither the Norwegian Labour and Welfare Administration, the University Hospital of North Norway, nor UiT The Arctic University of Norway are involved in randomization, collection, management, analysis, or interpretation of the data, writing of the report, or the decision to submit the report for publication, or have ultimate authority over any of these activities.

Multimedia Appendix 1
Administrative information about the trial, including the World Health Organization trial registration data set and the trial's informed consent form in original language (Norwegian).
[PDF File (Adobe PDF File), 635 KB - resprot_v11i4e36166_app1.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
HIW: Health in work
ITT: intention-to-treat
IWM: inclusive work measure
LO: Landsorganisasjonen i Norge
NAV: Norwegian Labour and Welfare Administration
NHO: Confederation of Norwegian Enterprises
NWC: Norwegian Labour and Welfare Administration work center
OM: outcome measure
PI: principal investigator
REC: Regional Committee for Medical and Health Research Ethics
REDCap: Research Electronic Data Capture
SINTEF: Stiftelsen for industriell og teknisk forskning
UNN: University Hospital of North Norway

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Protocol

Casting Without Reduction Versus Closed Reduction With or Without Fixation in the Treatment of Distal Radius Fractures in Children: Protocol for a Randomized Noninferiority Trial

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Abstract

Background: Acute treatment for distal radius fractures, the most frequent fractures in the pediatric population, represents a challenge to the orthopedic surgeon. Deciding on surgical restoration of the alignment or cast immobilization without reducing the fracture is a complex concern given the remodeling potential of bones in children. In addition, the lack of evidence-based safe boundaries of shortening and angulation, that will not jeopardize upper-extremity functionality in the future, further complicates this decision.

Objective: The authors aim to measure functional outcomes, assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Physical Function v2.0 instrument. The authors hypothesize that outcomes will not be worse in children treated with cast immobilization in situ compared with those treated with closed reduction with or without percutaneous fixation. The authors also aim to compare the following as secondary outcomes: ulnar variance and fracture alignment in the sagittal and coronal planes, range of motion, pressure ulcers, pain control, radius osteotomy due to deformity, pseudoarthrosis cure, and remanipulation.

Methods: This is the protocol of a randomized noninferiority trial comparing upper-extremity functionality in children aged 5 to 10 years, after sustaining a distal radius fracture, treated with either cast immobilization in situ or closed reduction with or without fixation in a single orthopedic hospital. Functional follow-up is projected at 6 months, while clinical and radiographic follow-up will occur at 2 weeks, 3 months, and 9 months.

Results: Recruitment commenced in July 2021. As of January 2022, 23 children have been randomized. Authors expect an average of 5 patients to be recruited monthly; therefore, recruitment and analysis should be complete by October 2024.

Conclusions: This experimental design that addresses upper-extremity functionality after cast immobilization in situ in children who have sustained a distal fracture of the radius may yield compelling information that could aid the clinician in deciding on the most suitable orthopedic treatment.

Trial Registration: ClinicalTrials.gov NCT05008029; https://clinicaltrials.gov/ct2/show/NCT05008029

International Registered Report Identifier (IRRID): DERR1-10.2196/34576

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KEYWORDS

radius fractures; distal radius; pediatric; remodeling; surgical reduction; cast immobilization; outcome measure

Introduction

Fractures are prevalent in the pediatric population, with rough estimates of at least one in every three individuals experiencing a fracture before adulthood [1]. Upper-limb fractures, specifically distal metaphyseal radius fractures, are the most frequent, with up to 35% of the fractures occurring during childhood and a significantly increasing trend during the past decades [2-5]. Unimodal age distribution and seasonal association linked to physical activity have been hypothesized [6]. Treatment options include in situ cast immobilization or fracture reduction with or without fixation with Kirschner wires (K-wires); however, deciding on either procedure has long been controversial [7]. As stated by Ploegmakers and Verheyen [8], the decision to accept, reduce, or operate on these kinds of fractures relies on the physician's experience and gut feelings. Hence, tolerated age-dependent angulation limits were systematically reviewed and presented as the sole criterion used to determine treatment. Alas, the authors declared methodology limitations due to the lack of adequately designed trials. Consequently, even between experienced pediatric orthopedic surgeons, treatment agreement has merely been considered as fair [9].

Distal radius fractures have a remarkable remodeling potential. It has been a long time since Friberg [10] described the intrinsic ability of epiphyseal plates to change inclination in relation to the forearm axis. Remodeling rate is related to angulation: higher rates occur with more severe deformities, and they progressively decrease as the alignment approaches to normality [11]. Observational designs have shown that fractures up to 29° of angulation and 19 mm of shortening immobilized in situ regain complete alignment after a year of follow-up [12]. In another series of children whose fractures were immobilized without restoring the length of the radius, neutral ulnar variance at final follow-up for the whole sample was reported [13].

Furthermore, usual radius morphology is present within 3 years when alignment is lost, even when the fracture is immobilized without any attempt to regain alignment [14]. In contrast, the effect of age on remodeling potential is doubtful. Shorter times to complete alignment have been reported in younger children, while it is believed that remodeling potential decreases toward skeletal maturity [12,15]. Remodeling potential has been recognized in children up to 14 years of age [16].

Percutaneous K-wire fixation has been recommended, but indications vary [17,18]. Classically, wiring should be considered when perfect reduction is not achievable or in the presence of instability or an intact ulna [19,20]. Recent research suggests that operative interventions are the treatment of choice when some angulation and shortening criteria are not met. Nonetheless, more research is needed to identify those who would benefit the most from fixation [21]. Some specialized centers reserve distal radius corrective osteotomy solely for fracture malunion in children approaching the end of growth or

associated physeal arrest. It is also the treatment of choice for children with congenital dysplastic conditions of the bone [22].

Upper-extremity functionality is the ability to reach, grasp, and manipulate objects to perform daily life activities [23]. Functionality is a major concern in these fractures, as residual angular deformities of the distal forearm decreases the range for pronation and supination [24,25]. Most of the instruments that assess upper-extremity functionality in the pediatric population are specifically designed for children with longitudinal deficiencies, amputations, or neurodevelopmental delay. Nonspecific instruments and questionnaires have been used as functional outcomes in clinical trials comparing interventions for wrist fractures in children [26-28]. Specific instruments for the adult population have also been published; however, several items refer to tasks that a 5-year-old might not properly execute [29,30].

The physical functioning domain of the Patient-Reported Outcomes Measurement Information System (PROMIS) has been available since 2011 for assessing children's functionality among those without any disability. It is a precise and easy-to-administer outcome measurement instrument suitable for children with orthopedic conditions. Children who are 8 years of age or older are able to effortlessly answer the questionnaire unaided. A parent-proxy version is also available for younger children. Upper-extremity functionality is a subdomain of the physical functioning domain. It comprises 29 Likert-type questions that inquire about the difficulty of performing activities during the past week [31].

We propose a noninferiority clinical trial where children who sustained a distal fracture of the radius will be randomly allocated, in the acute setting, to either in situ cast immobilization or closed reduction and cast immobilization, with or without K-wire fixation. The trial's primary goal is to establish whether upper-extremity functionality at 6 months follow-up, measured using the PROMIS physical functioning domain, has not become worse for the former group compared with the latter. Secondarily, range of motion (ROM), alignment, complications, and additional needed treatments will be contrasted.

Methods

Study Design and Procedures

A randomized noninferiority single-institution design is proposed. The trial will take place at a children's hospital that focuses on providing treatment for children with orthopedic and neuromuscular conditions. Following two accepted orthopedic treatments for distal radius fractures, namely cast immobilization in situ or closed reduction and immobilization with or without fixation, functional outcomes, as measured using the PROMIS physical functioning domain, will be compared [14,17,31].

Patient Selection

Children 5 to 10 years of age with a proven acute (ie, within 14 days after injury) metaphyseal fracture of the distal radius (23-M 2-3 or 23r-M 2-3 AO pediatric classification) will be regarded as eligible. Children will be included, granted that the fracture has either shortening from 0 mm to 10 mm or angulation from 10° to 20° in the oblique plane. Children will be excluded when a simultaneous fracture in the same limb (eg, fracture of the ulna) or a pathologic or open fracture is present, or in the scenario of polytrauma (Injury Severity Score ≥16), neuromuscular or metabolic bone diseases, associated neurologic or vascular lesions, or previous infection or fracture of the fractured radius. Children with longitudinal limb deficiencies will also be excluded.

Randomization

Randomization will be performed centrally by the institution's medical research department; therefore, allocation will be concealed to the orthopedic surgeons. The big stick design (BSD) method, with a maximum tolerated imbalance of 2, will be the methodology used for randomization. The BSD method has a very low probability of correctly guessing where the following individual will be allocated compared to other designs [32]. The randomizeR package for R statistical software (version 4.1.0; The R Foundation) will be used [33].

Interventions

Children will be routinely provided with conventional analgesics in the acute setting prior to orthopedic treatment. Afterward, the principal researcher will invite children and parents to enter the trial upon confirming admission criteria. Informed consent, along with informed assent, will be given. Children will be allocated in a 1:1 ratio to either the experimental or control group. In the former group, the fracture will be immobilized without reduction. In the latter group, the fracture will be reduced and immobilized. In the case of instability, K-wires will be used. Instability is considered when, after reduction, alignment is lost: a new displacement greater than 50% or angulation greater than 10°. General anesthesia will be mandatory for the control group. Discharge within 2 hours is the standard practice for both procedures. Casts and K-wires will be removed after 6 weeks.

Endpoints and Follow-Up

Children will be evaluated at about 2 and 6 weeks and 3, 6, and 9 months after randomization. The primary endpoint will be upper-extremity functional assessment using the PROMIS Pediatric Physical Function v2.0 instrument at 6 months [31]. Parents will serve as proxies of children younger than 8 years of age. Children 8 years of age or older will answer the questionnaire by themselves.

Secondary outcomes will be ulnar variance and fracture alignment in the sagittal and coronal planes measured in wrist radiographs with a conventional goniometer and ROM. Plain radiographs will be obtained immediately after orthopedic treatment and during follow-up at 2 weeks, 3 months, and 9 months. Additionally, anesthesia-related adverse effects, pressure ulcers according to the National Pressure Ulcer Advisory Panel, the number of days with oral analgesics, and Dahl classification of pin tract infections will also be registered [34]. Additional treatments, such as radius osteotomy due to deformity, pseudoarthrosis cure, and remanipulation, will also be registered. Figure 1 depicts the flow of the study.

Figure 1. Study design flowchart. ISS: Injury Severity Score; mo: month; PROMIS: Patient-Reported Outcomes Measurement Information System; ROM: range of motion; wk: week.
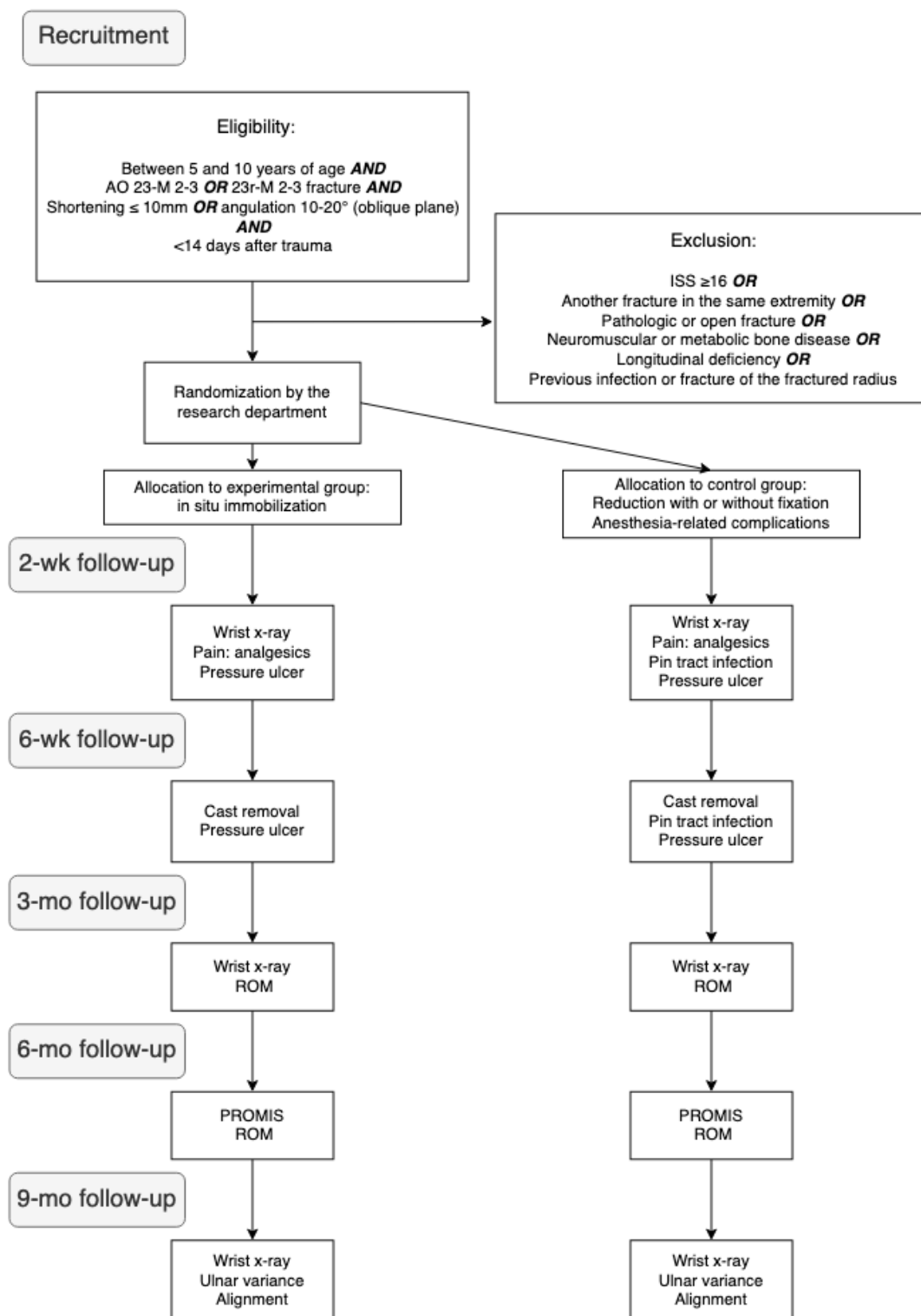
Power Analysis and Sample Calculation

For sample calculations, PROMIS data from children with an upper-extremity fracture were obtained from a recent publication [35]. Assuming a noninferiority threshold of 5 in the physical function domain, a sample of 126 children (63 per group) is required to demonstrate no significant difference between the groups (1-tailed $\alpha=.05$, $\beta=.2$). The sample will be inflated by about 20% to 152, expecting loss to follow-up.

Data Management

Participants' information will be entered into REDCap (Research Electronic Data Capture) software. Registries will be password protected, with access granted to the principal researcher and the study coordinator. Data will be kept at the institution's

medical research department. After completing the study, nonanonymized documents will be preserved for 2 years.

Statistical Analysis

Customary descriptive statistics will be used whether the variables are continuous or categorical. The intention-to-treat principle will be followed. Authors of the scale at Northwestern University will standardize PROMIS scores once data gathering is complete. Afterward, the primary outcome will be evaluated with a *t* test. The noninferiority threshold will be compared to the lower bound of the 95% CI of the mean difference. Continuous outcomes, namely ROM, ulnar variance, fracture alignment, and days with oral analgesics, will be compared with either a *t* test or a Mann-Whitney *U* test conforming to the distribution of the variables. Categorical outcomes, namely anesthesia-related adverse effects, pressure ulcers, pin tract infections, osteotomies, pseudoarthrosis, and remanipulations, will be compared with the Fisher exact test. Early termination of the trial is unlikely, so interim analyses are not being considered; given the proposed design, neither superiority nor futility of the experimental treatment is expected.

Ethics Approval

The ethics committees from Instituto Roosevelt and Pontificia Universidad Javeriana evaluated and approved the trial's protocol, research manual, consent and assent forms, and information brochures (approval Nos. 2021012101-002 and FM-CIE-0416-21) in April 2021.

Results

The authors' institution will fully fund the trial and all related expenses. No external sources of funding are associated with this trial. The trial was registered at ClinicalTrials.gov (NCT05008029). Recruitment commenced in July 2021. As of January 2022, 23 children have been randomized. At the time of enrollment, the principal researcher personally interviews parents and children, and the trial's general characteristics are explained fully. Benefits, such as a closer follow-up (eg,

radiographs, pain, and functionality), are also presented. Authors expect an average of 5 patients to be recruited monthly; therefore, recruitment and analysis should be complete by October 2024.

Discussion

This is the protocol for the first randomized trial that compares functional outcomes of nonreduced versus reduced distal radius fractures in children. To the authors' knowledge, medical literature lacks experimental designs that account for shortening and angulation of this type of fracture in this age group. Cadaveric studies have documented the effects on the motion of the distal radioulnar joint caused by angular deformities related to distal fractures of the radius [25,36]. Necessary pronation and supination ROMs for functional tasks in children and adolescents have also been ascertained with 3D-motion analysis systems [37]. A randomized clinical design would strengthen the evidence of secure shortening and angulation boundaries in terms of functional outcomes and would aid clinicians in the decision-making process in everyday practice.

A strength of this trial is the objective evaluation of the functional outcomes. The PROMIS scale was envisioned with modern measurement theory, which guarantees meaningful statistical results from a Likert-type scale. Further, the PROMIS was explicitly designed for the pediatric population, including previously healthy children who have sustained a wrist fracture [29].

The limitations of this trial are the lack of blinding for evident reasons and generalizability. Children will be recruited and treated in a specialized center. In most institutions in the authors' country that deal with fractures in children, a pediatric orthopedic surgeon is not accessible. The allocation will be open-labeled for patients, parents, and medical staff. This scenario may affect participants' feelings of well-being. However, analyses will be blinded. Finally, cost analyses were never an objective for this trial. The expected results may be relevant in terms of costs to health systems.

Authors' Contributions

MFGR, APBP, JFAGL, and FJAS were responsible for conception and design of the study; data acquisition, analysis, and interpretation; drafting of the manuscript; and approval of the final version. CMP was responsible for critically revising the manuscript, drafting of the manuscript, and acceptance of the final version.

Conflicts of Interest

None declared.

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Abbreviations

BSD: big stick design
K-wire: Kirschner wire
PROMIS: Patient-Reported Outcomes Measurement Information System
REDCap: Research Electronic Data Capture
ROM: range of motion

Protocol

The Effectiveness and Cost-effectiveness of Well Parent Japan for Japanese Mothers of Children With ADHD: Protocol for a Randomized Controlled Trial

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Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder associated with numerous functional deficits and poor long-term outcomes. Internationally, behavioral interventions are recommended as part of a multimodal treatment approach for children with ADHD. Currently, in Japan, there are limited interventions available to target ADHD. Well Parent Japan (WPJ), a new hybrid parent-training program, provides a culturally acceptable and effective way to help support Japanese children with ADHD and their parents.

Objective: This pragmatic multicenter randomized controlled trial aims to provide preliminary evidence about the effectiveness and cost-effectiveness of WPJ evaluated against treatment as usual (TAU) within routine Japanese mental health services.

Methods: Mothers of children (aged 6-12 years) diagnosed with ADHD were recruited from child and adolescent mental health care services at three hospital sites across Japan (Fukui, Fukuoka, and Okinawa). The mothers were randomized to receive immediate treatment or TAU. The effectiveness and cost-effectiveness of WPJ over TAU at the end of the intervention and at 3-month follow-up will be evaluated. The primary outcome is maternal parent domain stress in the parenting role. The following secondary outcomes will be explored: child behavior, including severity of ADHD symptoms; parenting practices; emotional well-being; and the parent-child relationship and maternal child domain parenting stress. Data analysis will follow intention-to-treat principles with treatment effects quantified through analysis of covariance using multilevel modeling. An incremental cost-effectiveness ratio will be used to analyze the cost-effectiveness of the WPJ intervention.

Results: Study funding was secured through a proof-of-concept grant in July 2018. Approval by the institutional review board for the data collection sites was obtained between 2017 and 2019. Data collection began in August 2019 and was completed in April 2022. Participant recruitment (N=124) was completed in May 2021. Effectiveness and cost-effectiveness analyses are expected to be completed by July 2022 and December 2022, respectively. These timelines are subject to change owing to the COVID-19 pandemic.

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Conclusions: This is the first multisite pragmatic trial of WPJ based on the recruitment of children referred directly to routine clinical services in Japan. This multisite randomized trial tests the effectiveness of WPJ in children and families by comparing WPJ directly with the usual clinical care offered for children diagnosed with ADHD in Japan. We also seek to assess and compare the cost-effectiveness of WPJ with TAU in Japan.

KEYWORDS

ADHD; parent training; Japan; New Forest Parent Programme; parent stress management

Introduction

Background

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with an estimated worldwide prevalence of approximately 5% [1]. In Japan, the prevalence estimates range from 2.5% [2] to 10% [3]. The disorder is associated with numerous functional impairments and poor long-term outcomes [4,5] and negatively affects parents' emotional well-being, parenting practices, and the parent-child relationship [6]. Effective interventions for children with ADHD and their families are therefore a high priority [7].

Current clinical guidelines recommend a multimodal treatment approach for ADHD that incorporates both pharmacological and nonpharmacological treatment options [8-10]. Parenting interventions are an example of a recommended nonpharmacological treatment option with proven efficacy in numerous clinical trials [11,12]. Recommended interventions generally provide parents with behavioral strategies aimed at increasing the frequency of appropriate behavior while reducing the frequency of unwanted behavior in children. The needs of families of children with ADHD have received less attention, with only a few studies directly targeting parental well-being [13,14].

Behavioral Interventions for ADHD in Japan

Parent-training interventions are becoming more widely accepted in Japan with increased implementation, especially in community settings. Although efforts have been made to develop programs to address the needs of families of children with a range of neurodevelopmental disorders [15], the availability of interventions specifically designed for ADHD remains limited.

To our knowledge, none of the behavior programs currently being implemented in Japan includes specific elements to address parental coping or emotional well-being. In addition, nothing is known about the cost-effectiveness of behavioral interventions for ADHD in Japan.

Development of Well Parent Japan

For Japanese families, the 8-session group-based New Forest Parenting Programme (NFPP) has been front-loaded with 5 additional sessions designed to increase mother's understanding of ADHD and to address their psychological well-being and readiness to complete the NFPP program. These sessions were added on the recommendation of participants in our pilot and proof-of-concept studies [16] to provide additional support for mothers. Culturally, Japanese mothers are held responsible for their child's behavior and struggle to request support for themselves and their children. These 5 sessions included auxiliary psychoeducation about ADHD and culturally tailored stress management training, cognitive restructuring, strategies for effective communication, and problem-solving skills, adapted from the 9-week parent stress management program [14].

The NFPP has been specifically developed for the treatment of ADHD. In addition to behavioral strategies to manage oppositional and defiant behavior, it includes games and activities targeting purported neuropsychological deficits underlying some of the symptoms of ADHD [17], designed to enhance the child's cognition and self-regulation [18]. Numerous randomized controlled trials (RCTs) have shown that the receipt of NFPP is associated with a reduction in ADHD symptoms and improvements in parental well-being [18-21]. With the support of the program developers, the NFPP sessions were specifically adapted for use with Japanese families [16].

A recent pilot RCT of Well Parent Japan (WPJ) [22] demonstrated that participation in the program was associated with several positive outcomes compared with the wait-list control group; that is, significant reductions in parenting stress, higher levels of parenting self-esteem and use of more effective parenting strategies, reduced child aggression, internalizing problems, and a trend toward reduced inattention. Mothers who participated in WPJ also responded less negatively toward their children. WPJ appears to be an efficacious psychosocial intervention for ADHD in Japan, with the group format and the session content well tolerated.

Objectives

This study aims to extend the results from the pilot RCT [22] to a larger multicenter pragmatic trial to assess the effectiveness and cost-effectiveness of WPJ compared with treatment as usual (TAU) in child and adolescent mental health care services in Japanese hospitals. WPJ will be compared against TAU at the end of the intervention and again after 3 months (short-term follow-up).

The primary objective is to compare the effectiveness of WPJ against TAU on maternal parent domain parenting stress, that is perceived stress in the parent-child dyad arising from

characteristics of the parent, measured with the Parent Stress Index [23,24]. Parent domain stress was selected as the primary outcome measure given WPJ's strong focus on the emotional well-being of participating mothers. Secondary objectives include comparison of the effectiveness of WPJ against TAU in improving child behavior, parental well-being, and parenting practices and to explore the cost-effectiveness of WPJ.

Methods

Study Design

A multisite pragmatic RCT comparing the effectiveness and cost-effectiveness of WPJ (treatment arm) with TAU (control arm). Both arms will be tested at baseline, immediately after the intervention arm completes WPJ at week 14, and at 3 months follow-up; that is, week 26. The study is being carried out through Japanese child and adolescent mental health care services at three different hospital sites in Japan (Fukui, Fukuoka, and Okinawa). Table 1 lists the schedule of parent self-report, teacher, and objective assessments at each time point, whereas Figure 1 summarizes the study design and flow of participants through the trial.

Table 1. Standard Protocol Items: Recommendations for Interventional Trials schedule.

Time point	Screening	Baseline	Intervention	Posttreatment (week 14)	3-month follow-up (week 26)
Enrollment					
Informed consent	✓				
Informed assent-child		✓			
Randomization					
Well Parent Japan			✓		
TAU[a]					
Assessments					
Diagnostic measures					
AQ[b]-child		✓			
CAARS[c]-adult		✓			
Child behavior rating scales—Mother					
SNAP[d] parent		✓		✓	✓
Vanderbilt-Parent		✓		✓	✓
Impairment Rating Scale		✓		✓	✓
Child behavior rating scales—Teacher					
SNAP teacher		✓		✓	✓
Vanderbilt-teacher		✓		✓	✓
Mother self-report scales					
PSI[e]		✓		✓	✓
Parenting scale		✓		✓	✓
PSOC[f]		✓		✓	✓
PLOC[g]		✓		✓	✓
Family strain		✓		✓	✓
BDI-2[h]		✓		✓	✓
Mother-child interaction measures					
SCIFF[i] and SCIPD[j]		✓		✓	
R-FMSS[k]		✓		✓	
Cost-effectiveness interview					
JHEC[l]		✓		✓	✓

[a]TAU: treatment as usual.

[b]AQ: Autism Quotient.

[c]CAARS: Conners Adult ADHD Rating Scales.

[d]SNAP: Swanson, Nolan, and Pelham Scale.

[e]PSI: Parenting Stress Index.

[f]PSOC: Parenting Sense of Competence.

[g]PLOC: Parental Locus of Control.

[h]BDI-2: Beck Depression Inventory-2.

[i]SCIFF: System for Coding Interactions and Family Functioning.

[j]SCIPD: System for Coding Interactions in Parent-Child Dyads.

[k]R-FMSS: Revised Five-Minute Speech Sample.

[l]JHEC: Japanese Health Economic Cost.

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Figure 1. Study design and participant flow. R-FMSS: revised Five-Minute Speech Sample; RA: research administrator; TAU: treatment as usual; WPJ: Well Parent Japan.
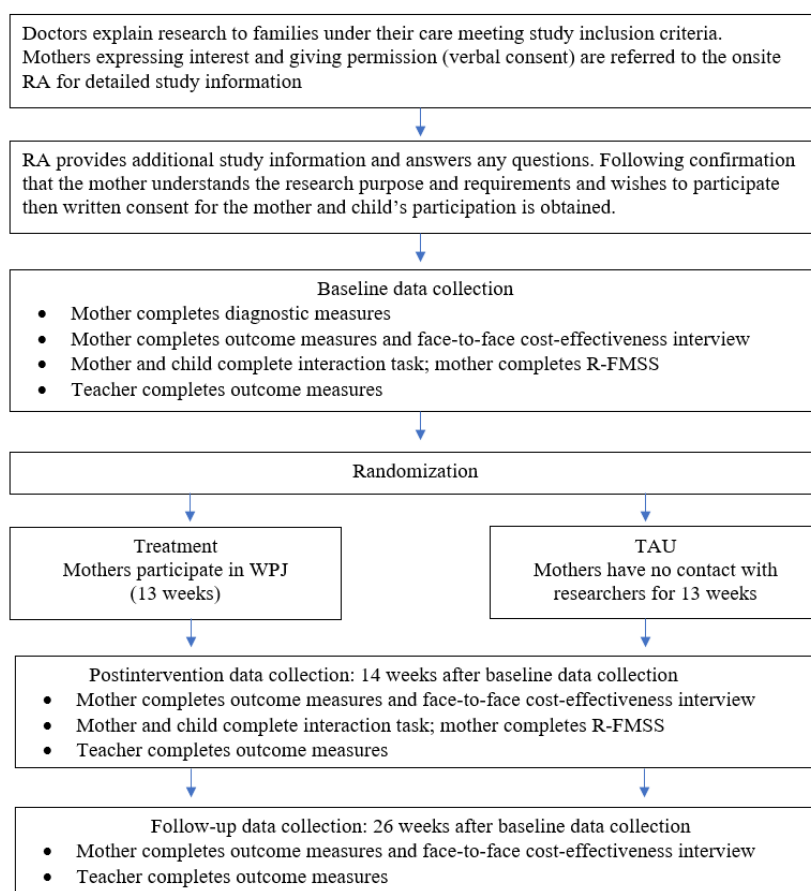
Trial Registration

The study was retrospectively registered with the International Standard Randomised Controlled Trial Number after the first of 3 waves of participant recruitment (trial registration number: ISRCTN66978270). Registration delay was an unintended consequence of ill health of one of the principal investigators, which disrupted study preparation. This oversight was identified after the first wave of participant recruitment and the trial was subsequently registered. Ethical approval for the trial, as described in the protocol, was obtained at all intervention sites before participant recruitment.

Sample Size Calculation

Parent domain parenting stress score at week 14 is the primary outcome measure and informed our sample size calculation. On the basis of the results of our pilot RCT [22], to detect a 0.5 standardized effect size at week 14 using 80% power at a 2-tailed .005 significance level, assuming the correlation between the baseline and follow-up measures is 0.35, 112 participants were required. After adjusting for a 15% attrition rate, the target sample size was inflated to 132.

Sample Selection

Overview

Mothers of children with a clinical diagnosis of ADHD [1] were identified by physicians working in hospitals or community clinics linked to the 3 research sites.

Inclusion Criteria

Mothers fluent in Japanese (reading and writing), parenting a child aged 6-12 years diagnosed with ADHD and attending elementary school, and for whom participation in a group-based behavioral intervention for the mother is not contraindicated were eligible for inclusion in the study. In addition, mothers of children diagnosed with ADHD and autism spectrum disorder were eligible to participate. Referring doctors were asked to exercise clinical judgment regarding mothers' ability to understand the program content and their suitability to participate in a group program.

Exclusion Criteria

Limited pragmatic speech or a functional intellectual disability in the child would exclude a family from participating in the study. Current or recent (ie, within 2 months of the starting date of WPJ) participation in another parenting program would also exclude participation. Mothers of children receiving medication for the management of their ADHD symptoms were asked to keep their child's medication constant throughout the study. Medication status changes will be recorded but will not result in the family being removed from the trial.

Consent and Randomization

Physicians at the 3 hospital study sites confirmed the eligibility of the mothers of their patients with ADHD to participate in the study. They briefly explained WPJ and the requirements for research participation. Interested mothers were referred to the

research site administrator for a detailed verbal and written explanation of the study procedures, including randomization to WPJ or TAU and the need to access the child's medical records. Those who agreed to participate provided written consent for their own participation and their child's participation. Written consent from teachers was obtained by mail. Children's informed consent was obtained at the first laboratory assessment session.

Baseline outcome measures were obtained from mothers and teachers, including the Revised Five-Minute Speech Sample (R-FMSS) and the parent-child interaction task, before randomization to the study arm (Table 1 provides the full list of baseline measures). Teachers remained blind to family treatment group allocation. When sufficient participants were recruited at a site (a minimum of 12), they were randomized to the study arm, that is, block randomization at each site, using a computer random number generator operated by DD.

Confidentiality

All participants were assigned an ID number at each site. Raw data were stored in locked storage at the collection sites. Only anonymized data were shared with researchers at the primary research site (Okinawa Institute of Science and Technology [OIST]) for database entry and analyses.

Intervention

Arm 1: WPJ

Participants received a 13-session group-based intervention for parents of children with ADHD. This includes an orientation to the intervention, psychoeducation about ADHD, 4 sessions devoted to enhancing mothers' psychological functioning adapted from the Parent Stress Management for ADHD program [14], followed by 8 sessions of behavior management based on the core components of the NFPP [18-22]. A summary of the session contents is presented in Table 2. Mothers and teachers completed outcome measures, including parent domain parenting stress, before randomization, after the intervention, and again after 3 months. Table 1 provides a complete list of the measures completed at each time point.

The 2-hour WPJ sessions are run by 2 group leaders at each site. Participants who are unable to attend a group session are invited to a 30-60 catch-up session before the next group session. The catch-up sessions are limited to a maximum of 2 sessions per participant. To maintain treatment fidelity, the groups are run according to the WPJ leader's manual. At the end of each session, the leaders complete a checklist of the topics covered. Missed information is presented at the beginning of the next group session. Approximately 20% of the sessions delivered at each site will be randomly selected to confirm fidelity. These recordings will be reviewed independently against a checklist of the key and minor points to be covered in each session. The percentage of inclusion of major and minor points will be calculated and reported.

Group leaders receive supervision from SS, a certified trainer in both interventions that comprise WPJ. Supervision sessions for the first wave of groups lasted 60-120 minutes, depending on the experience and requirements of therapists. The frequency and duration of supervision were reduced to 60 minutes biweekly thereafter. Supervision of the first 2 treatment groups was conducted separately by site. Group supervision, that is, 3 sites together, was planned from the beginning of the third group. All supervision took place via electronic platforms.

Table 2. Well Parent Japan session content.

Session	Content	Session function
1	Orientation to the program: What is ADHD[a], part 1	Psychoeducation
2	Stress management, relaxation training	Mothers emotional health
3	Cognitive restructuring	Mothers emotional health
4	Problem solving	Mothers emotional health
5	Communication skills	Mothers emotional health
6	What is ADHD, part 2; Recruiting attention, positive communication, praise	Psychoeducation; New Forest Parenting Programme
7	Zone of proximal development, choices, clear messages, countdowns, using a timer	New Forest Parenting Programme
8	Review of session 7 skills, use of play	New Forest Parenting Programme
9	House rules, routine, boundaries, reward, and punishment	New Forest Parenting Programme
10	Review of session 9, review of ADHD symptoms	New Forest Parenting Programme
11	Temper tantrums (time out, quiet time), anticipating, avoiding conflict	New Forest Parenting Programme
12	Emotion and language, child relaxation	New Forest Parenting Programme
13	Social stories, mindfulness, wrap up session	New Forest Parenting Programme

[a]ADHD: attention-deficit/hyperactivity disorder.

Arm 2: TAU

TAU within the context of this trial may consist of many forms of intervention, including the following: medical and psychological examinations, pharmacological treatment, ADHD psychoeducation and parenting guidance, psychological counseling, play therapy for the child, group-based cognitive training for the child, telephone counseling for parents and teachers, and parent and teacher conferences or anything deemed clinically necessary. Mothers in the TAU arm had no contact with the research team from randomization until the treatment group (arm 1) completed the 13-week WPJ program. At this time, they attended a second laboratory assessment session with their child and completed all questionnaires. They completed the questionnaires again 3 months later. Site principal investigators will review and report the treatment options provided to all participating families (WPJ and TAU groups) through the referring hospitals during the trial period. This information will be included in the primary trial paper. The treatment group parents are given a 1000-yen (US $8.5) voucher per intervention session attended to help cover travel costs. All parents received a 2000-yen (US $17) voucher for the prelaboratory and postlaboratory assessment sessions and a further 1000-yen (US $8.5) voucher for the third cost-effectiveness interview. Teachers were given a 1000-yen (US $8.5) voucher each time they filled out the study questionnaires.

Measurements

Diagnostic Measures

At baseline, autistic traits in the children were measured using the Autism-Spectrum Quotient [25]. This measure has excellent psychometric properties [26] and has been translated into Japanese and evaluated in both children [27] and adults [28]. The participating mothers' ADHD traits are assessed using the Conners Adult ADHD Rating Scale [29] to better quantify the sample. The Japanese version of the scale has good psychometric properties [30].

Outcome Measures

Overview

Some of the measures (ie, the Vanderbilt Assessment Scale-Parent and Teacher, Parenting Sense of Competence Scale, Parental Locus of Control Scale, Family Strain Index, and Impairment Rating Scale) were translated into Japanese by the first author (SS) and independently back-translated by 2 bilingual US trained counseling psychologists.

The primary outcome measure was the mother's reported parent domain parenting stress. This was assessed using the 78-item Japanese language version of the Parenting Stress Index [23]. The Parenting Stress Index assesses perceived stress in the parent-child dyad and yields the parent domain (sources of stress related to parent characteristics) and child domain stress (sources of stress related to child characteristics) scores and total stress score. The Japanese version of this measure has good psychometric properties [24].

Secondary outcome measures include parent and teacher ratings of the child's behavior and mothers' self-reports of their parenting style, competence, locus of control, family strain, mood, and objective measures of parent-child relationship quality. The measures are listed in Table 3.

All outcome measures, except for relationship quality, are administered at baseline, post treatment (week 14), and at the 3-month follow-up (week 26). Relationship quality measures are assessed at baseline and week 14 only. Teachers, but not parents, are blinded (probably) to parents' group membership; that is, parents are asked not to discuss their group assignment with the child's teacher.

Table 3. Primary and secondary outcomes, measures, and raters.

Outcomes	Measures	Raters
Primary		
Parent domain stress	Parent Stress Index	Mother
Secondary		
Child behavior		
ADHD[a] symptoms	Swanson, Nolan, and Pelham Scale	Mother and teacher
Impairment	Impairment Rating Scale	Mother
Other	Vanderbilt Assessment Scale	Mother and teacher
Parenting practices or attitudes		
Management practices	Parenting Scale	Mother
Locus of control	Parental Locus of Control	Mother
Sense of competence	Parenting Sense of Competence	Mother
Emotional well-being		
Depression	Beck Depression Inventory-2	Mother
Caregiver strain	Family Strain Index	Mother
Child domain stress	Parent Stress Index	Mother
Mother-child relationship		
Parent-child interactions	Pasta making task; SCIFF[b], SCIPD[c]	Independent coders
Expressed emotion	Revised 5-minute speech sample	Independent coders

[a]ADHD: attention-deficit/hyperactivity disorder.

[b]SCIFF: System for Coding Interactions and Family Functioning.

[c]SCIPD: System for Coding Interactions in Parent-Child Dyads.

Parent and Teacher Ratings of Child Outcomes

The 26-item Swanson, Nolan, and Pelham Scale [31] is used to measure the child's ADHD and oppositional defiant disorder symptoms. The Japanese translation has excellent psychometric properties [32]. The Parent and Teacher performance scales from the Vanderbilt Assessment Scale [33] are used to assess the child's behavioral and academic performance at school. The 8-item Impairment Rating Scale [34] is used to assess parents' perceptions of child impairment across a range of domains. This measure demonstrates acceptable psychometric properties including good temporal stability [34].

Parent Self-report Outcomes

Parenting practices are assessed using the 30-item Parenting Scale [35]. The Japanese version has a 2-factor solution and shows good internal consistency for overreactivity and low to moderate consistency for laxness in control and clinical samples [36]. The 17-item Parenting Sense of Competence Scale [37,38] is used to assess parenting competence or efficacy. The Japanese translation demonstrated adequate internal consistency in a normative Japanese sample [39]. The 47-item Parental Locus of Control Scale [40] is used to assess parents' perceived locus of control in child-rearing situations. The internal consistency of this measure in our pilot RCT was good [22]. The Family Strain Index [41] is used to assess the effects of ADHD on families. Items 3 and 5 of this 6-item index have been revised to make the descriptions more culturally appropriate for

Japanese parents. The second edition of the Beck Depression Inventory [42] is used to assess the mothers' levels of depression. The Japanese translation is psychometrically robust and can be used to measure depressive symptoms in Japanese populations [43].

Parent-Child Relationship Outcomes

The quality of mother-child interactions is evaluated through direct observation of behavior during a cooperative task. Each mother-child pair works together for 15 minutes to make pasta using the ingredients and equipment supplied. The interaction is video recorded for later coding using selected parent and child codes from the System for Coding Interactions and Family Functioning [44] and the System for Coding Interactions in Parent-Child Dyads [22,45]. Maternal expressed emotion is measured using the R-FMSS [46]. Parents speak for 5 minutes, without interruption, about their child and their relationship. The R-FMSS has demonstrated excellent psychometric properties [46]. Trained raters, at OIST, blind to group membership and time point, will code the parent-child interactions and the R-FMSS.

Economic Evaluation Measures

Health economic costs are measured using a study-specific measure (Japanese Health Economic Costs [JHEC]) to collect all available information to estimate the child's service utilization costs (medical treatment, education, nursing, and rehabilitation) and parents' opportunity costs for their child's

care. The JHEC is administered at baseline, after the intervention, and at 3-month follow-up. The JHEC was developed with reference to the Client Service Receipt Inventory [47].

Data Management Plan

All the participants are assigned an ID number at the trial site when they consent to participate in the study. This number is used on all questionnaires. Each site will maintain a list allowing them to link names and ID numbers.

Data collection at each clinical site is supported by a dedicated research assistant with oversight and support from the trial team at OIST. Anonymized questionnaire data will be scanned, password-protected, and saved in a shared Dropbox with the researchers at OIST. Video and audio recordings will be password-protected and saved in the same shared Dropbox. The OIST trial team will transfer the data from the shared Dropbox folder to secure electronic storage at OIST as soon as it is received. The OIST team will not have access to the data linking lists from any site. Data entry into a password-protected electronic database will be carried out by the trial staff at OIST.

Raw data (possibly containing names) will be maintained in secure storage at each site for 10 years after study completion. Access to these data is limited to the site principal investigator and dedicated research assistant. Once all data analyses are complete and manuscripts are prepared, OIST-maintained electronic password-locked files will be wiped. OIST will retain the anonymous password-protected data for 10 years after manuscript publication. GT will be responsible for the supervision of stored data.

Data analysis will be carried out by the trial statistician using an anonymized electronic database (see the Statistical Analysis section). Although there are no plans to make the data publicly available, requests for access to the data will be considered on a case-by-case basis, subject to Japanese law.

Safety Considerations

Therapists are asked to record and report any potential adverse events using a standard template, and the importance of adverse events is highlighted during supervision sessions. Any adverse events are required to be reported to the approving ethics committees. In addition, all adverse events will be reported to the independent data and ethics monitor and will be evaluated, recorded, and discussed in the final paper.

Statistical Analysis

Effectiveness Analyses

The analysis will be conducted on an intention-to-treat basis. Data will be explored first, and all variables will be summarized by treatment arm across measurement time, with mean (SD) presented for normally distributed measures, median (IQR) for skewed data, and frequency (%) for each observed level of categorical variables. Treatment effect estimates and their precision on the primary and secondary outcomes will be quantified through analysis of covariance modeling by means of multilevel modeling with baseline measure, arm, time, and interaction of arm × time included as covariates and participant

as a level 2 analytical unit. As participants are recruited from different locations, the site will be included as a higher-level analytical unit if exploratory data analysis shows greater variability at the site level. Skewed outcome variables will be transformed for parameter modeling. Missing value information will be explored first to inform the missing value imputation by means of a multiple imputation procedure for multilevel data under a missing-at-random assumption. The results from the observed data will be examined to check the robustness of the treatment effect estimates sensitive to missingness. Stata statistical software (version 17; StataCorp) [48] will be used for data analysis. A statistical analysis plan, including all the analytical details, will be conducted before the data are locked for final analysis.

An independent data and ethics monitor is responsible for reviewing the trial progress and data analysis once data collection is complete. The monitor is independent of both the study team and sponsor OIST.

Cost and Cost-effectiveness Analyses

The health economic evaluation will focus on the three following key areas:

1. Costs of the intervention: an average cost per intervention will be determined. This analysis will include staffing costs (hourly rate × time) from study time sheets, capital costs (eg, rooms and overheads), and consumables. Parent time costs will not be included in this analysis.
2. Cost-effectiveness: an incremental cost-effectiveness ratio will be used to analyze the cost-effectiveness of the WPJ intervention. The incremental cost-effectiveness ratio will be able to identify differences in costs such as health care and educational utilization between the intervention and TAU arms of the trial divided by the treatment effect, the proportion of participants meeting the criteria for positive treatment response (changes in maternal stress as measured by the Parenting Stress Index [24]) and child ADHD symptoms as measured by the index of the parent-completed SNAP [32]. The JHEC and medical receipts provided by the participants will be used to track the familial and societal costs of health and educational service resource use in both study arms. This study will seek to use a number of routine health service costs, where possible, using data from the Japanese Medical Fee Points system [49,50]. This analysis will be completed with and without family borne costs. Any loss of earnings will be calculated using the average wage rate.
3. Impact of intervention on service use: this study will measure the retrospective change in resource use across both trial arms from 3 months before each assessment point. This analysis will use data from the JHEC and medical receipts provided by the participants.

Data Sharing Statement

Although there are no plans to make the data publicly available, requests for access to the data will be considered on a case-by-case basis, subject to Japanese law.

Ethics Statement

The study has been approved by the OIST Graduate School Human Subject Research Review Committee (reference number: HSR-2019-014) following receipt of approval at each study site: University of Fukui Hospital (reference number: 20170085), Kurume University Hospital (reference number: 19052), and National Hospital Organization Ryukyu Hospital (reference number: 31-5).

Results

The Training and Nurturing Support for Mothers (TRANSFORM) study began in July 2019 with therapist training, and a practice intervention group was run at each site between July 2019 and October 2019. Trial recruitment began in July 2019 and was completed in May 2021. The timeline of the study has been extended because of the limitations imposed by the COVID-19 pandemic. This included a 5-month postponement of the second treatment group (all 3 sites) and suspension of the third treatment group (2 sites). At the time of protocol submission, the suspension remained in place at 1 site. These suspensions will be reported in the final paper.

Discussion

Principal Findings

This trial addresses the need to investigate the effect of nonpharmacological treatments for children with ADHD in everyday clinical practice in Japan. This trial combines 2 evidence-based interventions for families of children with ADHD within a hybrid program that has been developed and piloted to provide a culturally adapted and appropriately delivered behavioral intervention for families of children with ADHD in Japan. Combining support for families of children with ADHD with behavioral strategies that aim to target and alter the developmental trajectory of ADHD has implications for researchers and clinicians beyond Japan. The results will be reported at national and international conferences, published in peer-reviewed journals, disseminated to Japanese health care professionals, and communicated digitally to Japanese and international ADHD advocacy groups.

This is the first trial of WPJ based on the recruitment of children referred directly to routine clinical services in Japan. It is also the first pragmatic trial that combines the NFPP with specific and direct intervention support for parents of children with ADHD. In this sense, this multisite randomized trial tests the effectiveness of WPJ with children and families in a clinical setting for which the intervention is ultimately intended with very few exclusion criteria. It also compares WPJ directly with the usual clinical care offered for children diagnosed with ADHD in Japan. We also seek to assess and compare the cost-effectiveness of WPJ with that of TAU in Japan.

The stigma associated with ADHD in Japan and unfamiliarity with group-based interventions for ADHD posed challenges to recruitment. The COVID-19 pandemic continues to affect the trial, with local and national lockdowns and restrictions affecting recruitment and disrupting the process of delivering the intervention. The decision to provide supervision via web-based platforms ensured that this aspect of the study has not been disrupted by the COVID-19 pandemic. In principle, the group delivery model is a challenge for parents of children with ADHD, who often perform better with individual therapy, where a bespoke response can address the heterogeneity of the child's ADHD. However, in the proof-of-concept study, a group model was requested by Japanese mothers [16]. Culturally, it was felt that an individual approach might not be appropriate, which was supported by the pilot RCT that demonstrated considerable levels of efficacy against a wait-list control group [22] using a group-based mode of delivery. Establishing the cost-effectiveness of the intervention has also been challenging, as the academic discipline of health economics is not well-established in Japan. In addition, the process for calculating society and family borne costs, such as health care use in Japan, is complex, where health care costs are based on a point system that does not easily lend itself to economic evaluation. The COVID-19 pandemic has likely influenced family health service use, with families limiting their use of, and visits to, health care providers. We assume similar effects across the 2 study arms.

Limitations

In recruiting through hospital clinics, the study does not include self-referred families in the community, possibly reducing the generalizability of the findings. Having clinic doctors (in Japan, the diagnosis of ADHD is limited to medical doctors; thus, referrals to the research were made by those responsible for the diagnosis of ADHD in the children) identify eligible families may have resulted in the referral of those dealing with more severe or comorbid ADHD, or mothers deemed most in need or most likely to benefit from participation in WPJ. Nonetheless, this is consistent with the aim of the research; that is, to evaluate WPJ within the Japanese child and adolescent mental health care system with a view toward future implementation of the intervention within this system. As a pragmatic trial, study site differences will be evaluated; however, we do not control for the effects of group leader skills on treatment outcomes. All group leaders are provided with the same training and are supervised by SS, which should help minimize differences in program delivery. The registration of the protocol was retrospective, and participant recruitment is now complete. No changes were made in the study protocol.

Authors' Contributions

Conflicts of Interest

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
JHEC: Japanese Health Economic Costs
NFPP: New Forest Parenting Programme
OIST: Okinawa Institute of Science and Technology
R-FMSS: revised Five-Minute Speech Sample
RCT: randomized controlled trial
TAU: treatment as usual
WPJ: Well Parent Japan

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Protocol

Early Detection of Cardiotoxicity From Systemic and Radiation Therapy in Patients With Breast Cancer: Protocol for a Multi-Institutional Prospective Study

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Abstract

Background: The incidence of breast cancer is rising worldwide. Recent advances in systemic and local treatments have significantly improved survival rates of patients having early breast cancer. In the last decade, great attention has been paid to the prevention and early detection of cardiotoxicity induced by breast cancer treatments. Systemic therapy-related cardiac toxicities have been extensively studied. Radiotherapy, an essential component of breast cancer treatment, can also increase the risk of heart diseases. Consequently, it is important to balance the expected benefits of cancer treatment with cardiovascular risk and to identify strategies to prevent cardiotoxicity and improve long-term outcomes and quality of life for these patients.

Objective: This CardioTox Breast study aims to investigate the use of cardiac imaging, based on cardiac magnetic resonance and echocardiography, and to identify associated circulating biomarkers to assess early tissue changes in chemo-induced and radiation-induced cardiotoxicity in the time window of 12 months after the end of radiotherapy in patients with breast cancer.

Methods: The CardioTox Breast trial is a multicenter observational prospective longitudinal study. We aim to enroll 150 women with stage I-III unilateral breast cancer, treated with breast conserving surgery, who planned to receive radiotherapy with or without systemic therapy. Baseline and follow-up data include cardiac measurements based on cardiac magnetic resonance imaging, echocardiography, and circulating biomarkers of cardiac toxicity.

Results: This study details the protocol of the CardioTox Breast trial. Recruitment started in September 2020. The results of this study will not be published until data are mature for the final analysis of the primary study end point.

Conclusions: The CardioTox Breast study is designed to investigate the effects of systemic and radiation therapy on myocardial function and structure, thus providing additional evidence on whether cardiac magnetic resonance is the optimal screening imaging for cardiotoxicity.

Trial Registration: ClinicalTrials.gov NCT04790266; https://clinicaltrials.gov/ct2/show/NCT04790266

International Registered Report Identifier (IRRID): DERR1-10.2196/31887

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KEYWORDS

breast cancer; cardiotoxicity; cardiac diagnostic imaging; radiotherapy; chemotherapy

Introduction

Incidence of breast cancer is rising worldwide. Due to developments in systemic and local therapies, median survival of early breast cancer patients has increased [1], resulting in decreased risk of local recurrence and breast cancer death, as well as longer life expectancy [2-4]. Consequently, the reduction in treatments' side effects and the improvement of patients' quality of life are becoming increasingly important in treatment prescription and planning. The most frequent toxicities described in literature are neurological, hematological, gastrointestinal, cutaneous, and cardiological ones. In the last decade, great attention has been paid to prevention and early detection of cardiotoxicity because heart diseases are the main nononcological cause of death in these patients [5].

Our understanding of the pathophysiology and natural history of iatrogenic cardiotoxicity remains limited, and the diagnosis is carried out frequently only when cardiovascular disease presents clinically [6]. Cardiovascular complications from cancer therapies are widely heterogeneous (eg, myocardial dysfunction, heart failure [HF], coronary artery disease, valvular disease, arrhythmias, and arterial hypertension). Myocardial dysfunction and HF are the most frequent complications after breast cancer treatments. It is believed that cardiotoxicity is a continuous phenomenon beginning with myocardial injury and changes in myocardial strain; subsequently, a progressive left ventricular ejection fraction (LVEF) decline may gradually lead to symptomatic HF [7]. If HF treatment is delayed, it is possible that the cardiac function may never restore to what it was at baseline [8]. It is therefore fundamental to distinguish asymptomatic patients who are at risk for cardiotoxicity and, if possible, give them protective treatment for avoiding side effects.

Therefore, cardio-oncology is a rapidly developing subspecialty within cardiology, which aims to optimize the diagnosis and management of cancer treatment cardiac complications [9].

The American Society of Echocardiography and the European Association of Cardiovascular Imaging define cardiotoxicity as a decline of LVEF ≥10% with a final LVEF <53%.

Anthracyclines-based systemic therapy is considered as the prototype of type I cardiotoxic agents [10]. It is believed that agents belonging to this group cause irreversible continuous progressive decline in LVEF, which is dose dependent and can lead to dilated cardiomyopathy [11]. Anthracycline-induced cardiotoxicity may present during or immediately after the infusion (acute), within the first year of treatment (early) and years after treatment (late) [12,13].

Trastuzumab, an anti-human epidermal growth factor receptor 2 (HER2) agent is considered a standard treatment in breast cancer overexpressing HER2. As a type II cardiotoxic agent, it induces cardiotoxicity that is usually reversible with its interruption or with HF treatment. Toxicity from type II agents is not related to cumulative dose and usually develops during treatment [11].

The incidence of anthracycline-related cardiotoxicity is 3%-48% while it varies from 1.7% to 20.1% with trastuzumab.

Due to their potential cardiotoxicity, anthracycline and trastuzumab are usually not administered concurrently [11].

Radiotherapy (RT) can also increase the risk of several heart diseases [14]. The relative risk varies from 3.5 (for left-sided) to 1.2 (for right-sided) breast cancer [15]. Radiation-induced cardiotoxicity usually develops even more than 10 years after RT with an interstitial myocardial fibrosis [8,15]. RT may induce ischemic heart disease through the development of severe atherosclerotic and nonatherosclerotic disease, complicated by plaque rupture and thrombosis, and potentially with coronary spasm [11,16]. Cardiac damage has a strict correlation with the mean heart dose, with a 7.4% increase in relative risk of major cardiac event for each additional 1 Gy of mean heart dose [15]. The mean heart dose has to be as low as possible, almost 0 Gy, albeit at the critical portions of the heart, as left ventricle or left anterior descending artery can receive more than 40 Gy in a very limited volume [17]. Technological developments in RT techniques such as intensity-modulated RT or volumetric modulated arc therapy and deep inspiration breath hold have allowed a reduction in cardiac doses, particularly for patients with left-sided breast cancer, lowering the risk of cardiotoxicity.

A synergistic effect on cardiac risk between left breast RT and cardiotoxic chemotherapy has been described even if its actual incidence is difficult to quantify and evaluate.

Cardiotoxicity can be detected by different diagnostic methods. Circulating biomarkers could detect and predict cardiotoxicity. The 2014 American Society of Echocardiography guidelines the recommend measurement of troponin at baseline, before systemic therapy and 24 hours after, to aid in the detection of subclinical cardiotoxicity.

Troponin and brain natriuretic peptide (BNP) have been investigated in many trials, but unfortunately with different results. Several studies have shown that the elevation of Troponin I may predict the development of future LVEF depression, and N-terminal pro b-type natriuretic peptide can predict the risk for radiation-induced cardiotoxicity [7,8]. Of note, 1 study has showed that a reduction in longitudinal strain and an increase in high-sensitivity troponin, after the end of anthracycline therapy, predicted future left ventricular dysfunction [7].

Several epidemiologic studies have shown a significant association between elevated plasma concentrations of high-sensitivity C-reactive protein (hs-CRP) and the prevalence of underlying atherosclerotic vascular disease, as well as the risk of recurrent cardiovascular events among patients with established disease and apparently healthy individuals [18-20].

In 2012, Onitilo and his colleagues [21] published a pilot study about hs-CRP as a biomarker for trastuzumab-induced

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cardiotoxicity. They showed that abnormal hs-CRP (≥3 mg/L) predicted decreased LVEF with a sensitivity of 92.9%.

Cardiac biomarkers could also be potential candidates to monitor cardiac damage after RT. Echocardiography (ECHO) is currently the standard method for detecting cardiotoxicity, usually by monitoring serial LVEF. A 3-dimensional modality is preferred to a 2-dimensional one because of better reproducibility [22]. LVEF is not directly correlated to early toxicity and usually decreases months after myocardial cell injury has happened. A recent advanced echocardiographic technique, automated 2-dimensional speckle tracking echocardiography (cardiac strain), has been used for detecting and quantifying subclinical changes in left ventricular strain and function. The use of global longitudinal strain (GLS) by speckle tracking echocardiography is strongly recommended because of its feasibility and biological reproducibility [22]. GLS is changing earlier than LVEF, corresponding to myocardial deformation; consequently, this technique could diagnose cardiotoxicity more quickly [8,23].

Current guidelines suggest ECHO at baseline, after the end of anthracycline therapy, before the start of trastuzumab treatment, and every 3 months during trastuzumab treatment.

Cardiac magnetic resonance (CMR) is the most accurate methodology for the evaluation of volumes and function of heart chambers. Additionally, it is exceptionally capable of providing myocardial tissue characterization, including the presence and extension of myocardial oedema (reflected in increased T2-weighted magnetic resonance imaging), hyperemia (assessed by an increment in early enhancement), and fibrosis (visualized with late enhancement techniques) [24].

Serial CMR imaging showed reduction in LVEF, 12 to 24 months after therapy, in women treated for breast cancer with anthracycline-based chemotherapy. Few recent studies have suggested that LVEF could start to decline earlier; however, the prognostic implications of these changes are not yet known. Recent preliminary experimental data suggest that the decline in contractile function is preceded by CMR evidence of myocardial oedema with T2 (transverse relaxation time) sequences and T2 mapping [25-27]. Furthermore, T1 (longitudinal relaxation time) mapping is a promising technique to quantify morphologic tissue injuries, such as interstitial or diffuse myocardial fibrosis. If treated with radiation therapy, patients diagnosed with breast cancer have an increased risk of acute asymptomatic pericardial effusion, which can also be detected by CMR. CMR is the most sensitive and reproducible measure of LVEF.

When biomarkers and cardiac imaging methods (eg, GLS on ECHO and oedema on CMR) are integrated, we could detect preclinical cardiotoxicity and prevent left ventricular dysfunction.

Unfortunately, thus far, these studies have had a small sample size, and therefore we cannot draw any practice changing conclusion.

In our opinion, it is important to better define high-risk patients who need intensive cardiovascular screening during and after cardiotoxic treatment. Our purpose is to detect toxicity when it is still subclinical and reversible and to prevent its deterioration with protective drugs administered to "the right patient at the right time."

Methods

Study Design

This CardioTox Breast study (registered with ClinicalTrials; registration number NCT04790266) is a multicenter, observational, prospective, longitudinal study that includes female patients with left-breast and right-breast cancer treated with postoperative RT, with or without chemotherapy or hormonal therapy after primary breast conservative surgery. The patients will be followed for at least 1 year after RT, with cardiac imaging and circulating biomarkers (further detailed below). Three investigating centers are involved in the study: the Oncology Institute of Southern Switzerland (Bellinzona, Switzeralnd), the North Estonia Medical Center (Tallinn, Estonia), and Fondazione IRCCS Policlinico San Matteo (Pavia, Italy). Furthermore, Cardiocentro Ticino is involved in the study as the center of analysis of CMR and echocardiography in Switzerland.

Study Population

We aim to enroll 150 female patients aged ≥18 years with stage I-III unilateral breast cancer treated with breast conserving surgery and planned to receive radiation therapy with or without systemic therapy.

Eligibility Criteria

Inclusion criteria are as follows: (1) written informed consent must be obtained before any assessment is performed; (2) female, aged ≥18 years at visit 1; (3) performance status Eastern Cooperative Oncology Group (ECOG) 0-1; (4) stage I-III histology proven breast cancer (Swiss center allows inclusion of ductal carcinoma in situ); (5) adjuvant RT and neoadjuvant anthracycline and/or trastuzumab-based therapy with or without hormonal therapy; and (6) negative pregnancy test (plasma human chorionic gonadotropin [hCG]) for all female participants of childbearing potential (ie, not permanently sterilized—posthysterectomy or tubal ligation status).

Exclusion criteria are as follows: (1) known metastatic spread of any cancer; (2) known active or recurrent hepatic disorder (cirrhosis, hepatitis), aspartate aminotransferase to alanine aminotransferase ratio of 2 x upper limits of normal; (3) renal function decrease (estimated glomerular filtration rate <30 ml/min); (4) known coronary artery disease; (5) angina pectoris; (6) positive or missing pregnancy test (pre- and perimenopausal women) at enrollment visit; (7) patients with baseline LVEF <53% and GLS <15%; and (8) patients with pacemaker.

Pretreatment Evaluation

The patients will be recruited in participating centers. The investigators ensure that women will meet the inclusion criteria in the study and sign the written informed consent. On inclusion, patient demographics and proper medical history, including current medications and family history of cardiovascular disease will be recorded. A physical examination will be performed, including the measurement of blood pressure and pulse rate.

A baseline assessment will be conducted before the start of adjuvant treatment by checking CMR, ECHO, an electrocardiogram to detect any arrhythmia, and blood sampling to analyze circulating biomarkers.

CMR Protocol

CMR will be performed with Siemens Skyra 3T or a 1.5T scanner. All patients will undergo a standard protocol, including late gadolinium enhancement for estimated glomerular filtration rate >30 ml/min. For native T1 and postcontrast mapping, basal, midventricular, apical short axis, and 4-4-3 and 2 chamber apical images will be acquired by "ECG-triggered Modified Look-Locker Inversion recovery" sequence. Additionally, T2 mapping (T2-prepared True-FISP [fast imaging with steady-state free precession]) will be acquired on the same plane. The CMR images and maps will be analyzed offline. Late gadolinium enhancement will be quantified on short-axis stacks using a semiautomatic approach.

Echocardiography

Transthoracic echocardiography will be performed by using a Philips Epiq or General Electric Vivid E95. Images will be digitally stored for offline analysis on custom software. We will collect the parameters to detect myocardial dysfunction and deformation.

Blood Sampling Procedures and Biochemical Assays

Blood sampling will be carried out to analyze circulating biomarkers of cardiac injury. High-sensitivity cardiac troponin T, high-sensitivity cardiac troponin I, N-terminal pro-BNP, and inflammatory and anti-inflammatory mediators such as hs-CRP will be measured.

Treatment

Chemotherapy

patients will receive adjuvant chemotherapy in accordance with the international guidelines. Patients receiving cardiotoxic

chemotherapy will be drawn blood before and, if possible, 24 hours after chemotherapy administration.

Patients who receive anthracycline have an ECHO and electrocardiography after the end of this schedule.

During trastuzumab, blood sample will be taken before every administration (every 3 weeks), and ECHO will be conducted after every 4 cycles (every 3 months).

Radiation Therapy

Patients will undergo a simulation chest computed tomography (CT) in free breathing and breath hold modality. Clinical target volume, the planning target volume, and the organs at risk will be drawn on the breath hold modality imaging if this modality improves the distance between breast and heart or left coronary artery (left anterior descending artery). An appropriate physical dosimetric study will be processed using treatment planning system and will be generated to achieve maximum coverage for the planning target volume region by minimizing the dose to the surrounding healthy tissues.

For each contoured volume, we will analyze the minimum, maximum, and mean dose, and dose volume histogram will be evaluated for obtaining the best treatment.

Follow-up

During follow-up, imaging (CMR and ECHO) and biomarkers will be checked 2 weeks after the end of RT and 1 year later. If a patient has symptomatic heart failure during the treatment, or if LVEF declines greater than 10% with a final LVEF <53% on ECHO, the patient will be referred to the cardiologist for a specific treatment. Adverse events will be classified according to the Common Terminology Criteria for Adverse Events. Figure 1 describes the protocol flow chart of the CardioTox Breast study.

Figure 1. Protocol flow chart description. Blood: blood sample for circulating biomarkers; CMR: cardiac magnetic resonance; ECHO: echocardiography; RT: radiotherapy.
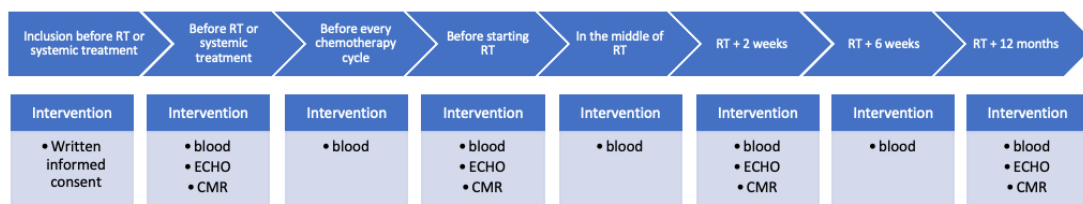
Data Collection

Data will be collected in a dedicated database. An accurate patient history, the type of cancer, and information on the main risk factors for a cardiac event are collected at the inclusion time. Cardiac imaging data (ECHO and CMR) and circulating biomarkers measurements are registered in the database.

Ethical Considerations

This study will be conducted in accordance with the Declaration of Helsinki (amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013) and in

accordance with the principles of "Good Clinical Practice" and the Medical Research Involving Human Subjects Act. This study was approved by the ethics committee of the Oncology Institute of Southern Switzerland (ID 2019-01395) and by the local ethical committees of the other 2 investigating centers.

Study End Points

Primary End Point

The primary end point is the incidence of cardiotoxicity, as defined by consensus guidelines (decline of LVEF ≥10% points with a final LVEF of <53%), measured on CMR and ECHO

over the time window of 12 months from the end of radiation therapy.

Primary Objective

The primary objective is to assess the role of myocardial oedema on CMR (T2 mapping) after radiation and cardiotoxic systemic therapy in predicting the incidence of cardiotoxicity, as defined by consensus guidelines (decline of LVEF ≥10% points with a final LVEF <53%), measured on CMR and ECHO over the time window of 12 months from the end of radiation therapy.

Secondary Objectives

The secondary objectives are the following: (1) detect GLS decrease >15% from baseline, measured on ECHO over the time window of 12 months; (2) see if the changes in biomarkers will correlate with LVEF measurements, assessed by ECHO and CMR; (3) see if the changes in biomarkers will correlate with GLS measurements, assessed by ECHO; (4) compare the time to the biomarkers' positivity to the time to decrease in GLS >15% or decline of LVEF ≥10% with a final LVEF of <53% measured on ECHO; (5) find out if patients with increased baseline biomarkers will develop cardiotoxicity, and identify predictors of cardiotoxicity by multivariable analysis; (6) detect major cardiovascular events (defined as acute myocardial infarction, hospitalization due to heart failure, atrial flutter or fibrillation, and ventricular tachycardia) or death due cardiac problems during follow-up; (7) assess the role of fibrosis on

CMR (T1 mapping with evaluation of extracellular volume) after cardiotoxic radiation therapy or systemic therapy in predicting the incidence of cardiotoxicity; (8) detect the incidence of acute asymptomatic pericarditis after radiation therapy, measured on CMR; (9) investigate if the area of the oedema on CMR correlates with RT dose distribution; and (10) assess the incidence of myocardial oedema on CMR (T2 mapping) after radiation therapy and cardiotoxic systemic therapy, measured on CMR and ECHO over the time window of 12 months from the end of radiation therapy.

Statistical Analysis

Sample Size Calculation

Sample size of this multicenter study is evaluated based on feasibility. We hypothesize to be able to enroll 150 patients satisfying the enrollment criteria and giving consent to participate into the study. We base calculations on the primary end point.

Table 1 summarizes the effect size for the primary end point that can be detected for the expected sample size, given a power of 80% and different rates of prevalence of myocardial oedema after cardiotoxic systemic therapy or radiation therapy.

We use an alpha level of 10% one-sided test, given the lack of strong evidence in the literature ("early evidence" study). We used Stata 15 (Stata Corp) for computation.

Table 1. Effect size computation assuming a rate of cardiac toxicity at 12 months of p1=17% in the cohort without oedema at magnetic resonance. Power 80%, alpha (2-sided) 20%.

Hypothesized points with MR[a] oedema at the end of RT[b], %	Detectable effect size in the oedema population, %
5	52 (25)
10	43 (26)
15	39 (22)
20	37 (20)
25	35 (18)

[a]MR: magnetic resonance.

[b]RT: radiotherapy.

Planned Analysis

Data at enrollment will be described as mean and standard deviation or median and 25th-75th percentiles if continuous and as counts and percent if categorical. They will be compared between groups of patients with and without oedema at the end of RT with the Student t test (or the Mann Whitney U test, based on the distribution) and the Fisher exact test, respectively.

Analysis of the Primary End Point

The number of patients with cardiac toxicity at 12 months will be compared between groups with the Fisher exact test. The mean difference in proportions of cardiac toxicity at 12 months and its 80% confidence interval will be reported. Logistic regression will be used to adjust for potential confounders. We do not expect losses to follow-up. A sensitivity analysis will

classify them as no cardiac toxicity patients. If the mortality or losses to follow-up are above 10%, we will also compare groups using survival analysis methods to account for the different follow-ups between patients, using the same strategies.

Analysis of the Secondary Objectives

The data will be compared as described above. The time-to-event end points will be compared using survival analysis methods. The association of changes in biomarkers and changes in cardiac function will be assessed with linear regression models. Data transformation will be applied as needed. The details are provided in Table 2.

Multivariable analysis to identify potential predictors of cardiac toxicity will be performed, while considering a predictor-to-events ratio of 1:10 to avoid overfitting.

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Table 2. Analysis of the secondary end points.

Secondary end point	Analysis
Detect GLS[a] decrease of >15% from baseline, measured on ECHO[b] over the time window of 12 months.	The number of patients with a >15% decrease will be compared between groups with the Fisher exact test. The mean difference in proportions at 12 months and its 80% CI will be reported.
See if the changes in biomarkers will correlate with LVEF[c] measurements, assessed by ECHO and CMR[d].	The association of changes in biomarkers and LVEF will be assessed with a linear regression model, while adjusting for oedema.
See if the changes in biomarkers will correlate with GLS measurements, assessed by ECHO.	The association of changes in biomarkers and GLS will be assessed with a linear regression model, while adjusting for oedema.
Compare the time to biomarkers' positivity to the time to decrease in GLS >15% or decline in LVEF ≥10% in points with a final LVEF of <53% measured on ECHO.	The times will be compared with the Mann Whitney U test.
Find out if patients with increased baseline biomarkers will develop cardiotoxicity; identify predictors of cardiotoxicity by multivariable analysis.	A univariable and multivariable logistic model will be used.
Detect MACE[e] (defined as acute myocardial infarction, hospitalization due to heart failure, atrial flutter or fibrillation, and ventricular tachycardia) or death due cardiac problems during follow-up.	The rate of each overall MACE and that of each event will be computed per 100 person-year with 80% CI. Kaplan Meier curves will be plotted.
Assess the role of fibrosis on CMR (T1[f] mapping with evaluation of extracellular volume) after cardiotoxic radiation therapy or systemic therapy in predicting the incidence of cardiotoxicity.	A univariable and multivariable logistic model will be used.
Detect incidence of acute asymptomatic pericarditis after RT[g], measured on CMR.	The proportion of patients with acute asymptomatic pericarditis and 80% CI will be computed.
Investigate if the area of the oedema on CMR correlates with RT dose distribution.	The Spearman correlation coefficient and 80% CI will be computed.
To assess the incidence of myocardial oedema on CMR (T2[h] mapping) after radiation therapy and cardiotoxic systemic therapy measured on CMR and ECHO over the time window of 12 months from the end of radiation therapy.	The proportion of patients with oedema and 80% CI will be computed.

[a]GLS: global longitudinal strain.

[b]ECHO: echocardiography.

[c]LVEF: left ventricular ejection fraction.

[d]CMR: cardiac magnetic resonance.

[e]MACE: major cardiovascular events.

[f]T1: longitudinal relaxation time.

[g]RT: radiotherapy.

[h]T2: transverse relaxation time.

Results

Recruitment started in September 2020. The results of this study will not be published until data are mature for the final analysis of the primary study end point.

Discussion

Summary

CardioTox Breast is a multicenter prospective longitudinal study testing the role of CMR in predicting cardiotoxicity in patients with breast cancer. The study is designed to combine both cardiac imaging information regarding potential early myocardial dysfunction and anatomical coronary changes, as well as variations in circulating cardiac damage biomarkers.

We will investigate the effects of systemic therapy and radiation therapy on myocardial function and structure, thus providing additional evidence on whether CMR is the optimal screening tool for cardiotoxicity. CMR is very promising for assessing the function and structure of the cardiovascular system and is starting to be investigated further in prospective studies [28].

Conclusions

Cardiotoxicity can affect the quality of life of breast cancer survivors, whose numbers are increasing. It is important to distinguish high-risk patients who need intensive cardiovascular screening during and after cardiotoxic treatment.

Cardiotox Breast results should improve the prediction and prevention of potential lesions to normal cardiac tissue and ultimately enhance patients' care and quality of life.

To our knowledge, this study is one of the first longitudinal studies with the primary aim of identifying any change in cardiac imaging (based on CMR and ECHO) and circulating biomarkers to predict the incidence of cardiotoxicity.

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Conflicts of Interest

None declared.

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Abbreviations

BNP: brain natriuretic peptide
CMR: cardiac magnetic resonance
CT: computed tomography
ECHO: echocardiography
ECOG: Eastern Cooperative Oncology Group
FISP: fast imaging with steady-state free precession
GLS: global longitudinal strain
hCG: human chorionic gonadotropin
HER2: human epidermal growth factor receptor 2
HF: heart failure
hs-CRP: high-sensitivity C-reactive protein
LVEF: left ventricular ejection fraction
RT: radiotherapy

Protocol

Overcoming Decisional Gaps in High-Risk Prescribing by Junior Physicians Using Simulation-Based Training: Protocol for a Randomized Controlled Trial

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Abstract

Background: Gaps between rational thought and actual decisions are increasingly recognized as a reason why people make suboptimal choices in states of heightened emotion, such as stress. These observations may help explain why high-risk medications continue to be prescribed to acutely ill hospitalized older adults despite widely accepted recommendations against these practices. Role playing and other efforts, such as simulation training, have demonstrated benefits to help people avoid decisional gaps but have not been tested to reduce overprescribing of high-risk medications.

Objective: This study aims to evaluate the impact of a simulation-based training program designed to address decisional gaps on prescribing of high-risk medications compared with control.

Methods: In this 2-arm pragmatic trial, we are randomizing at least 36 first-year medical resident physicians (ie, interns) who provide care on inpatient general medicine services at a large academic medical center to either intervention (simulation-based training) or control (online educational training). The intervention comprises a 40-minute immersive individual simulation training consisting of a reality-based patient care scenario in a simulated environment at the beginning of their inpatient service rotation. The simulation focuses on 3 types of high-risk medications, including benzodiazepines, antipsychotics, and sedative hypnotics (Z-drugs), in older adults, and is specifically designed to help the physicians identify their reactions and prescribing decisions in stressful situations that are common in the inpatient setting. The simulation scenario is followed by a semistructured debriefing with an expert facilitator. The trial's primary outcome is the number of medication doses for any of the high-risk medications prescribed by the interns to patients aged 65 years or older who were not taking one of the medications upon admission. Secondary outcomes include prescribing by all providers on the care team, being discharged on 1 of the medications, and prescribing of related medications (eg, melatonin, trazodone), or the medications of interest for the control intervention. These outcomes will be measured using electronic health record data.

Results: Recruitment of interns began on March 29, 2021. Recruitment for the trial ended in Q42021, with follow-up completed by Q12022.

Conclusions: This trial will evaluate the impact of a simulation-based training program designed using behavioral science principles on prescribing of high-risk medications by junior physicians. If the intervention is shown to be effective, this approach could potentially be reproducible by others and for a broader set of behaviors.

Trial Registration: ClinicalTrials.gov NCT04668248; https://clinicaltrials.gov/ct2/show/NCT04668248

International Registered Report Identifier (IRRID): PRR1-10.2196/31464

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Introduction

Decisional gaps between how individuals behave when in an emotional or "hot" state (sometimes called "System 1" thinking) in contrast to when they are better able to consider issues more rationally (ie, "System 2" thinking) are increasingly being recognized as a reason why people make suboptimal decisions in stressful situations [1-6]. For example, the "hot-cold empathy gap" helps to explain the observation that when people are in rational or "cold" states, they incorrectly predict what their behavior will be during "hot states" [5]. Other related behavioral principles describe deliberative versus impulsive thinking and have found similar gaps in behaviors when people are in different states [7-9]. Moreover, often in these "hot states," there may be limited time to make decisions leading to mental shortcuts, often called "heuristics," that could lead to suboptimal decision making [10].

These decisional gaps are believed to be a central reason why health care providers underestimate the likelihood that they will make suboptimal prescribing decisions in stressful situations [11]. For example, the use of medications such as antipsychotics, benzodiazepines, and sedative hypnotic "Z-drugs," to manage delirium and agitation for hospitalized patients remains highly prevalent despite considerable risks associated with their use and guidelines that recommend their avoidance in older adults [12-15]. In this context, there are numerous factors that are stressful for physicians which promote System 1 thinking. These include clinical complexity, perceived pressure from nursing staff, patients and their caregivers, and fatigue [11,16,17]. These issues may be particularly challenging for junior physicians, especially medical residents, given their relative lack of experience. Further, interventions to reduce the prescribing of these high-risk medications have typically focused on educating providers by transmitting facts alone, and have only been modestly successful, perhaps, because they have underestimated the importance of stress faced by clinicians in the real-life care of complex and acutely ill inpatients [1,18-22].

Efforts to address decisional gaps between System 1 and System 2 thinking in other fields have involved role-playing or other games to simulate System 2 thinking states, such as having participants evaluate their cravings for tobacco during hot state and cold state sessions [1,2,23,24]. In clinical medicine, simulation has increasingly been used to help health care professionals, alone and in teams, practice how they would handle stressful situations such as cardiac arrest or emergent trauma situations in emergency rooms [25-34]. By extension, these approaches could help address decisional gaps for prescribing high-risk medications for older adults.

Accordingly, we launched a pilot trial to evaluate the impact of a simulation-based training program designed to address decisional gaps between System 1– and System 2–driven choices compared with online educational training on high-risk prescribing by first-year medical residents (ie, interns) at a large academic medical center. We hypothesized that the simulation-based training program would reduce high-risk prescribing by interns compared with online educational training.

Methods

Overall Study Design

We designed and launched a 2-arm pragmatic randomized trial to evaluate the impact of a simulation-based training program on the prescribing of high-risk medications to hospitalized older adults (Figure 1). The specific medication classes of interest are benzodiazepines, antipsychotics, and sedative hypnotics (Z-drugs), the use of which is strongly discouraged by major clinical guidelines [15,35].

The authors will be responsible for performing the study analyses, writing the first draft of the manuscript, substantive edits, and submitting its final contents for publication. Data analysts at the end of the study will be blinded to arm assignment; residents are not blinded due to the nature of the interventions and need to provide informed consent for participation.

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Figure 1. Overall trial design.
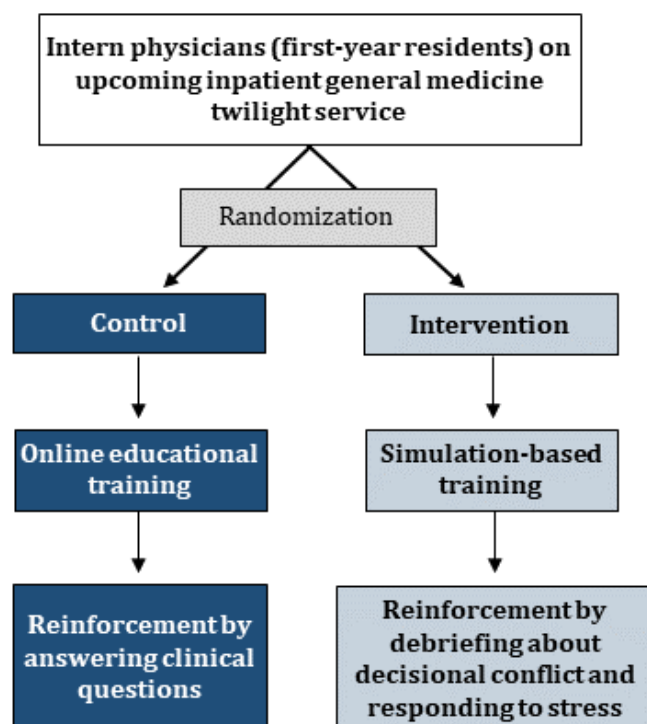
Ethical Approval

The trial is approved by the Institutional Review Board of Brigham and Women's Hospital (BWH; Mass General Brigham) approval number 2020P003643, and registered with ClinicalTrials.gov (NCT04668248).

Study Setting and Participants

The study is being conducted at the BWH Main and Faulkner campuses, an academic medical center in Boston, Massachusetts, affiliated with Harvard Medical School. Potentially eligible participants are physician interns (ie, first-year medical resident physicians) practicing on the general medicine inpatient services at BWH assigned to an evening rotation. At BWH Main campus, these services include the General Medicine Service or Integrated Teaching Unit; at BWH Faulkner, this service includes a General Medicine Service. These services consist of 8 teams of residents and interns, rotating on daytime and evening shifts.

We chose to focus on interns starting on an evening rotation as they cover the shifts during which the high-risk medications of interest are most often prescribed. In addition to being the least experienced physicians on the medical team, they are also the first and primary point of contact for nurses, pharmacists, and other specialists. Given the busy pace of these evening rotations [36,37], the interns may also be prone to make decisions using System 1 thinking, which was supported by interviews we

conducted (see the section "Intervention: Simulation Training" for more detail).

Older adults (≥65 years) admitted to 1 of these services not previously taking 1 of the high-risk medications of interest upon admission will be the target population for analyses.

Study Procedures and Randomization

The timeline of study procedures is shown in Figure 2. Potentially eligible interns were invited by email to join a study using educational training to reduce prescribing of "high-risk medications." No information was provided in advance about the exact medication classes to avoid any potential bias in the educational trainings.

Interns interested in participating were asked to provide written informed consent and complete a baseline questionnaire administered and collected through the REDCap electronic data capture tool housed at BWH prior to randomization. REDCap is a secure web-based software platform supporting data collection for research studies and is housed on the BWH server [38,39]. The baseline assessment includes questions about demographic information, specifically sex, age, race, and ethnicity; the 6-item State-Trait Anxiety Inventory (STAI-6) questions [40,41], which measure types of anxiety and we used these questions to query about stressful prescribing decisions specifically (Multimedia Appendix 1); and the 8-item Revised Physicians' Reactions to Uncertainty Scales, which ask about anxiety due to uncertainty and concern for bad outcomes (Multimedia Appendix 2) [42].

Figure 2. Timeline of study procedures.
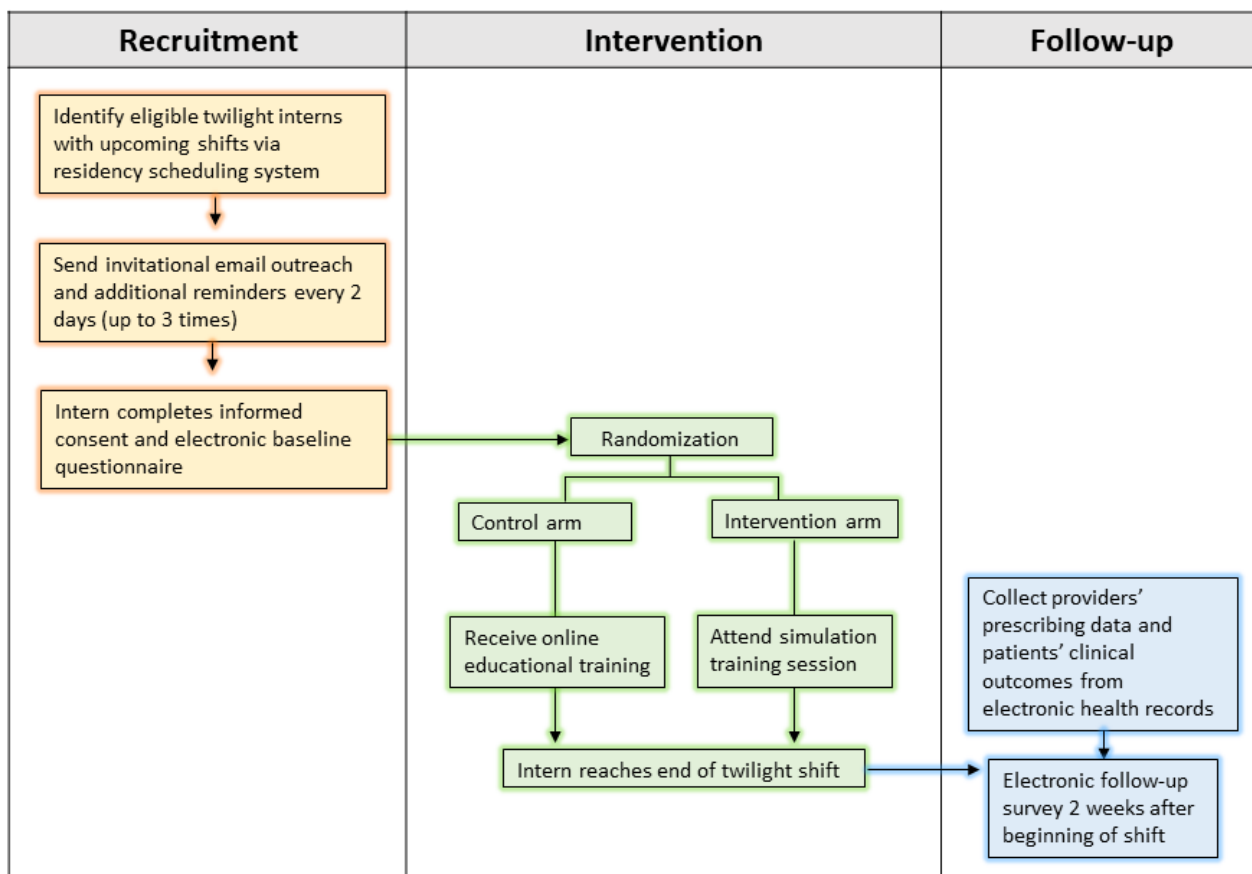
Interns who consent were randomized in a 1:1 ratio to 1 of 2 arms: (1) Arm 1—simulation training; and (2) Arm 2—control (online educational training) using a simple random number generator within REDCap. To improve baseline participant balance between the 2 treatment arms, we used stratified block randomization based on their service (ie, General Medicine Service, Integrated Teaching Unit, or Faulkner). Each potentially eligible intern will only participate in the trial once. Both intervention and control trainings were designed to be completed on the same day of the interns' evening rotation (eg, the second day of their rotation). They were also similar in duration, both designed to take about 40 minutes altogether.

Interns in both arms were asked to complete a follow-up survey 2 weeks after they begin their eligible evening rotation. This follow-up questionnaire repeats the STAI-6, the Revised Physicians' Reactions to Uncertainty Scales, and asks about satisfaction with the clarity and relevance of the information provided, timing of information, extent of knowledge gained, and expectations for using this information moving forward [40-42]. As described in the informed consent documentation, providers in both arms received US $25 for completing the baseline survey, US $75 for completing the training (either intervention or control as applicable), and US $50 after completing the follow-up questionnaire.

Intervention: Simulation Training

Design Process

Prior to designing the simulation-based training program, we conducted in-depth qualitative interviews with 25 medical residents and allied health professionals to understand barriers to reducing prescribing of high-risk medications in stressful situations. To avoid potential contamination with the trial, the medical trainees were based at a different academic medical center in Boston (Massachusetts General Hospital) or had recently finished their medicine internship and were currently pursuing residency training in other noninternal medicine programs (ie, neurology or dermatology). These interviews clarified the contributors to decisional conflict and factors associated with high-risk prescribing and stress, including most notably time pressures, perceived pressure from nurses, and stress due to lack of familiarity with new patients (data shown elsewhere). The interns also clarified a general lack of didactic training on prescribing of high-risk medications.

Simulation-Based Intervention

The simulation intervention consists of a 40-minute immersive simulation conducted at the Neil and Elise Wallace STRATUS Center for Medical Simulation at BWH. The intervention includes the scenario itself and a debriefing session. Each session is led and moderated by an expert physician facilitator and staffed by 2 different clinically trained "actors" (ie, practicing nurses) in simulated hospital rooms.

Based upon the qualitative interviews, the simulation-based training was designed to help interns identify their reactions and prescribing decisions common in the inpatient setting when they are in the "hot state" triaging multiple demands for their attention. The scenarios require the participants to simultaneously care for several patients through in-person, telephone, and pager-based interactions with patients and nurses. Each of the patient cases and nursing actions are designed to heighten stress and simulate a "hot state" (System 1 thinking) environment by leveraging behavioral principles such as creating time pressure, increasing cognitive load, and reduced control (Table 1). Several irritants, including alerts from telemetry and intravenous pumps, also trigger throughout the cases to heighten stress, as literature suggests that noise annoyance is associated with increased anxiety [43,44]. Other behavioral strategies to induce stress and decisional conflict, such as action bias and social norming, are also incorporated in the scenario [45,46]. The scenario is also designed to help the physicians improve their communication skills with nurses, develop differential diagnoses, and consider alternative therapeutic options.

Table 1. Behavioral strategies implemented in simulation scenario and application to stressful prescribing situations.

Simulation behavioral strategy	Implementation in simulation scenario	Application to heightened stress and decisional conflict in high-risk prescribing
Time pressure	Repeated pages and demands by nursing for actively decompensating patients	Limited time is available to make treatment decisions; the need to be efficient enables affect heuristics and mental shortcuts
Cognitive load	Addressing and triaging 3 different patients and nurses with acute needs	Vast amounts of information must be processed to make prescribing decisions; the need to be efficient provokes System 1 thinking
Distraction/diverted attention	Telemetry beeping and patient intravenous pump alarms trigger loudly	These types of noises reduce the ability to easily process information and induce attentional bias
Reduced control	Clinically urgent patient with rapid ventricular response	Reduced ability to quickly respond to other patients enhances stress and urgency to prescribe quickly
Action bias	Nursing and patient demands for high-risk medication treatments	Tendency to favor action (eg, prescribing) over perceived inaction (eg, nonpharmacologic treatments), especially in stressful situations
Ambiguity effect	Nursing and patient demands for high-risk medication treatments and express displeasure with any alternatives	Clinical medicine curricula heavily focus on medications, priming interns to prescribe riskier medications
Social norming	Nursing pushback includes reference to what prior physicians have prescribed	Tendency to follow social "norms" presented by nurses and experiential training from peers enhance likelihood of poor prescribing

Prior to beginning each simulation, the facilitator briefly introduces the case and provides a shift-change handoff note with details of 5 hypothetical patients under their care, including brief summaries, tasks, and contingency plans. The simulation involves 3 patients set in the early evening. The intern is first called to the bedside by a nurse actor to address dyspnea for Patient 1, a 55-year-old man recently hospitalized for cellulitis and readmitted with pneumonia. Patient 1 develops atrial fibrillation with rapid ventricular response. While caring for Patient 1, a second nurse pages the intern several times about Patient 2, a 79-year-old man with mild cognitive impairment admitted with a wrist fracture after falling at home. The patient is agitated and disoriented. The nurse requests the intern to prescribe a sedating medication, despite its risks. When the intern goes to see Patient 2 in his hospital room, the simulated patient is attempting to get out of bed and yelling but is not physically violent. The patient is also attempting to remove his intravenous line and catheter.

As the scenario proceeds, another nurse pages twice about Patient 3, a 71-year-old woman admitted for an exacerbation of chronic obstructive pulmonary disease. She is distressed about having trouble sleeping and requesting a sleep medication. The nurse explains that the patient has already received melatonin without effect.

The intern will interact with the nurses for Patients 1 and 2 in person but will communicate with the nurse for Patient 3 only by telephone and pager, simulating the real-world distributed nature of care across units in hospital settings. If the intern tries to order nonpharmacological treatments for Patients 2 and 3, the nurses will also request that the intern prescribe antipsychotics, benzodiazepines, or sedative hypnotics, as applicable. If the intern refuses, the nurses will acquiesce initially but then continue to express concern. The scenario ends after the intern interacts twice with the nurse or patient, for all 3 patients.

Simulation Debriefing

Immediately after the scenario, the facilitator debriefs individually with each intern using a semistructured guide developed by the study team (Multimedia Appendix 3). The goal of the debriefing session is to reinforce the simulation session by discussing the decisional conflicts the intern experienced during the simulation. The facilitator asks each intern how they responded to stress and what choices they may have made if they had experienced less pressure. The debriefing also covers factors that led to increased stress, reasons for their prescribing decisions, alternative nonpharmacologic and pharmacologic options for managing insomnia and agitated

delirium, and ways to improve communication with nursing staff and patients in future interactions. The debriefing lasts about 20 minutes for each intern.

Control: Online Educational Training

Providers assigned to the control arm will receive self-directed online educational training about other treatments that are often overprescribed to hospitalized patients, specifically the transfusion of blood products, such as albumin and red blood cells [47,48]. Providing education about other high-risk medications will reduce nonspecific attention. This information is provided in the form of a 35-minute video lecture previously delivered several years prior by a local attending physician about transfusion reactions and management of blood products during a grand rounds talk. The lecture is housed on a website behind the hospital firewall (ie, not accessible outside of the hospital). After watching the video, the interns are asked to answer several clinical knowledge questions from the Biomedical Excellence for Safer Transfusion (BEST) Collaborative and American Society for Clinical Pathology's validated physician knowledge examination and the study team [47]. We chose to use this mode

of online training as lectures (and videotapes of the lectures) are commonly used during residency programs, and we wanted to evaluate the potential for spillover effects on other types of medications. As described above, both intervention and control arms were each designed to take about 40 minutes.

Outcomes

The trial outcomes will be evaluated using structured electronic health record (EHR) data on the patient-level and a follow-up survey of the interns 2 weeks after they begin their evening rotation (Table 2). The trial's primary outcome is the number of high-risk medication doses of antipsychotics, benzodiazepines, and sedative hypnotics prescribed per day to eligible patients (ie, ≥65 years of age, not on one of the medications upon admission) by the interns beginning on the day the trainings are delivered until the end of follow-up. We plan to exclude patients for the analysis who were on the relevant high-risk medication of interest prior to admission. For example, patients who were admitted on a benzodiazepine will not be included in the benzodiazepine/sedative hypnotic analysis but will be in the antipsychotic analysis.

Table 2. Study outcomes.

Outcome	Measurement	Assessment
Primary	High-risk medications prescribed per day: intern	Quantity of prescribed medication doses of high-risk medications (antipsychotics, benzodiazepines, sedative hypnotics) by the intern to patients ≥65 years not on treatment prior to admission over the follow-up period
Secondary	High-risk medications prescribed per day: all prescribers	Quantity of prescribed medication doses of high-risk medications (antipsychotics, benzodiazepines, sedative hypnotics) by all prescribers to patients ≥65 years not on treatment prior to admission over the follow-up period
Secondary	High-risk doses and types of medications prescribed per day	Strengths and types of medications of high-risk medications (antipsychotics, benzodiazepines, sedative hypnotics) by the intern to patients ≥65 years not on treatment prior to admission over the follow-up period
Secondary	Discharge medication order for high-risk medication: all prescribers	High-risk medication (antipsychotics, benzodiazepines, sedative hypnotics) prescribed to patients ≥65 years not on treatment prior to admission at hospital discharge
Secondary	Doses of spillover medications prescribed per day: intern	Quantity of prescribed medication doses for related medications (opioids, trazodone, melatonin) by the intern to patients ≥65 years not on treatment prior to admission over the follow-up period
Secondary	Doses of control medications prescribed per day: intern	Quantity of prescribed medication doses for control medications (eg, blood products) by the intern over the follow-up period

Given that patients have variable lengths of stay and, as a result, duration under the interns' care, we will measure this outcome on the patient-day level to enable the fairest comparison between the arms. We will censor follow-up time on when patients transition from the intern's service, including interns completing their evening service or death or hospital discharge. Medications ordered as needed will be treated the same as standing orders for the primary analysis. In secondary analyses, we will only measure doses that are standing orders and doses actually administered to patients. If patients are eligible to be measured for multiple medication classes (ie, antipsychotics and benzodiazepines or sedative hypnotics), we will sum the medication doses across the classes.

As secondary outcomes, we will measure: (1) the number of high-risk medication doses prescribed per eligible patient by all prescribers (ie, not only the enrolled intern) during the

follow-up period; (2) the dose and type of high-risk medication doses prescribed during the follow-up period; (3) whether patients are ultimately discharged on 1 of these medications; (4) prescribing by the interns of other related medications such as opioids, trazodone, or melatonin, to measure spillover effects; and (5) rates of prescribing of blood products and albumin (eg, control medications to allow comparisons between the arms). We will also evaluate implementation outcomes informed by the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework [49,50] from EHR and questionnaire data, including baseline characteristics of consenting and nonconsenting providers, whether the simulation training was completed, feedback and issues reported during the study, reported satisfaction with the intervention, and likelihood of incorporating insights into future practice. These other adoption and implementation outcomes will help us

explore the extent to which the intervention could be used at scale.

Analytic Plan and Sample Size Estimates

Analytic Plan

We will report means and frequencies of prerandomization variables in the intervention and control arms separately, comparing these values using absolute standardized differences.

To evaluate the primary outcome, we will use generalized estimating equations with a log-link function and Poisson-distributed errors, adjusting for patient- and physician-level clustering, and the block randomized design. We will include fixed effects for the treatment group and month of the year to account for seasonality. This approach will account for correlations between clustered observations. Because this is a randomized trial, our primary analyses are planned as unadjusted; however, if there are strong predictors of the outcomes not balanced by stratified randomization, we will adjust for these in the primary analyses. We will conduct analyses using intention-to-treat principles.

We will use a similar approach for the secondary outcomes. For discharge medication orders (secondary outcomes), we will also use generalized estimating equations that adjust for physician- and patient-level clustering and the block-randomized design using a logit-link function, binary-distributed errors, and fixed effects for the treatment group and month of the year. For the other secondary outcomes measuring prescribing by all prescribers, spillover effects, and prescribing of control medications, the approach will be the same, except using a log-link function and Poisson-distributed errors. Given the nature of the data, there will not be missing data for the primary outcome; however, there may be up to 25% of missingness for survey-based outcomes. Implementation outcomes, the STAI-6, and the Reactions to Uncertainty items will be descriptively compared at the provider level.

As secondary analyses, we plan to conduct subgroup analyses by provider sex, as prior work and the qualitative interviews with other medical resident physicians suggest a relationship between perceived authority on prescribing decisions and sex of the medical resident, which could affect high-risk prescribing decision making [51]. We will also explore differences by month of the year and inpatient service level, as System 1 thinking may be greater earlier in their training. In addition, we will also evaluate any time trends in prescribing outcomes over the follow-up period to explore whether the potential effect of being observed wanes over time.

Sample Size

We plan to recruit at least 36 interns for this trial (18 per arm), which should provide sufficient power to detect clinically meaningful differences in the primary outcome. Specifically, we estimated that we would have more than 80% power to detect a mean difference of 0.5 high-risk medication doses per patient-day in the intervention arm compared with the control arm, assuming an SD of 1.1, 2-sided α of .05, and intracluster correlations of 0.2 [21].

Results

Recruitment of interns began on March 29, 2021. Recruitment for the trial ended in December 2021 with 40 total interns. Follow-up for study outcomes finished in January 2022. As of January 2022, we have begun data extraction and statistical analysis.

Discussion

While gaps in System 1 and System 2 thinking are thought to contribute to decisional conflict in prescribing, this behavioral principle has not, to our knowledge, been explicitly addressed as part of a simulation intervention [1]. Accordingly, we launched a pilot trial evaluating the impact of a simulation-based training program designed to address decisional gaps between System 1– and System 2–driven choices on high-risk prescribing by medical resident physicians at a large academic medical center.

Simulation has increasingly been used to help health care professionals, alone and in teams, practice how they would handle stressful situations such as cardiac arrest or traumas in emergency rooms [25,27,28,30,31,52-54]. By extension, leveraging behavioral science principles within simulation to address decisional gaps between System 1– and System 2–driven choices holds great promise for reducing prescribing of high-risk medications for older adults. Prior interventions to specifically reduce the use of high-risk medications may only have been modestly successful because they have typically focused on educating providers and may not have adequately prepared them for making complex and urgent therapeutic decisions [1,22].

Further, despite growing knowledge and an evidence base for simulation-based interventions for providers and health care professionals, most existing studies on simulation have often evaluated changes in "cold-state" outcomes such as self-reported knowledge, changes in attitudes, or prescribing for simulated patients rather than clinical outcomes of patients in real-world practice [25-27,31]. Conversely, we are leveraging data directly from EHRs about participants' actual prescribing to evaluate real-world clinical outcomes of simulation-based interventions.

There are several limitations that should be acknowledged. First, owing to the nature of the residency schedule, the length of follow-up for outcomes will be limited, and it will not be possible to evaluate long-term durability of outcomes. Second, while we are using expert facilitators and trained actors for the simulation sessions, there may be some variability in the actual scenarios based on intern prescribing decisions, as with any simulation. Third, it is possible that some prescribing decisions during follow-up in the real-world may not be fully the intern's choice, but the intern is largely responsible for the care of patients during evening shifts, and we do not expect this or pressure by others on the care team, such as nurses, to be differential between arms. Similarly, the interns may prescribe slightly differently owing to their knowing they are participating in a trial, but we will explore the extent to which this occurs using a sensitivity analysis. Fourth, the content of the high-risk medications training differed between the arms, but we are

measuring and comparing prescribing to both types of high-risk medications as outcomes. Fifth, while the interventions in both arms are only accessible to interns assigned to those arms, there is a hypothetical risk of contamination, but this would bias results toward the null. Sixth, System 1 thinking may be efficient in some clinical settings, so addressing this principle may be insufficient to optimize prescribing [55-57]. Finally, these findings may not generalize to medical residents in nontertiary health care systems or more senior physicians.

In conclusion, this trial will evaluate the impact of a simulation-based training program designed using behavioral science on prescribing of high-risk medications by junior physicians. If the intervention is shown to be effective, this approach is expected to be reproducible in other clinical environments and for a broader set of behaviors. Regardless of outcome, the trial will also provide additional insight into the real-world effectiveness of simulation-based training and help tailor evidence-based medicine education.

Conflicts of Interest

NC is a consultant to and holds equity in RxAnte, unrelated to this work. He receives grant funding, payable to his institution, from Boehringer Ingelheim and Humana, also unrelated to this work. RB is now an employee at Vytalize Health. The other authors report no conflicts.

Multimedia Appendix 1
6-item State-Trait Anxiety Inventory (STAI-6).
[DOCX File , 14 KB - resprot_v11i4e31464_app1.docx]

Multimedia Appendix 2
The Revised Physicians' Reactions to Uncertainty Scales.
[DOCX File , 15 KB - resprot_v11i4e31464_app2.docx]

Multimedia Appendix 3
Debriefing guide.
[DOCX File , 16 KB - resprot_v11i4e31464_app3.docx]

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Abbreviations

BEST: Biomedical Excellence for Safer Transfusion
BWH: Brigham and Women's Hospital
EHR: electronic health record
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
STAI-6: 6-item State-Trait Anxiety Inventory

Protocol

The Effect of Transcranial Alternating Current Stimulation With Cognitive Training on Executive Brain Function in Individuals With Dementia: Protocol for a Crossover Randomized Controlled Trial

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Abstract

Background: Although memory and cognitive declines are associated with normal brain aging, they may also be precursors to dementia.

Objective: We aim to offer a novel approach to prevent or slow the progress of neurodegenerative dementia, or plausibly, improve the cognitive functions of individuals with dementia.

Methods: We will recruit and enroll 75 participants (older than 50 years old with either mild cognitive impairment or probable early or moderate dementia) for this double-blind randomized controlled study to estimate the efficacy of active transcranial alternating current stimulation with cognitive treatment (in comparison with sham transcranial alternating current stimulation). This will be a crossover study; a cycle consists of sham or active treatment for a period of 4 weeks (5 days per week, in two 30-minute sessions with a half-hour break in between), and participants are randomized into 2 groups, with stratification by age, sex, and cognitive level (measured with the Montreal Cognitive Assessment). Outcomes will be assessed before and after each treatment cycle. The primary outcomes are changes in Wechsler Memory Scale Older Adult Battery and Alzheimer Disease Assessment Scale scores. Secondary outcomes are changes in performance on tests of frontal lobe functioning (verbal fluency), neuropsychiatric symptoms (Neuropsychiatric Inventory Questionnaire), mood changes (Montgomery-Åsberg Depression Rating Scale), and short-term recall (visual 1-back task). Exploratory outcome measures will also be assessed: static and dynamic vestibular response using electrovestibulography, neuronal changes using functional near-infrared spectroscopy, and change in spatial orientation using virtual reality navigation.

Results: As of February 10, 2022, the study is ongoing: 7 patients have been screened, and all were deemed eligible for and enrolled in the study; 4 participants have completed baseline assessments.

Conclusions: We anticipate that transcranial alternating current stimulation will be a well-tolerated treatment, with no serious side effects and with considerable short- and long-term cognitive improvements.

Trial Registration: Clinicaltrials.gov NCT05203523; https://clinicaltrials.gov/show/NCT05203523

International Registered Report Identifier (IRRID): DERR1-10.2196/37282

KEYWORDS

transcranial alternating current stimulation; Alzheimer disease; cognitive impairment; double blind; treatment; placebo-controlled; randomized; crossover; dementia; cognitive

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Introduction

Background

Due to medical advancements and healthier lifestyles, lifespans are increasing. However, as longevity increases, cognitive abilities such as executive function, memory, reasoning, and processing speed deteriorate [1]. While deterioration may be part of normal aging [2], declines in cognitive function or associative and spatial memories can also be precursors to dementia [3]. There is currently no cure for dementia, however, there is hope that the onset of the disease can be delayed, or its progression slowed, by living a brain-healthy lifestyle. This hope is based on brain neuroplasticity, as well as individuals' cognitive reserves [4]. It has been suggested that constructing a cognitive "reserve capacity" [5] can help seniors to maintain cognitive function, which was later supported by neuroimaging studies that showed increased contralateral hemispheric activity in right frontal regions for both working memory [6] and episodic memory [7] in aging populations.

Recently, many interventions and studies [8-10] have reportedly demonstrated cognitive improvement in older adults from cognitive training (brain exercises or brain games), if they are used frequently and regularly; however, cognitive improvements were largely observed in the same tasks, with minimal far-transfer effects being observed. A 2018 study with 72 participants (20 to 62 years) showed evidence against transferable gains from cognitive function training that consisted of spatial training and working memory tasks [11]. However, in almost all studies that have considered the effect of brain exercises on the cognitive function of adults and older adults, participants performed their exercises without a trainer [8,11]. Conversely, significant cognitive improvement in individuals with mild or moderate dementia has been demonstrated when they participated in daily brain exercises in a regimented, structured learning environment with the help of a tutor, and improvements transferred to their daily life beyond the practiced exercises as the outcome measures were independent of the practiced tasks [9,12-14].

The application of transcranial alternating current stimulation—an external oscillating electrical field that induces cortical activity—either in addition to or independent of brain exercises, on cognition has been explored. It is a relatively inexpensive, easy to administer, and safe tool for noninvasive brain stimulation. Transcranial alternating current stimulation has been demonstrated to both modulate and entrain the ongoing network oscillations in a frequency-specific manner [15], by using appropriate stimulation parameters (ie, frequency, intensity, duration, and anatomical location) to manipulate the phase, the rhythm, and the power of neural oscillations, through in vitro and in vivo experiments [16]. Because it operates in a frequency- and phase-specific manner, which offers the possibility to demonstrate causal relations between oscillations and behavior [17,18], interest in transcranial alternating current stimulation has significantly increased in the past decade. Furthermore, the therapeutic potential of transcranial alternating current stimulation has led many researchers to study its applicability as a treatment option for numerous neurological

and psychological disorders [14,18,19]. However, there has been little investigation into the potential effect of transcranial alternating current stimulation on older adults with cognitive impairments associated with dementia. Moreover, much of the research on transcranial alternating current stimulation involves testing participants' cognitive performance during or immediately after stimulation sessions.

In a recent pilot study [14], we demonstrated that the addition of transcranial alternating current stimulation to a cognitive training program improved participants' working memory, and improvements remained for a longer period after the intervention; however, there were several shortcomings in this study. Aside from having a limited sample size, the main shortcoming was that placebo effect was not analyzed. We aim to address shortcomings by employing a better study design to investigate the efficacy of combined transcranial alternating current stimulation and cognitive training on the dementia population (Clinicaltrials.gov NCT05203523).

Objective

We aim to investigate the effect of transcranial alternating current stimulation when paired with simultaneous cognitive training on the cognitive status of the dementia population as well as the predictability of participant responses to active transcranial alternating current stimulation at baseline.

Hypotheses

We hypothesize that (1) better cognitive performance will be evident for patients' active treatment periods compared with those from the sham periods; (2) in both groups, statistically significant improvement in cognitive performance will be evident immediately postintervention compared with baseline, and (3) a statistically significant difference in cognitive improvement will be found between the active and sham transcranial alternating current stimulation groups.

Methods

Experimental Design

This is a randomized, crossover, double-blind, placebo-controlled study. Participants with cognitive impairments are recruited at 1 of 2 sites (Manitoba and Alberta) and randomized into 2 groups, with stratification by age, sex, and cognitive level (measured with Montreal Cognitive Assessment [20]) for randomization. Group 1 participants receive active transcranial alternating current stimulation simultaneously with cognitive exercises. Group 2 participants receive sham transcranial alternating current stimulation simultaneously with cognitive exercises. Participants who cannot tolerate the application of transcranial alternating current stimulation and focus on the cognitive exercises at the same time are enrolled in a third group, in which they only receive cognitive exercises but otherwise follow the same protocol as those in group 1 and group 2. The outcomes of group 3 will be analyzed separately. Standard cognitive assessments are performed before and after treatment, as well as at a scheduled follow-up visit 3 months postintervention. Both participants and assessors remain blind to the type of treatment (active versus placebo) until the end of the study.

Recruitment

Approximately 75 patients with either mild cognitive impairment or probable early or moderate dementia, excluding Parkinsonian dementia, as confirmed by their treating physician will be recruited and tested over the course of this study. Participants are recruited from volunteers or doctor referrals.

Participant eligibility is confirmed in-person using the Montreal Cognitive Assessment, to assess the severity of dementia, and the Montgomery-Åsberg Depression Rating Scale, to assess for comorbid depression. Inclusion criteria are (all must be met): age between 50 and 95 years old; Montreal Cognitive Assessment score between 5 and 24; and the ability to read, write, and speak English fluently.

The exclusion criteria are diagnosis of Parkinson, Parkinsonian dementia, Huntington disease, speech-significant aphasia, intellectual disability, major depression or anxiety, bipolar disorder, schizophrenia, or any other major mood disorder; a history of epileptic seizures or epilepsy; inability to adequately communicate in English; vision or hearing that is sufficiently impaired to affect performance in cognitive tests; current substance abuse disorder; current participation in another therapeutic study for dementia; or a plan to change medication during the study period.

After the initial screening process and before randomization (Proc Plan, version 9.4; SAS Institute), participant tolerance to transcranial alternating current stimulation is tested with a 1-minute application as they focus on a cognitive exercise. If the participant cannot tolerate the application of transcranial alternating current stimulation, they are offered a chance to participate in the study as part of group 3. If they can tolerate the transcranial alternating current stimulation, they are randomized into either group 1 or group 2.

Prior to study participation, all patients and their primary caregivers are required to sign an informed consent form approved by the ethics board of each site of the study.

Randomization

Using stratified block randomization (block size of 6) [21], participants are assigned into 1 of the 2 equal-size age-, sex-, and severity-matched groups: group 1 and group 2 (Table 1). Balanced randomization is applied within each block, such that 3 participants receive the active transcranial alternating current stimulation treatment and the rest receive the sham treatment. This randomization procedure is used to avoid bias in statistical analyses comparing the 2 groups.

Table 1. Stratified blocks using 2 levels for 3 factors.

Block number	Factor		
	Age (years)	Sex	Severity (Montreal Cognitive Assessment score)
1	≥70	Female	≥18
2	≥70	Female	<18
3	≥70	Male	≥18
4	≥70	Male	<18
5	<70	Female	≥18
6	<70	Female	<18
7	<70	Male	≥18
8	<70	Male	<18

Treatment Protocol

Training for all groups occurs in-person over the course of 4 weeks, 5 days per week (excluding weekends); there is an 8-week wash-out period prior to group crossover. On each day, participants attend two 30-minute training sessions using an app (MindTriggers) with a 30-minute break in between. Assessments occur at baseline (week 0), postintervention (weeks 5 and 11), at a follow-up (week 16), and at a long-term follow-up (week 27). Assessment at week 11 is considered to be baseline for the second cycle. No crossover occurs for participants assigned to group 3 (Figure 1).

Figure 1. Study flowchart for groups 1 to 3.
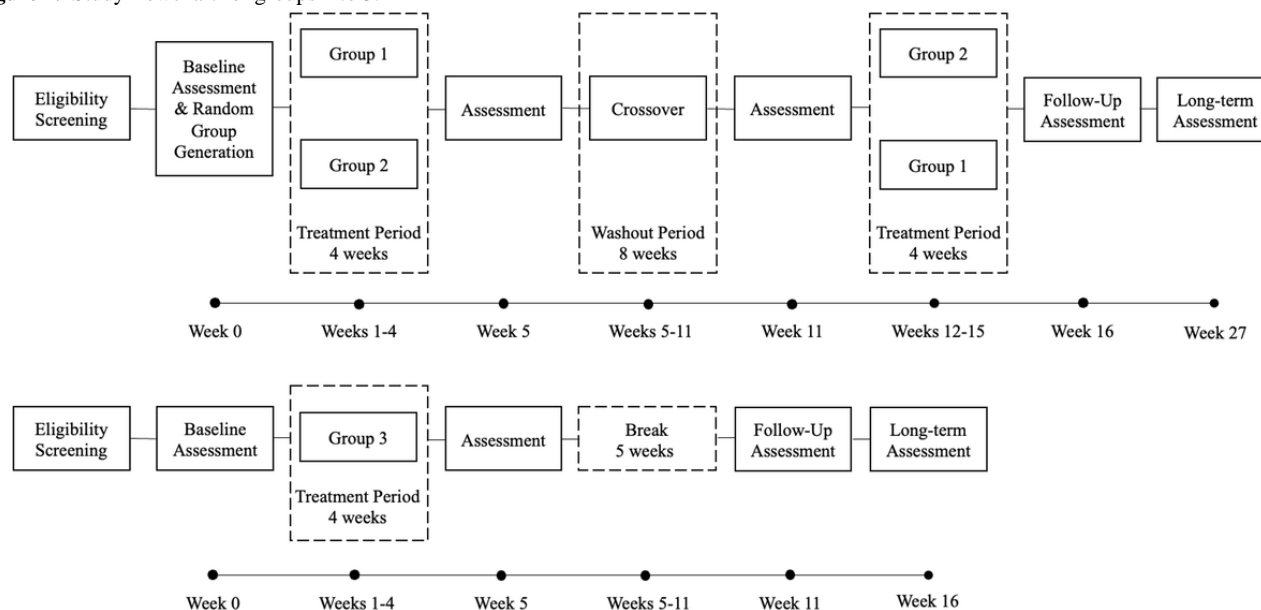
During a learning or problem-solving task, it has been shown that gamma band waves (brain waves faster than 30 Hz) are generated [22]. Previous work has suggested the potential of gamma band stimulation to improve cognitive performance in dementia patients [23], improve working memory [24], and increase attentiveness [25]. Furthermore, the reduction of intracerebral tau protein burden has been proposed as an added benefit of gamma band stimulation [26]. Transcranial alternating current stimulation is one such means of gamma band stimulation. Recent work [14] further supported cognitive improvement in older adults with more sustained improvement in participants who underwent transcranial alternating current stimulation. However, the use of small sample sizes in all studies [14,23-26] limited the conclusions that could be drawn. Thus, given the benefits of gamma band stimulation, transcranial alternating current stimulation is applied at a frequency of 40 Hz with a current density of 0.04 mA/cm^2.

Therefore, participants in group 1 and group 2 receive transcranial alternating current stimulation treatment simultaneously with cognitive exercises. The transcranial alternating current stimulation treatment (Model 2001; Soterix Medication) is applied with a sinusoidal waveform at 40 Hz, with a current amplitude of –0.75 mA to 0.75 mA (1.5 mA peak-to-peak). Electrode placement is measured at the first training session, with the active electrode being placed over the left dorsolateral prefrontal cortex, and the reference electrode being placed on the contralateral supraorbital area.

To prevent unblinding, the auto-sham toggle on the transcranial alternating current stimulation machine is hidden from assessors with a physical barrier. The auto-sham sequence provides the same sensory experience as active transcranial alternating current stimulation by providing a ramp up and down to 1.5 mA at the start of treatment, and again after 10 minutes.

Outcome Measures

At each assessment, 9 tests are conducted over 2 days due to time constraints. The first assessment day comprises the Wechsler Memory Scale Older Adult Battery [27], Montgomery-Åsberg Depression Rating Scale, a verbal fluency test for speech analysis, a visual 1-back task [28], virtual reality navigation [29], the Neuropsychiatric Inventory Questionnaire, and functional near-infrared spectroscopy. The second assessment day includes electrovestibulography and the Alzheimer Disease Assessment Scale (ADAS) cognitive subscale. An assessor is assigned to each participant and performs all 4 assessments with the assigned participant. Only the study participant and the research personnel designated to administer assessments are present during assessments.

The primary outcomes are the changes in patients' scores from baseline in the Wechsler Memory Scale Older Adult Battery and ADAS cognitive subscale assessments. Alternate forms of the ADAS cognitive subscale word lists are employed at each visit to reduce possible practice effects. The secondary outcomes are change in 1-back, Neuropsychiatric Inventory Questionnaire, and Montgomery-Åsberg Depression Rating Scale performance. The 1-back test presents a sequence of random shapes and participants must recall whether a presented object is a repeat of the previous object [28]. Neuropsychiatric Inventory Questionnaire is used to assesses neuropsychiatric symptoms and caregiver burden. Finally, to establish the presence of confounding variables, namely mood disorders, Montgomery-Åsberg Depression Rating Scale is evaluated at each assessment. The secondary exploratory outcome measures use a series of physiological monitoring tools to examine physiological changes in study participants before and after the intervention: (1) virtual reality navigation test to assess spatial orientation [29], (2) electrovestibulography [30-32] to assess static and dynamic vestibular response, (3) functional near-infrared spectroscopy (OctaMonas) [33] to record prefrontal cortex brain activities, and (4) verbal fluency to evaluate acoustic and linguistic changes (Table 2). It should be noted that the exploratory assessments will only be conducted at the Manitoba site.

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Table 2. Study outcome measures.

Outcome measures	Assessments
Primary	
Wechsler Memory Scale Older Adult Battery	Older adult memory
Alzheimer Disease Assessment Scale cognitive subscale	Cognitive dysfunction level in Alzheimer disease
Secondary	
Visual 1-back task	Immediate recall
Neuropsychiatric Inventory Questionnaire	Neuropsychiatric symptoms; caregiver burden
Montgomery-Åsberg Depression Rating Scale	Mood disorders
Exploratory	
Functional near-infrared spectroscopy	Functional brain activity
Virtual reality navigation	Spatial orientation
Electrovestibulography	Static and dynamic vestibular response
Verbal fluency	Acoustic and linguistic changes

Virtual Reality Navigation as a Test for Spatial Orientation

Virtual reality navigation assists in the detection of cognitive impairment by measuring how people orient themselves in an unfamiliar environment [29]. The virtual reality navigation test has two stages of assessment, which are completed on a laptop: (1) target localization from outside a building, and (2) target location inside a building.

Electrovestibulography

Electrovestibulography is a noninvasive recording made from the vestibulo-acoustic system with no motion and with passive whole-body tilt [30-32]. For this study, measurements are performed before and after treatment in order to assess the ability of electrovestibulography to predict treatment outcomes.

Functional Near-Infrared Spectroscopy

Functional near-infrared spectroscopy is an optical technique that uses near-infrared light, which is capable of penetrating the scalp, skull, and other brain tissues to reach gray matter, in order to noninvasively monitor functional brain activity by measuring the flow of oxygenated and deoxygenated blood [33]. Its main benefits are portability, noninvasiveness, and relatively high temporal resolution (100 ms) [33].

Safety Considerations

The transcranial alternating current stimulation procedure used in this study is of minimal risk, though discomfort may arise. Common adverse effects of transcranial alternating current stimulation include mild headache, facial twitches, itching, redness under the electrodes, and light flashes [18]. The application of transcranial alternating current stimulation should be stopped if facial twitches or light flashes are experienced by the participant. Participants are asked at each visit if they have experienced any adverse effects from the treatment. Participants' self-assessment of any pain or discomfort from the treatment are also recorded at every visit. To match similar studies [34], participant transcranial alternating current stimulation sensations are rated on a scale from 1 to 5 at each session, with 1 indicating

no sensations, 2 indicating mild sensations, 3 indicating moderate sensations, 4 indicating strong sensations, and 5 indicating very strong sensations.

Assessment technologies also incur minimal risk. Dizziness may occur during virtual reality navigation, the head band used in functional near-infrared spectroscopy may cause discomfort, and electrovestibulography can result in ear infection if the ears are not properly cleaned after the assessment. In the case of any unexpected issue, or pain and intolerance experienced by a participant, assessments will be halted and risks will be reassessed. All issues will be reported to the appropriate ethics board.

Statistical Analysis

Sample Size Estimation

This study will have 2 equal-sized groups, and it is hypothesized that one group's mean will be significantly different from the other's in one primary outcome measure. As such, the sample size for each group can be calculated [35]. The expected difference and standard deviation for Wechsler Memory Scale Older Adult Battery mean scores between the 2 groups were 20 and 38, respectively, based on the results from a pilot study [14], from which individuals with a Montreal Cognitive Assessment score <5 were removed. With a test power of 80% and significance of 5%, the minimum sample size was estimated as 58 per group. However, due to the study's crossover design, this number was halved. Allowing for a 5% dropout rate, and 20% transcranial alternating current stimulation intolerance rate [14], a total of 75 participants should be enrolled across all 3 groups. Of the total participants, approximately 30 are expected to be recruited at the Alberta study site, and the remaining participants are expected to be recruited at the Manitoba study site.

Analysis

Both parametric and nonparametric statistical techniques will be used. Analysis of the repeated measures crossover data will be performed using fixed and random effect models to investigate different sources of variations in the data set such

as period effect, direct treatment effect, and carryover treatment effects [36]. If raw data are found to not be normally distributed, the Box-Cox transformation will be employed to satisfy the normality assumption needed to perform the analysis [37].

In addition, the differences between study cycle data of the basic crossover design will be analyzed (that is, the differences between active and sham transcranial alternating current stimulation results). Study cycle data differences are used to transform the repeated measurements crossover design to a completely randomized repeated measurements design. With the transformed repeated measurements completely randomized design, analysis is completed by a univariate split-plot analysis of variance or multivariate (over time) F tests [38]. Should normality be in question due to the relatively small sample size, an alternative approach will be used based on nonparametric tests using ranks [39]. Nonparametric tests will include Wilcoxon rank sum and permutation tests to investigate hypotheses 1 and 2 and examine the absence of carryover effects in the study [39].

To have a better understanding of the data set, baseline measurements will be used to perform analysis of covariance. As such, the baseline crossover differences of each outcome measure (Table 2) are regarded as independent explanatory variables and regression of the basic estimators is calculated on said variables [36].

The abovementioned statistical analysis will be applied to the secondary outcome measures, as well.

Ethics

Only participants able to give informed consent are recruited into the study. However, because the study population contains those with memory problems, a family member (or legal guardian) will be required to accompany the patient to the initial interview and sign the consent form for all participants.

Should a patient with Alzheimer disease be unable to provide informed consent, the person's guardian, or an authority or other person having that responsibility at law, is required to provide consent to participate in the research on the individual's behalf. Patients are advised that their participation is voluntary and that they are free to withdraw from the study at any stage.

Study data (participant medical and demographic data, treatment records, and assessment results) are maintained on a password-protected database accessible only to active research team members. All participants are assigned code numbers to ensure anonymity, with study files referencing participant code only. Regular backups of the database are performed and stored on a secure server. Identifying information (name, phone number, address) is not stored on the same system as study data and remains accessible only to staff members who need to contact participants.

Ethical approval for this study was received from the Biomedical Ethics Research Board at the University of Manitoba prior to participant recruitment at the Manitoba study location (HS25171 [B2021:089]). All participants or their legal guardians provide informed consent during the study.

Results

As of February 10, 2022, the study is ongoing: 7 patients have been screened, and all were deemed eligible and enrolled in the study; 4 have completed baseline assessments.

Discussion

This study's design addresses both the short- and long-term effects of transcranial alternating current stimulation in a large study sample, by making comparisons with a sham treatment. Due to the COVID-19 pandemic, recruitment and enrollment slowed as a result of lockdowns imposed by the universities and health authorities.

The major limitation of the protocol is the lack of distinction between transcranial alternating current stimulation effects and cognitive training. A pilot study [14] showed cognitive improvement in patients with and without active transcranial alternating current stimulation treatment due to the combined effect of personal cognitive training. Thus, the independent effects of active transcranial alternating current stimulation treatment in comparison to sham transcranial alternating current stimulation are not discernible using this protocol. However, given the older age of study participants and often rapid degradation of cognitive function in dementia patients, it is the conscious effort of the research team to support brain stimulation even during sham treatments despite its confounding effect on results.

The study has been progressing as expected. Participants have found transcranial alternating current stimulation treatment to be agreeable and have adhered to outset eligibility criteria. Minor side effects, including fatigue and dizziness, have been appropriately addressed and managed during treatment.

Conflicts of Interest

ZM holds the copyright of the MindTriggers app, which is one of the tools used in this study; however, none of the participants are required to purchase the app because practice is conducted onsite where the app is provided for them.

Multimedia Appendix 1

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Peer-review reports (1) from Mitacs Accelerate - Funded Internship Projects (Canada).
[PDF File (Adobe PDF File), 93 KB - resprot_v11i4e37282_app1.pdf]

Multimedia Appendix 2
Peer-review reports (2) from Mitacs Accelerate - Funded Internship Projects (Canada).
[PDF File (Adobe PDF File), 102 KB - resprot_v11i4e37282_app2.pdf]

Multimedia Appendix 3
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 378 KB - resprot_v11i4e37282_app3.pdf]

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Abbreviations

ADAS: Alzheimer Disease Assessment Scale

Protocol

Development and Effectiveness of a Mobile Health Intervention in Improving Health Literacy and Self-management of Patients With Multimorbidity and Heart Failure: Protocol for a Randomized Controlled Trial

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2022/12/e44570

Abstract

Background: Patients with multimorbidity and complex health needs are defined as a priority by the World Health Organization (WHO) and the European Union. There is a need to develop appropriate strategies with effective measures to meet the challenge of chronicity, reorienting national health systems. The increasing expansion of mobile health (mHealth) interventions in patient communication, the reduction of health inequalities, improved access to health care resources, adherence to treatment, and self-care of chronic diseases all point to an optimistic outlook. However, only few mobile apps demonstrate their effectiveness in these patients, which is diminished when they are not based on evidence, or when they are not designed by and for users with different levels of health literacy (HL).

Objective: This study aims to evaluate the efficacy of an mHealth intervention relative to routine clinical practice in improving HL and self-management in patients with multimorbidity with heart failure (HF) and complex health needs.

Methods: This is a randomized, multicenter, blinded clinical trial evaluating 2 groups, namely, a control group (standard clinical practice) and an intervention group (standard clinical practice and an ad hoc designed mHealth intervention previously developed), for 12 months.

Results: The contents of the mHealth intervention will address user-perceived needs based on the development of user stories regarding diet, physical exercise, cardiac rehabilitation, therapeutic adherence, warning signs and symptoms, and emotional management. These contents have been validated by expert consensus. The creation and development of the contents of the mHealth intervention (app) took 18 months and was completed during 2021. The mobile app is expected to be developed by the end of 2022, after which it will be applied to the experimental group as an adjunct to standard clinical care during 12 months.

Conclusions: The trial will demonstrate whether the mobile app improves HL and self-management in patients with HF and complex health needs, improves therapeutic adherence, and reduces hospital admissions. This study can serve as a starting point for developing other mHealth tools in other pathologies and for their generalization to other contexts.

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Introduction

Care of Patients With Multimorbidity and Heart Failure

Although increased life expectancy, socioeconomic improvements, and biomedical innovations have led to a reduction in mortality, they have also led to a considerable increase in chronic conditions. A prevalent paradigm of these socio-health phenomena is the multimorbidity of patients, which is one of the leading health problems of the 21st century. Multimorbidity can alter health outcomes and lead to disability that is more significant or can lead to worse quality of life or frailty [1].

Heart failure (HF) has a high and increasing prevalence and incidence, and is one of the leading causes of morbidity and mortality in the Western world [2]. Further, if we add to this the significant impact of chronic diseases, mainly cardiovascular diseases, cancer, diabetes, and chronic lung diseases [3], the situation becomes even more complicated by the fact that patients are responsible for most of the avoidable hospital admissions. In this line, both the World Health Organization (WHO) and the European Union define a patient with chronic disease as a priority and point out the need to develop appropriate strategies with effective measures to meet the challenge of chronicity, reorienting national health systems [4,5].

According to the latest data published by the WHO [4], heart disease continues to be the leading cause of mortality worldwide. Globally, it was estimated that in 2019, 197.2 million people were living with ischemic heart disease (IHD), and it was more prevalent in males than in females (113.7 and 83.6 million people, respectively). North Africa and the Middle East, Central Asia, and Eastern Europe had the highest prevalence rates of IHD in the world. The number of deaths due to heart disease has increased since 2000 by more than 2 million people, from 6-7 million to almost 9 million people, representing 16% of all deaths. In 2019, IHD mortality rates were 118.0 per 100,000. IHD mortality rates were highest in parts of North Africa and the Middle East, Eastern Europe, and Central Asia [6,7].

In Spain, HF remains an enormous health challenge (estimates suggest that there are more than 1,300,000 people with HF). Besides, more than 17,000 people die from this disease every year, making it the fourth leading cause of death [8] and the third leading cause of cardiovascular death after IHD and cerebrovascular disease. It is also the leading cause of hospitalization in people over 65 years of age; furthermore, 50% die within 5 years of diagnosis. The prevalence of HF increases progressively with age, reaching prevalence rates of 1%, 10%, and 17.4% in the population over 40, 70, and 85 years of age,

respectively. There are more than 80,000 admissions per year in Spain for HF, and half of the hospitalized patients are readmitted within 1 year due to decompensation. Likewise, the use of pharmacological and nonpharmacological resources (resynchronizers or defibrillators) in people with HF is growing exponentially [9].

Although there is a growing interest in patients with comorbidity and multimorbidity, from an evidence perspective, this population has been excluded from most clinical trials and intervention studies [10,11]. Interdisciplinary teams based on the collaboration of different care settings and sustainable interventions adjusted to the public system are recommended. Similarly, a model centered on the patient's needs is reinforced, based on primary care and shared action with hospital care, with proactive and planned interventions aimed at promotion and prevention [12].

Health Literacy as a Health Asset in Patients With Multimorbidity

In the field of public health and health promotion, health literacy (HL) is presented as a means that allows individuals to exercise significant control over their health and over the personal, social, and environmental determinants that determine it, being considered as an individual asset to be built.

Following the theoretical framework proposed by the European Health Literacy Project (European Health Literacy Survey [HLS-EU]) [13], HL is determined by the combination of the 3 dimensions of health (being sick/health care; being at risk/disease prevention, and being healthy/health promotion) and the 4 ways of managing information (finding it, understanding it, evaluating it, and applying it to one's own life to make informed decisions). *Access* refers to the ability to seek, find, and obtain health information; *understanding* refers to the individual's ability to understand the info accessed; *evaluation* describes the ability to interpret, filter, judge, and assess the health information accessed and understood; and *application* refers to the ability to communicate and use the information to decide to maintain and improve health.

Populations that are more likely to experience difficulties in self-managing their diseases are those with low levels of HL [14]. Having poor HL is an independent risk factor for poorer health [15] because of medication errors and a poorer understanding of disease and treatments [16]. Similarly, there is evidence of a relationship between low HL and higher rates of hospital admissions, poorer therapeutic adherence on care plans, and poor use of preventive services [17,18]. In the particular case of people with chronic diseases, HL plays a crucial role in the self-management of their disease [19].

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mHealth: A Digital Health Literacy Proposal

In the last few years, mobile health (mHealth) has emerged prominently as a result of the tremendous sociological and cultural impact of smartphones and tablets.

The Global Observatory for eHealth defines it as "medical and public health practice carried out with the support of mobile devices such as phones, personal digital assistants, Tablets and other wireless communication devices to carry out public health activities and assist in clinical practice" [20].

Despite its expansion in recent years, few studies demonstrate the effectiveness and utility of mHealth in chronic disease self-management beyond diabetes [21,22]. A recent systematic review of clinical trials involving mHealth interventions to improve self-management of patients with chronic diseases, including patients with cancer, HF, fibromyalgia, asthma, and spine bifida, achieved statistically significant effects on health outcomes after the incorporation of mobile apps in disease management [23]. Existing evidence promises an optimistic horizon regarding their effectiveness in chronic diseases [23,24] and, in particular, in patients with cardiac diseases [25,26]. Despite this, we still find contradictory results. For example, the study by Hägglund et al [27] in patients with HF revealed improvements in self-care and quality of life and a reduction in the number of hospitalization days. By contrast, the study by Vuorinen et al [28] found no difference in the number of hospitalization days.

At present, there is a severe deficiency of mHealth tools, which are developed in collaboration with target patients and multidisciplinary teams, are incorporated into daily care practice, and have proven their efficacy in clinical trials [29,30], to improve the self-management of patients with HF having complex health problems. Systematic reviews recently published on this topic [23,25,26] reflect the scarcity of studies aimed at patients with multimorbidity.

Therefore, we aim to develop an app based on the needs of users and deficiencies identified by professionals, which motivates behavior change through gamification strategies, as per scientific evidence and adapted to the user's level of HL, and to test its effectiveness in terms of self-management and improvement of personal autonomy to perform basic activities of daily living, reduce hospital admissions, promote therapeutic adherence, and increase HL.

Methods

Study Design

A randomized, controlled, multicenter clinical trial evaluated the efficacy of an mHealth intervention with 2 groups: a control group (standard clinical practice) and an experimental group (standard clinical practice together with an ad hoc designed mHealth intervention).

Patient Selection

Setting

A total of 4 basic health areas located in the south of Spain, including 2 hospitals, will participate. The health care centers belonging to the clinical management units with the best mortality rates during hospital admission and at 30 days after discharge (12.7% and 14.3 %, respectively) and those with the highest rates (28% and 30.4%, respectively) were considered.

Participants

Patients with multimorbidity with HF and complex health need to be attended by the nurse case manager of the primary care or hospital care centers, nurse or family doctor, or specialized care nurse, or area specialist physician of the study area.

Diagnostic Criteria

Patients with multimorbidity and HF and complex health needs who meet the following diagnostic criteria [12] will be considered:

- Be classified in clinical category A of chronic pathologies for HF that, in a situation of clinical stability, has been in grade II of the New York Heart Association (NYHA) [31], being able to be simultaneously classified, or not, in other clinical categories for having another chronic disease(s) included in these categories.
- Patients with at least one of the following complexity criteria [12]: extreme polypharmacy (≥10 chronically prescribed active ingredients); sociofamilial risk (Gijon scale score [32] >10 points); pressure ulcers of stage II or higher; malnutrition (body mass index <18.5 kg/m^2); nasogastric feeding (≥3 months); 2 or more hospital admissions in the previous 12 months.

Inclusion Criteria

The following inclusion criteria will be applied:

- patients of both sexes over 18 years of age;
- patients attended by health care professionals of the basic health areas participating in the study;
- patients who give their agreement to participate in the study by signing an informed consent form;
- patients who have a mobile device (smartphone or tablet) compatible with the Android or iOS operating system;
- considered as a patient with multimorbidity based on the criteria described in the previous section.

Exclusion Criteria

The following exclusion criteria will be applied:

- patients with sensory deficits or upper limb mobility problems that prevent them from using the app correctly, despite using the accessibility features on mobile devices;
- patients with persistent cognitive impairment (Pfeiffer [33] with ≥5 errors or Lobo Mini-Cognitive Test score <23 [34]) or severe mental disorder;
- patients with severe limitations for basic activities of daily living (Barthel Index <20 points [35]).

Eligibility Criteria

Meet all inclusion criteria and none of the exclusion criteria.

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Completion Criteria and Withdrawal

A patient will be considered to have completed the study when he/she completes the postintervention evaluation. The criteria for withdrawal of a participant will be

- failure to receive the complete intervention (unsolvable technical failures in the device) or by the protocol (failure to use the app);
- loss of compliance with the eligibility criteria during the study or withdrawal of consent to participate;
- inability to contact for follow-up.

Sample Size

The HL will be selected as the main outcome to evaluate the effectiveness. This outcome will be measured using the Spanish version of the 47-Item European Health Literacy Questionnaire (HLS-EU-Q47), which achieved a mean score of 32.88, over a possible range of 0 to 50 points, with an SD of 6.10 in the study setting [36]. An increase of at least 10% in the score will be considered clinically relevant due to the mHealth intervention. Accepting an α risk of .05 and a β risk of .90 in a bilateral contrast, 118 participants were needed in every group. A loss to follow-up rate of 30% was considered. However, the calculation is based on a minimum reference of sample observations, so an effort will be made to recruit as many participants as possible to increase the precision of the estimates.

Intervention

Design of the mHealth App

For the design of the mHealth app, the expert consensus and the modified Delphi will be used. The consensus conference will consist of 12 experts, with 2 representatives having each of the following profiles: (1) health care professional with experience (>5 years) in the care of patients with multimorbidity or HF; (2) university teaching and research staff with experience in research projects in the thematic areas addressed (HL; intervention programs, or patients with multimorbidity); (3) other professionals with experience in research, assistance, or care of patients with multimorbidity (social workers, psychologists, communication professionals); (4) computer engineers with experience in the design of information and communication technology tools; (5) representatives of associations of patients with chronic diseases; and (6) patients with multimorbidity and HF. The consensus sessions will incorporate the main agreements adopted regarding the contents of the intervention program, format, logistical coordination for the development of the program, and proposals for sustainability. Once consensus has been reached, the contents will be established together with the graphic script of the future tool. Delphi rounds will validate the content of the wireframes and the storyboard in terms of relevance (significance of the content for the objective of the intervention program) and appropriateness (content fit). The optimal size for a Delphi group is estimated to be between 6 (minimum) and 30 (maximum) [37]. Considering the response/abandonment rate, we will try to tend to the maximum number of experts who will be different from those that participated in the consensus conference but will meet the same criteria. A 4-point Likert scale (1=no relevance/adequacy and 4=high relevance/adequacy) will be included with each content screen. The experts will be required to evaluate the content's relevance and appropriateness in each screen. The Content Validity Index (CVI) [38] of each screen will be calculated.

Similarly, the Adequacy Index (AI) will be analyzed. The relevance/appropriateness of the screens will be considered good if the CVI and AI are greater than or equal to 0.78 [38]. Those screens that do not reach the preset value in the aforesaid indices will be reviewed and reformulated. Screens' content will also be modified based on the feedback collected and subjected to the same process described above until a final version is agreed upon. This prototype will be sent to a developer to create the mHealth tool under an agile approach. This process (designing, creating, and developing the mobile app) will take 18 months.

Description of the Intervention

The mHealth app aimed at empowering HL and self-management of the patients with multimorbidity with HF and complex health needs. It will be developed ad hoc based on the information obtained from the consensus sessions of experts (patients and professionals) and in accordance with the gamification methodology [39]. Although the final choice of the content will depend on the resulting decisions of the experts, it is intended to offer information and resources to the patient according to the level of HL identified and considering the main actions recommended to be incorporated to improve the overall health outcomes of these patients [12]. Thus, the participants in the experimental group will receive the mHealth app and will agree with the health care professional on 3 objectives related to the self-management of their disease, which they will have to achieve within a proposed period, being assisted by the mobile app, which will provide feedback and reinforcement in the achievement of these objectives. The stages and timing are described in Table 1. The intervention carried out in the control group participants will be based on usual clinical practice. Like the experimental group, they will agree with the health professional on 3 objectives they will have to achieve within the proposed time frame. This process (evaluation of the efficacy of the mHealth intervention with 2 groups) will last 12 months.

Table 1. Stages of intervention.

Stage	Description	Timing (months)
0	Detection of potential study participants. Presentation of the project and collection of informed consent.	✓[a]
1	Baseline data collection for both groups.	✓
2	For both groups, the patient and the practitioner will agree on the first health goal. On an individual basis, the nurse will present the main aspects related to the use and management of the app to the members of the expert group. The patient's expectation of self-efficacy in using the app will be assessed to prevent adherence problems concerning the use of mobile health and difficulties in using the app (digital literacy) will be resolved.	✓ ✓ ✓
3	The patient will come for a consultation to check compliance with the chosen objective. If necessary, a simulation test will be performed to confirm that the challenge has been met. At the end of this stage, the patient and the multidisciplinary team will agree on the second objective.	✓ ✓ ✓ ✓
4	Check compliance with the second objective. Perform simulation test, if required. At the end of this stage, the patient and the multidisciplinary team will agree on the third objective.	✓ ✓ ✓ ✓
5	Check compliance with the third objective. Perform simulation test, if required.	✓
6	Postintervention evaluation: all health objectives were achieved by the patient and postintervention evaluation is performed	✓ ✓ ✓
7	Follow-up	At 12 months after the intervention

[a]✓: achievement record.

Process

Assessment Eligibility

The health care professionals participating in the study will verify that the patient meets the eligibility criteria by consulting the digital history and interviewing the patient.

Randomization

Block randomization has been considered. The total number of participants will be divided by the number of study centers in equal parts. The number assigned will be for each center and will be considered a block in terms of randomization. An external collaborator (blinded) will use a computer-generated randomization list to assign patients to the groups such that, in each block (center), 50% of the patients will go to the control group (usual clinical practice) and 50% to the intervention group (usual clinical practice and mHealth app). This information will be available only to the principal investigator.

Masking

Because of the characteristics of the study, it is not possible to blind it to the participants or to the researchers who will carry out the intervention. However, it will be masked to the researchers who will perform the effectiveness evaluation and data analysis. For this purpose, the coding of the randomization variable will be hidden from them and will be guarded by a person outside the project selected by the principal investigator. In this way, it will not be possible to know which groups received the intervention until the analyses are completed.

Sample Recruitment

Contact with the participants will be established through consultations with the nurse case manager of the basic primary care team of each participating center or the consultations with the hospitals belonging to the scope of the study and patient associations. Once they have ensured that the patient meets the eligibility criteria, the patient will be invited to join the study.

Evaluation of Effectiveness

Sample Characterization, Primary and Secondary Assessment Variables, and Data Source.

See summary in Tables 2 and 3.

Table 2. Measurement, recording, and data source of variables of characterization.

Type of variable	Register rank/format	Measurement	Source of data
Characterization: sociodemographic			
Sex	• Male • Female	Registration	Medical history
Age	• 18-99	Registration	Medical history
Marital status	• Single • Married • Widower • Divorced/separated	Registration	Registration
Nationality	• Spanish • European Union • Rest of Europe • North America • Latin America • Africa • Asia • Other	Registration	Registration
Education level	• No education • Primary school • Secondary school • University degree • Master's degree • Doctorate	Registration	Registration
Occupation	• Employed • Self-employed • Unemployed • Retired • Permanently disabled • Homemaker • Student • Other	Registration	Registration
Characterization: clinical			

Type of variable	Register rank/format	Measurement	Source of data

Main diagnosis	• ICD-9-CM[a] codes:
	  • 402.01
	  • 402.11
	  • 402.91
	  • 404.01
	  • 404.11
	  • 409.91
	  • 428.x
		Registration	Medical history

Years since diagnosis	• 0-100	Registration	Medical history
Other secondary chronic pathologies	• ICD-9-CM codes	Registration	Medical history
HF[b] signs/symptoms (dyspnea, orthopnea, fatigue, edema, oliguria, paroxysmal nocturnal dyspnea, high venous pressure, crackles R3/R4, murmurs and hepatomegaly)	• Yes • No	Registration or exploration or anamnesis	Medical history
Cardiovascular risk factors (smoking, diabetes mellitus II, obesity [weight/BMI], hypertension, previous heart disease, dyslipidemia)	• Yes • No	Registration or exploration or anamnesis	Medical history
HF functional classification (establishes the functional severity of HF based on stress tolerance)	• I: No limitation. Regular physical activity does not cause dyspnea, fatigue, or palpitations. • II: Slight limitation. Usual physical activity causes dyspnea, fatigue, or palpitations. • III: Marked limitation (minor activities cause symptoms). • IV: Inability to perform any activity. Symptoms even at rest.	NYHA[c] Functional Classification [31]	Registration medical history

[a]ICD-9-CM: International Classification of Diseases, 9th revision, Clinical Modification.

[b]HF: heart failure.

[c]NYHA: New York Heart Association.

Table 3. Measurement, recording, and data source of variables of main and secondary responses.

Type of variable	Register rank/format	Measurement	Source of data
Of main response			
Health literacy	• 0/50	• HLS-EU-Q47[a] [36]	• Registration
	• 1-5/indicator	• NOC[b] code: 2015 [29]	• Nursing record
Self-management	• 1-5/indicator	• NOC codes: 3102; 1803; 1830 [9,40]	• Nursing record
	• 12-60	• European Heart Failure Self-Care Behavior Scale [41]	• Nursing record
Number of readmissions 1m;12m	• 0-99	• Registration	• Registration medical history
Secondary response			
Personal autonomy basic activities of daily living	• 0-100	• Barthel Index [35]	• Registration
Personal autonomy instrumental activities of daily living	• 0-8	• Lawton-Brody Index [42]	• Registration
Therapeutic adherence	• 0-4	• Morisky-Green Adaptation Questionnaire [43] and Recipe XXI	• Registration
Vital forecast	• 0-30	• PROFUND Index [44]	• Registration
Satisfaction with service	• 0-10	• Satisfaction Scale	• Nursing record
Mobile health device satisfaction	• 1-5	• Satisfaction Scale	• Built-in mobile health device registration

[a]HLS-EU-Q47: 47-item European Health Literacy Questionnaire.

[b]NOC: Nursing Outcomes Classification.

Security Variables

No adverse effects of patients' exposure in the experimental group were considered, so no safety variables were included in the study.

Data Collection and Custody

Participating nurses and physicians will be responsible for data recording during all stages of the intervention (before training) and the collection and custody of informed consent (Multimedia Appendix 1). A password-coded data file will be created for researchers for the collection of a case. The necessary technical and logistical means will be established to ensure that the processing, communication, and transfer of personal data of all participants comply with the provisions of Organic Law 15/1999 of December 13 to protect personal data [45].

Data Analysis: Data Encoding

A data matrix will be created, and data will be processed statistically using SPSS, version 22 (IBM). Statistical significance will be set at 95% (α=.05).

A uni-bivariate descriptive analysis will be performed to determine the sample distribution for each of the variables studied, both for the total sample and for each group. The characterization variables will be summarized using descriptive statistics, expressing qualitative variables in terms of frequency and percentages and quantitative variables in terms of mean and SD.

Before the analysis, the normality of the variables will be evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Baseline differences in the variables related to the sample profile between the intervention and control groups will be compared using the Student *t* test when these are normally distributed and the nonparametric Mann-Whitney *U* test in case they are not. Differences between dichotomous qualitative variables will be established using the chi-square test or Fisher statistic when appropriate.

A contrast of means will be applied to test the efficacy of the intervention in terms of the normality distribution of the variables. The results will be analyzed using the nonparametric Wilcoxon signed-rank test, which will allow us to check if there are differences between 2 populations from 2 dependent or related samples, or the Student *t* test for normally distributed samples. For independent samples, the nonparametric Mann-Whitney *U* test will be used.

The strength of the relationship between continuous data will be determined from the Pearson or Spearman correlation. The intraclass correlation coefficient will be used if it is necessary to measure concordance between measurements at different times of the study. To identify sociodemographic and clinical characterization variables (independent variables) related to the intervention and the different response variables (dependent variables), multivariate, linear, logistic, or Cox proportional analyses will be performed, as appropriate for each response variable.

Ethics and Dissemination

This study has been approved by the Cadiz Research Ethics Committee. The aim of the study and the anonymity of participants, as well as the voluntary nature of participation, will be explained before the participants start and their informed consent will be requested. The participants will also be informed that the data obtained would be used for research purposes only. Findings from this study will be disseminated through peer-reviewed scientific journals and at key national and international scientific events. The study was registered in ClinicalTrials.gov (trial registration number: NCT04725526) on January 26, 2021.

Public/Patient Involvement Statement

Neither the patients nor the general public were involved in the design, or conduct, or reporting, or dissemination plans of the study.

Results

The content validation to develop the mobile app was completed in 2021. To optimize material and human resources, the research team has been divided into 6 working subgroups that correspond to the main areas of action for patients with multimorbidity with HF: (1) physical exercise and cardiac rehabilitation, (2) nutrition, (3) medication and therapeutic adherence, (4) warning signs and symptoms, (5) self-care/self-management (which includes the elimination of toxic habits), and (6) emotional management.

Throughout the first year of the project, comprehensive/systematic bibliographic reviews of the scientific evidence on mHealth interventions (by the thematic areas described above) aimed at improving the evolution/care of patients with multimorbidity with HF have been carried out.

Individualized telephone interviews with patients were conducted to obtain information on their opinions, needs, and experiences about the disease management. This information has been incorporated into the objectives/contents of the mHealth app. Based on these data, an expert consensus (professionals and patients) has been conducted to establish the contents and structure of the mobile app to proceed with the content validation and its beta version.

The results of the primary and secondary variables recorded in the experimental group (health literacy, number of readmissions, self-management, therapeutic adherence, general satisfaction, and performance in activities of daily living) will improve and there will be significant differences with the control group. The findings will be disseminated to stakeholders using various methods, including peer-reviewed journals, academic conferences, and other verbal and digital communication channels. In relation to the patentability of project results, the resulting mHealth app will be registered as an intellectual property.

Discussion

Study Summary

To our knowledge, this is the first study to develop a protocol for a randomized controlled trial of an mHealth intervention to improve HL and self-management in patients with multimorbidity with HF and complex health needs that is based on patients' perceived needs. The content of the intervention has already been validated.

We will investigate the efficacy, effectiveness, and usability of the proposed intervention in patients with multimorbidity and HF. The experimental group will use the app, hoping that the results of the primary and secondary variables recorded will improve and that significant differences will become evident after use and after comparison with the control group.

It is expected that the intervention developed will be effective and, therefore, improve the level of HL, self-management and therapeutic adherence, reduce the number of admissions per year due to decompensation, and that the incidence rates of HF mortality (adjusted for age, sex, and risk) or 30-day postdischarge mortality of the experimental group under study will be lower than that of the control group.

Limitations

This study has some limitations that should be acknowledged. The lack of adequate mobile devices or the sensory or cognitive deficits of the target population is taken into account. Likewise, their digital illiteracy could be another limitation. Therefore, and being aware of the population group, digital training is contemplated. As for cognitive impairment, the usual caregiver is included in the intervention.

When evaluating the effectiveness of the intervention, we can find the influence of the variable "time of use of the app" (a record of access to the app will be obtained and monitored).

Finally, we must be aware of the possible loss of participants due to their clinical characteristics. Therefore, when determining the sample size, a loss rate of 30% has been taken into account. The aim is to obtain as many participants as possible to increase the precision of the estimates.

Strengths

With the aim of overcoming the aforementioned limitations, a qualitative analysis of the risks has been carried out and has been prioritized according to the factor of exposure and urgency.

Randomized controlled trials are considered the "gold standard for assessing efficacy in clinical research and constitute evidence for treatment" [46]. By adopting such a trial and ensuring internal and external validity, we maximized the robustness of our study.

In addition, the multidisciplinary nature of this project is evident in the composition of the research team (psychologist, nurses, physicians, computer engineers), in the incorporation of professionals and patients for its development, and in the association of the 2 public organizations involved in it.

Finally, the cross-cutting nature of this project is reflected in the consideration of the different dimensions of health and the different levels of health care (primary and hospital care). By contrast, the main variable of this project (HL) has a cross-cutting nature as it has been recognized as a basic social determinant for improving health outcomes.

Conclusions

The results of this intervention support the coordinated work between hospital care and primary care, which will have an impact on the improvement of health care and management, thus favoring the continuity of care and the reduction of hospital readmissions in this population.

The incorporation of the mobile app developed will optimize the work performed by professionals while increasing patients' HL and reducing the number of consultations requested and, ultimately, health care costs.

This study can serve as a starting point for developing other mHealth interventions in other pathologies and for their generalization to other contexts.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed consent.
[DOCX File , 20 KB - resprot_v11i4e35945_app1.docx]

Multimedia Appendix 2
Peer-Review report from El Instituto de Investigación e Innovación en Ciencias Biomédicas de la Provincia de Cádiz (INiBICA) - Fundación Biomédica Cádiz - Proyectos Investigacion Innovacion (Cádiz, Spain).
[PDF File (Adobe PDF File), 44 KB - resprot_v11i4e35945_app2.pdf]

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Abbreviations

AI: Adequacy Index
CVI: Content Validity Index
HF: heart failure
HL: health literacy
HLS-EU: European Health Literacy Survey
HLS-EU-Q47: 47-item European Health Literacy Questionnaire
ICD-9-CM: International Classification of Diseases, Ninth Revision, clinical modification

IHD: ischemic heart disease
mHealth: mobile health
NOC: Nursing Outcomes Classification
NYHA: New York Heart Association
WHO: World Health Organization

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Protocol

Effectiveness of Hydrotherapy on Neuropathic Pain and Pain Catastrophization in Patients With Spinal Cord Injury: Protocol for a Pilot Trial Study

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Abstract

Background: Neuropathic pain (NP) is one of the most frequent spinal cord injury (SCI) complications. Pain, quality of life, and functionality are associated and can lead to pain catastrophization. Pharmacological management of patients with NP secondary to SCI is widely known and there is increasing evidence in the area. Nevertheless, nonpharmacological management is not fully elucidated since its efficacy is inconclusive.

Objective: We hypothesize that (1) hydrotherapy is effective in reducing NP secondary to SCI. Additionally, our secondary hypotheses are that (2) hydrotherapy decreases the catastrophization of NP, and that (3) hydrotherapy improves life quality and minimizes the degree of disability, when compared to physical therapy.

Methods: A sample of approximately 20 participants will be randomly assigned to either the intervention (hydrotherapy) or control group (standard physical therapy). Both interventions will be administered twice a week over a 9-week period (18 sessions in total). Primary outcomes are changes in neuropathic pain perception and pain catastrophization. Secondary outcomes are changes in disability and quality of life scores. They will be assessed at baseline and follow-up at 4 weeks after discharge. Validated Spanish language scales that will be used are the following: Numerical Pain Rating Scale, Pain Catastrophization, Health-related Quality of life, and the World Health Organization's Disability Assessment Schedule 2.0. Generalized mixed linear models will be used for comparing baseline and postintervention means of each group and their differences, together with 95% CIs and *P* values. A *P* value of less than .05 will be considered significant.

Results: Recruitment began in April 2019, and we recruited the last participants by December 2019, with 10 individuals assigned to hydrotherapy and 8 to physical therapy (control). Results from this study will be disseminated via scientific publication, in ClinicalTrials.gov, and in national and international conferences in the latter half of 2022.

Conclusions: This trial will explore the effects of hydrotherapy on neuropathic pain, together with functionality and quality of life, in patients with SCI. Furthermore, this study aims to evaluate these therapeutic modalities, including perception variables, and mental processes, which may affect the clinical condition and rehabilitation outcomes in these patients. Hydrotherapy is

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likely to be a safe, efficient, and cost-effective alternative to the current standard of care for NP secondary to SCI, with comparable results between the two.

Introduction

Background

Neuropathic pain (NP) is one of the most frequent spinal cord injury (SCI) complications, with the most negative impact on quality of life [1]. Patients with NP show significant differences in quality of life when compared to those without it [2]. The prevalence of NP secondary to SCI varies depending on the population characteristics, chronicity of the lesion, and the criteria of defining it. In a meta-analysis, the prevalence of NP in patients SCI was 53% (95% CI 38.58-67.47) [3], with a prevalence of 47.8% being observed in Cali, Colombia [4-6]. Pain, quality of life, and functionality are proven to be associated, and patients with secondary NP to SCI are affected in these areas [7,8], thus limiting participation in daily activities and self-care. Chronic pain has an effect on emotional state, as well as cognition, in regard to pain anticipation, which can further lead to catastrophization.

The term "pain catastrophization" is of a recent use, consisting of three components: rumination (putting excessive focus on the painful sensation), magnification (exaggerating the damage), and perception of inability to control the symptom [9]. Different strategies have been proposed to alleviate the complications of SCI [10-12]. The pharmacological management of patients with NP secondary to SCI is widely known, and there is increasing evidence of anticonvulsant and antidepressant use for its management [13,14]. Nevertheless, the nonpharmacological management is not fully elucidated since the efficacy is inconclusive. Previous studies reported interventions such as transcranial electrical stimulation, acupuncture, and transcutaneous electrical nerve stimulation [15,16], which improved NP in patients with SCI; however, more evidence on other nonpharmacological interventions is needed.

The physiological mechanisms of hydrotherapy on pain are well established [17,18], and there is evidence of its use in the management of painful syndromes such as fibromyalgia and chronic lower back pain [19-21]. In patients with multiple sclerosis, it has been found that hydrotherapy improves quality of life [22]; this also holds true for patients with mild Parkinson disease, where hydrotherapy had improvements on functional mobility [23,24]. Additionally, there have been registered improvements in active neck mobility in cases of cervical dystonia [25] and in postural balance of patients with stroke [26,27]. The effects of hydrotherapy in patients with NP secondary to SCI are currently unknown.

Primary and Secondary Objectives

The main study hypothesis is that (1) hydrotherapy is effective in reducing NP in patients with SCI. Additionally, our secondary hypotheses are that (2) hydrotherapy decreases the catastrophization of neuropathic pain, and that (3) hydrotherapy improves life quality and minimizes the degree of disability, when compared to the other physical therapy techniques.

Methods

Trial Design

We will carry out a single-masked pilot trial of parallel groups in usual clinical practice conditions, with an allocation ratio of 1:1 (SPIRIT checklist in Multimedia Appendix 1 and the World Health Organization's Trial Registration Data Set in Multimedia Appendix 2).

Participants

Participants will be recruited in two strategies: the first one involves screening eligible people in the SCI clinic in a prospective manner among those with appointments, and the second one involves calling participants in a follow-up call from the spinal cord service to check for their eligibility (Multimedia Appendix 3). Those eligible to participate in the study are patients who have a confirmed diagnosis of NP secondary to trauma in accordance with the International Spinal Cord Injury Pain classification [28], based on their clinical evaluation and physical examination, and those who meet the following criteria: ≥18 years of age, Douleur Neuropathique-4 (DN-4) score of ≥4 [29], and level of injury below C3. Exclusion criteria are as follows: active pressure ulcers, grade E of the American Spinal Cord Injury Association (ASIA) classification [28], cognitive impairment, ostomies, permanent bladder catheter, signs of systemic inflammatory response or urinary symptoms, major surgery in the past 2 months, noncontrolled hypertension (defined as a systolic blood pressure of >185 mm Hg or a diastolic blood pressure of >110 mm Hg refractory to treatment), active dyspeptic ulcer, severe liver fibrosis or portal hypertension, acute pericarditis or pancreatitis, known renal failure or requirement of hemodialysis or peritoneal dialysis, in-hospital stroke, and current participation in another clinical trial.

Medical Assessment

The evaluation will begin with sociodemographic questions and presence of complications secondary to the SCI (participant questionnaire in Multimedia Appendix 4). In addition, the checklist of exclusion criteria for participation in the study will

be verified (checklist of inclusion and exclusion criteria in Multimedia Appendix 5). In this initial evaluation, first measurement (baseline) will be performed. The medical examination will last 20 minutes and will be performed by a resident of the physical medicine and rehabilitation program. Once the medical evaluation is finished, the participants will be randomized into the control or intervention groups.

Randomization

Participants will be assigned to one of the 2 groups by means of random blocks of 4, constructed with all possible combinations of the order of assignment based on random numbers (randomization protocol in Multimedia Appendix 6). The randomization list will remain with the coordinator for the whole duration of the study. Thus, randomization will be

conducted without any influence of the principal investigators, interviewers, clinical evaluators, or therapists. The data analyst will be masked of participants' allocation.

Assignment of Interventions

The groups compared in this study are the intervention (hydrotherapy) and control (standard physical therapy) groups. This control group was chosen as the current standard of care for nonpharmacological management of NP in SCI is physical therapy [30-32].

Participants will be assessed as follows: at the beginning of the intervention (baseline; Time 1) and at the end of the intervention (4 weeks after discharge; Time 2). Table 1 describes the schedule with procedures and the assessments scales in the trial timeline.

Table 1. Schedule of enrollment and assessments.

Time point (T)	T1: baseline (week 0)	T2: follow-up (week 4)
Enrollment		
Project information: written or oral communication	✓	
Written informed consent	✓	
Eligibility assessment	✓	
Randomization	✓	
Assessment		
Douleur Neuropathique-4 items	✓	
Primary outcomes		
Pain catastrophization Scale	✓	✓
Numerical Pain Rating Scale	✓	✓
Secondary outcomes		
Quality Short-Form Health Survey 36	✓	✓
World Health Organization Disability Assessment Schedule 2.0	✓	✓

Interventions

Participants in both groups will receive treatments twice a week for 9 weeks, resulting in a total of 18 sessions. Each session will last 1 hour. A 9-week period of interventions is considered because antidepressant and anticonvulsant drugs, which act on the intensity of neuropathic pain, cause effects after 3 weeks of administration. Since the pathophysiological mechanisms of interventions are similar [33], we are expecting to see initial effects only after this period. Additionally, previous studies with hydrotherapy and physical therapy also provided interventions in a 4-8–week period [34,35]. The second assessment has been scheduled 4 weeks after discharge since that time frame has proven as an adequate threshold for evaluating short-term training program efficacy in patients with SPI [30]. Participants will be scheduled for the therapy sessions and will be followed-up by a research coordinator who will remind the participants about their appointments.

The department of physical medicine and rehabilitation has 3 physical therapists specialized in hydrotherapy under different modalities, and a pool equipped to perform this type of intervention. The most commonly used techniques in the

institution are Bad Ragaz [36] for motor control and the Watsu technique [37] for relaxation and spasticity management. The standard physical therapy protocol and the hydrotherapy protocol were reviewed by a panel of therapists and researchers. These protocols include technical and clinical adjustments to standardize therapeutic objectives of the interventions (standard physical therapy protocol in Multimedia Appendix 7 and the hydrotherapy protocol in Multimedia Appendix 8). Participants in any group can receive alternative treatments including medications for pain and physical therapy. They will inform researchers through the surveys and measurements of the study, so that the effects of those extra interventions in the analysis can be accounted for. Interventions will be discontinued if the participant requests it or owing to the appearance of exclusion criteria or severe adverse events (adverse event report form in Multimedia Appendix 9).

Follow-up

After assignment to the intervention or control group, it is possible that participants voluntarily leave the study, withdraw owing to medical indications, are lost during follow-up, or deviate from the protocol. These will be defined in accordance

with the CONSORT statement and will be recorded in a specific format for follow-up (form: causes of withdrawal in Multimedia Appendix 10) [38]. Participants who withdraw from the interventions will be invited to answer the follow-up questionnaire at least three times via phone call.

Data Collection

To identify the presence of neuropathic pain, the DN-4 will be used [29], which consists of ten items: 7 related to pain characteristics through an interview and the other 3 items through a clinical examination. This questionnaire, which is validated in Spanish [39], consists of descriptions and pain signs, which are evaluated dichotomously (Yes/No) in order to identify patients who have a high probability of having NP. The scores of the individual items are added together to obtain a maximum total score of 10, with a cut-off point of ≥4 (participant questionnaire in Multimedia Appendix 4).

Primary outcomes will be assessed with the Pain Catastrophization Scale (PCS) [40], the Numerical Pain Rating Scale (NPRS) [41,42], and the ASIA impairment scale [43]. The PCS is an instrument validated in Spanish for pathologies such as fibromyalgia, amputees, and patients with NP following SCI [44,45]. It inquiries about the thoughts and feelings that arise in the presence of physical pain caused by diseases, wounds, surgeries, etc. This scale has 13 items rated on a Likert scale from 0 to 4 (0=nothing at all, 1=a little, 2=moderately, 3=a lot, and 4=all time) [40,46,47]. The NPRS is a scale used in various clinical settings for multiple health conditions and measures pain intensity subjectively through a rating of 0 to 10, where 0 indicates no pain and 10 indicates the worst pain ever experienced [41,42,48]. The ASIA impairment scale is used as a universal classification tool for SCI, determining the level of sensory and motor impairment on each side of the body, single neurological level of injury, and whether the injury is complete. It will be used to quantitate sensory testing, limited by the point upon which the level and nature of SCI are present [43].

Secondary outcomes will be assessed with the Spanish version of the Quality Short-Form Health Survey, a generic scale evaluated in numerous studies [49]. This scale assesses health-related quality of life, and has been used in patients with SCIs, among other health conditions [2,50,51]. It has 36 items distributed in subscales of physical functioning, physical role, body pain, general health, vitality, social function, emotional role, and mental health. It contains Likert-type and dichotomous (Yes/No) questions with a minimum score of 0 and maximum of 100. Similarly, disability will be assessed using the World Health Organization's Disability Assessment Schedule 2.0 questionnaire, which inquiries about difficulties that the individual has owing to a particular health condition [52]. For this study, the 12-item version will be used, which is composed up of a Likert scale ranging from 1="no difficulty" to 5="extreme difficulty" or "cannot do it." The scores will be averaged for analysis [52]. In addition, sociodemographic and clinical questions will be asked for the adjustment of the analysis in a general information format (participant questionnaire in Multimedia Appendix 4). There will not be a run-in or washout period.

Data Management, Monitoring, and Auditing

The Steering Committee (SC) is formed by the team of researchers and presided by the principal investigator. It will meet on weekly basis to analyze the therapists' clinical notes, which will be recorded after each session of therapy from both groups in order to verify participants' attendance, their adaptation to therapy, adverse effects, contraindications, and clinical evolution. The follow-up survey (exit survey) will be scheduled 4 weeks after the end of the therapies in both groups. Participants will be assessed twice: in a baseline survey, and in a follow-up survey at the end of the interventions. To identify the survey as baseline or follow-up, the numbers "_0" or "_1" will be used at the end of the code of each survey to indicate the type of measurement. This database will be managed in accordance with the rules of security and confidentiality of the information, which govern the health care institution and Universidad del Valle. Any serious adverse event will be assessed and classified by the Data Safety Monitoring Committee. The trial will be ended using a P value of <.001 as a stop boundary. There will not be any interim analysis.

Ethics Approval

The study is endorsed by the Department of Physical Medicine and Rehabilitation, Hospital Universitario del Valle, Cali, Colombia. It was approved by the institutional review board of Universidad del Valle and Hospital Universitario del Valle (Internal Code 143-018/research ethics approval act 011-018). Additionally, the research complies with ethical standards of the Declaration of Helsinki; and in Colombia, it complies with the Ministry of Health resolution number 8430 of 1993. Since this study is considered to have "greater than minimum risk," as it is a pilot trial where clinical interventions are conducted, there is, among other things, a risk of falls when entering and leaving the pool or a presence of fungal skin infections due to moisture. Before starting the medical evaluation, written informed consent for the study will be presented to participants by trained interviewers. These interviewers are not part of the medical assessment or randomization. Participants who agree to participate will sign the consent form, together with the required signatures of two witnesses (informed consent in Multimedia Appendix 11). Patient identities will be kept confidential, and an alphanumeric code will be used to identify each patient without enabling the distribution of personal data. The information that will be obtained in this study will be kept confidential, its use will be exclusive to the researchers, and disaggregated data will not be presented or used in a particular way that may lead to disclosure of confidential information, violation of any of the participants' rights, or to the participants feeling stigmatized or discriminated against.

Availability of Data and Material

Data cannot be made publicly available since that would compromise confidentiality and might reveal the identity or location of participants. Additionally, public availability of data would be in violation of the Colombian Law 1581 of 2012 and the Regulatory Act 1377 of 2013 and Article 15 of the Colombian Constitution for treatment and protection of personal data. The SC could consider those requests once the data are fully collected, and identifiers have been destroyed with

approval of the institutional review board of the participating institutions. There are no contractual agreements that limit investigators' access to data.

Statistical Analysis

Sample Size and Power Calculation

In order to demonstrate recruitment feasibility, 20 participants will be enrolled (10 per group) in accordance with sample size recommendations for pilot studies [53]. As this is a pilot study, power calculations were not performed.

Descriptive Analysis

The categorical variables will be described in terms of frequency and percentage, and for hypothesis testing, chi-square test or the Fisher exact test will be used. Quantitative variables will be described with measures of central tendency and dispersion, and hypothesis tests based on the type of variables to be analyzed as well as the assumptions of each test.

Effectiveness of the Intervention

Treatment effects will be derived using longitudinal modeling of within-person change in mean scores of the scales and subscales' scores from baseline to follow-up. Baseline characteristics of participants in both groups will be compared using the chi-square or 2-tailed Fisher exact test for categorical variables, and the Student t test or Wilcoxon test for continuous variables, after assessing the tests' assumptions. Statistical significance will be set at a 2-tailed α of .05, expressed as a 95% CI.

Analysis of Outcomes

An intent-to-treat analysis, which will include all study participants based on participants' arm allocation will be used. A random effects model will be used to estimate the effect of hydrotherapy by including time points (0 = baseline, 1 = follow-up) and participant ID as random effects to account for within-person correlation across time and between-person correlation. Participants lost to follow-up will be handled using single imputation procedures on the basis of the amount of missing and their distribution.

Results

The first patient was enrolled in the study on March 30, 2019. The project timeline was changed owing to the COVID-19 pandemic and therefore delayed. Recruitment began in April 2019 and we recruited the final participants by December 2019. Figure 1 shows the flow diagram of the study. Participants were selected from the database of patients registered at the Spinal Trauma Clinic, Physical Medicine and Rehabilitation Unit of a Specialized Trauma Center [54]. We have collected information from 18 participants, including 10 in the hydrotherapy group and 8 in the physical therapy group. Results from the study will be disseminated via scientific publication, in ClinicalTrials.gov, and in national and international conferences in the second part of 2022. Authorship will be defined on the basis of the International Committee of Medical Journal Editors' criteria for authorship. The authors do not have publication restrictions and will not use professional writers when reporting the results.

Figure 1. Flow of the study.
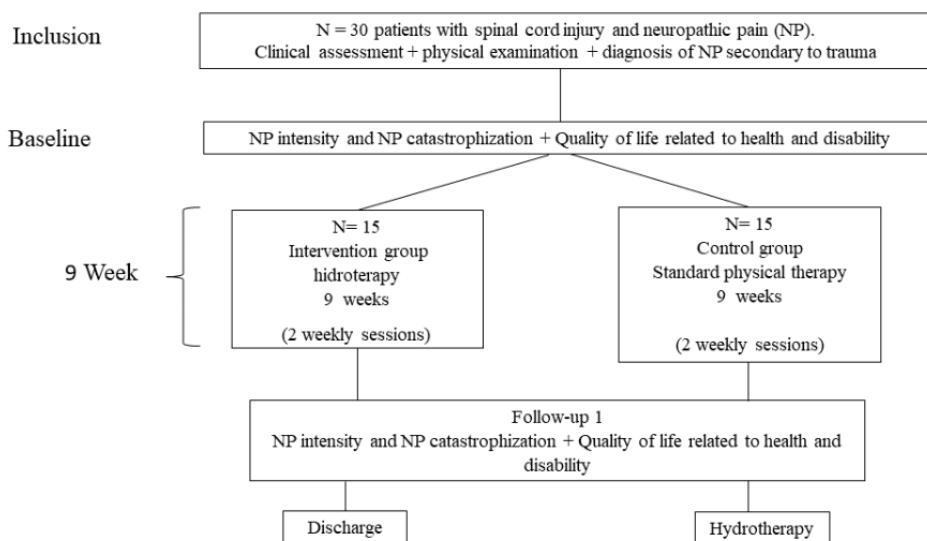
Discussion

Expected Findings

The expected main findings of this study are as follows: (1) effects on minimizing disability and improving quality of life between current standard and novel hydrotherapeutic approach are comparable; (2) hydrotherapy is a safe, efficient, and effective alternative to the current management of NP secondary to SCI; (3) given a choice, patients are more likely to choose hydrotherapy rather than the current standard of care if both options are presented to them. To our best knowledge, this is the first trial that proposes to evaluate the effects of hydrotherapy in the NP reduction in Latin America.

The purpose of rehabilitation is to maximize patients' daily functional independence through a goal-oriented treatment [55]. Heterogenous results from previous hydrotherapeutic studies on patients with diabetic or other metabolic neuropathies do not allow for definitive conclusions [56]. Conversely, the hydrotherapeutic approach for patients with peripheral neuropathies has yielded positive results on gait and balance, which, besides pain, are the most commonly presented symptoms in our patient cohort [6,57].

The presence of a control group is necessary, since there are no currently available nonpharmacological treatments with evidence for NP management in patients with SCI. The pilot trial design with parallel groups aims to provide preliminary evidence on the clinical efficacy of hydrotherapy on NP secondary to SCI, with a single-masked study design being performed in order to alleviate bias. Consideration of a DN-4 score of ≥4 out of 10 for the identification of NP and mixed pain syndromes [39] ensures adequate screening in our trial population. This questionnaire has been suggested for epidemiological studies, where accurate identification of NP symptoms is also crucial to test in order improve therapeutic approaches.

Assessment of an alternative treatment to pharmacological management of neuropathic pain is reasonable, considering preclinical evidence on neuroendocrine changes facilitated by aquatic treatment, at the level of encephalin, corticotropins, endorphins, and prolactin, who are responsible for conduction of pain stimuli [58]. Accordingly, it may improve the prognosis of pain and its catastrophization [9,59]. Furthermore, this study will explore the evaluation of these therapeutic modalities, including variables related to perception and mental processes, which may affect the clinical condition and rehabilitation outcomes of these patients [46].

Limitations

This study has some limitations. Given the single-center design of our study, the generalizability of our results will be limited. Even though we have accounted for patients lost to follow-up, true percentages might be higher than expected, therefore skewing our findings. Despite the advantages of a single-masked trial design, double-masked trials are prone to less pitfalls [60].

Conclusions

Hydrotherapy is likely to be a safe, efficient, and cost-effective alternative to the current standard of care for NP secondary to SCI, with comparable results between the two.

Since this is a pilot trial, randomized controlled trials with calculated power levels and sample sizes will be warranted in order to provide conclusive answers on noninferiority or superiority of the proposed treatment effect.

Authors' Contributions

ARC, FJBE, SGPQ, MATS, and OMHO conceptualized the study. MATS, FJBE, SGPQ, ARC, and OMHO acquired funding. FJBE, SGPQ, MATS, ARC, OMHO, LMLP, GPAH, and AM designed the study methodology. MATS, FJBE, and SGPQ were in charge of the administration of the study. MATS and FJBE supervised the study. SGPQ, ARC, LMLP, and FJBE drafted the manuscript. FJBE, SGPQ, MATS, ARC, OMHO, LMLP, GPAH, and AM reviewed and critically revised the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[DOCX File , 55 KB - resprot_v11i4e37255_app1.docx]

Multimedia Appendix 2
World Health Organization trial registration data set.
[DOCX File , 17 KB - resprot_v11i4e37255_app2.docx]

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Multimedia Appendix 3
Telephone contact protocol.
[DOCX File , 24 KB - resprot_v11i4e37255_app3.docx]

Multimedia Appendix 4
Participant questionnaire.
[DOCX File , 71 KB - resprot_v11i4e37255_app4.docx]

Multimedia Appendix 5
Checklist of inclusion and exclusion criteria.
[DOCX File , 19 KB - resprot_v11i4e37255_app5.docx]

Multimedia Appendix 6
Randomization protocol.
[DOCX File , 37 KB - resprot_v11i4e37255_app6.docx]

Multimedia Appendix 7
Standard physical therapy protocol.
[DOCX File , 22 KB - resprot_v11i4e37255_app7.docx]

Multimedia Appendix 8
Hydrotherapy protocol.
[DOCX File , 22 KB - resprot_v11i4e37255_app8.docx]

Multimedia Appendix 9
Adverse event report form.
[DOCX File , 21 KB - resprot_v11i4e37255_app9.docx]

Multimedia Appendix 10
Form: cause for withdrawal.
[DOCX File , 17 KB - resprot_v11i4e37255_app10.docx]

Multimedia Appendix 11
Informed consent.
[DOCX File , 36 KB - resprot_v11i4e37255_app11.docx]

Multimedia Appendix 12
Peer review report 1 from the Universidad del Valle - Vicerrectoría de Investigaciones (Cali, Colombia).
[PDF File (Adobe PDF File), 34 KB - resprot_v11i4e37255_app12.pdf]

Multimedia Appendix 13
Peer review report 2 from the Universidad del Valle - Vicerrectoría de Investigaciones (Cali, Colombia).
[PDF File (Adobe PDF File), 36 KB - resprot_v11i4e37255_app13.pdf]

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Abbreviations

ASIA: American Spinal Cord Injury Association
DN-4: Douleur Neuropathique-4
NP: neuropathic pain
NPRS: Numerical Pain Rating Scale
PCS: Pain Catastrophizing Scale
SC: Steering Committee
SCI: spinal cord injury

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Protocol

Developing a Clinic-Based, Vaccine-Promoting Intervention for African American Youth in Rural Alabama: Protocol for a Pilot Cluster-Randomized Controlled Implementation Science Trial

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Abstract

Background: African American youth in rural Alabama are clinically underserved and have limited knowledge about the human papillomavirus and the novel coronavirus 2019 (COVID-19) vaccines, including knowledge about the risk for developing cervical or oropharyngeal cancers or COVID-19.

Objective: In this 30-month study, we propose to develop an in-clinic, youth-tailored, vaccine-promoting intervention for vaccine hesitancy reduction that can be seamlessly integrated into the existing environments of pediatric and family practice settings in rural Alabama.

Methods: This exploratory, sequential mixed methods study will be conducted in 3 phases. In the first phase, we will assess stakeholders' knowledge, sentiments, and beliefs related to vaccination in general, COVID-19 vaccination, and human papillomavirus vaccination. We will also assess stakeholders' perceptions of barriers to vaccination that exist in rural Alabama. This will be followed by a second phase wherein we will use the data collected in the first phase to inform the development and finalization of a noninvasive, modular, synchronous counseling intervention that targets the behaviors of 15- to 26-year-old adolescents. In the third phase, we will conduct a pilot hybrid type 1 effectiveness-implementation cluster-randomized controlled trial to assess intervention acceptability and feasibility (clinics: N=4; African American youth: N=120) while assessing a "clinical signal" of effectiveness. We will document implementation contexts to provide real-world insight and support dissemination and scale-up.

Results: The study was funded at the end of December 2020. Approval from the University of Alabama at Birmingham Institutional Review Board was obtained in May 2021, and the qualitative data collection process outlined in the first phase of this project concluded in November 2021. The entire study is expected to be complete at the end of December 2023.

Conclusions: The results of the trial will provide much needed information on vaccine hesitancy in rural Alabama, and if found efficacious, the intervention could notably increase rates of vaccinations in one of the most underserved parts of the United States. The results from the trial will provide information that is valuable to public health practitioners and providers in rural settings to inform their efforts in increasing vaccination rates among 15- to 26-year-old African American youth in rural southern United States.

Trial Registration: ClinicalTrials.gov NCT04604743; https://clinicaltrials.gov/ct2/show/NCT04604743

International Registered Report Identifier (IRRID): DERR1-10.2196/33982

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Introduction

Background

National estimates indicate that about half (49%) of adolescents (aged 13-17 years) are up-to-date on their human papillomavirus (HPV) vaccines, with about 66% of same-aged adolescents having received at least 1 dose of the HPV vaccine [1]. Notably, fewer adolescents in rural settings accept the HPV vaccine [1]. Adolescents in rural communities have an HPV vaccination rate that is 15% lower than that of their peers in urban centers (at about 34%) [2]. In Alabama, the average HPV vaccination rate (series completion) is about 20%—nearly 30% lower than the national average and 14% lower than the average for rural communities [3]. Some Alabama rural counties have HPV vaccination rates that are as low as 9%, with many Alabama counties clustering between 10% and 25% [3]. These rural counties exhibit high rates of poverty, have limited access to health care, and are home to many African Americans. For example, Alabama's Greene Country has an HPV vaccination rate of 18%. Further, 80% of Greene Country residents identify as African American, residents' average household income is US $21,339, and only 16% of residents hold a college degree or higher [4].

To date, almost 1 million American lives have been lost to COVID-19 [5]. African Americans are disproportionally affected by COVID-19 morbidity and mortality. Reducing COVID-19 vaccine hesitancy in rural Alabama is a high-priority, urgently warranted public health target. Focusing on increasing HPV vaccine uptake and concurrently examining COVID-19 vaccine hesitancy are timely and warranted targets due to low rates of HPV vaccination and high levels of COVID-19 vaccine hesitancy [6], of which both are devastating African American populations in rural communities.

Research elucidating the barriers to HPV and COVID-19 vaccination in rural settings is urgently warranted. Findings from such research can be applied to developing sustainable and scalable interventions that, if acceptable and feasible, could lead to improved rates of vaccination and reduced rates of vaccine-preventable disease among African Americans living in rural America.

Theoretical Framing

Our study is guided by the Information-Motivation-Behavioral Skills (IMB) theory, which is widely used to guide the development of prevention interventions [7]. The IMB theory was developed by considering the psychological determinants of risk and prevention behavior; IMB integrate constructs of social and health psychology theories (eg, social cognitive theory) [8-11]. IMB translate theories into potential intervention targets. Our proposed intervention will improve knowledge of HPV, the HPV vaccine, and the COVID-19 vaccine (information) and reduce stigma, distrust, and hesitancy (motivation), leading to improved vaccine confidence and higher vaccination rates (behavior skills).

Vaccine Hesitancy

The IMB theory is particularly suited to addressing vaccine hesitancy—a complex and multifaceted phenomenon [12,13] harming individuals and broader communities. Although vaccine-focused health disparities research has indicated gaps in uptake [14-16], studies that hone in on vaccine hesitancy have noted reasons for these gaps. A recent study of adolescent perspectives in rural Alabama found significant misinformation and institutional distrust, which resulted in vaccine skepticism [6]. Additionally, since adolescents are often ambivalent or apathetic to behavior change, including seeking preventive health care [17], theoretical orientations that enhance motivation without critique or judgment have the potential to resolve barriers to vaccination. The IMB theory is designed to address information (or misinformation) while building motivation, leading to enhanced behavior skills or behavior change, such as vaccine uptake.

Protocol Summary

The purpose of this protocol is to present the design of a pilot hybrid type 1 effectiveness-implementation cluster-randomized controlled intervention trial for improving HPV and COVID-19 vaccine acceptance by African American adolescents in rural Alabama.

Methods

Ethics Review and Approval

All study materials and procedures were reviewed and approved by the University of Alabama at Birmingham Institutional Review Board (approval number: IRB-300006490).

Study Design

Our study will follow an exploratory, sequential mixed methods design [18] that begins with an exploratory, qualitative phase and then moves sequentially to a single quantitative phase or multiple quantitative phases. Simultaneity is the basis for the selection of a sequential design [19]; in this sequential design, the qualitative component (phase 1) will precede the quantitative components (phases 2 and 3). The results of the qualitative phase will be used to inform the next phases [18]. The study will be conducted over the following three phases: the exploratory, qualitative phase; the intervention development phase; and the implementation and evaluation phase (Figure 1). In the third phase, we will conduct a pilot hybrid type 1 effectiveness-implementation cluster randomized controlled trial [20] to assess intervention acceptability and feasibility (clinics: N=4; adolescents: N=120).

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Figure 1. The three phases of the study.
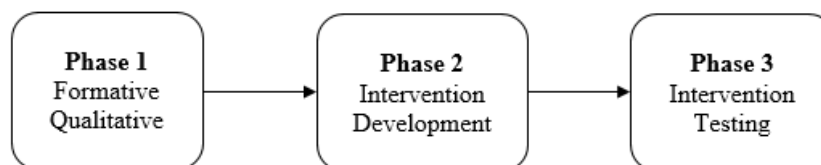
Recruitment

For the first and second phases of the study, participants will be recruited through our health care partner—the University of Alabama at Birmingham Selma Family Medicine clinic—and their local community–based network, which includes high schools and nonprofit agencies. During the third phase, in which the newly crafted intervention will be tested, participants will be recruited in enrolled clinics. Screening for eligibility (eg, vaccine status, age, etc) will occur via self-report and be corroborated via clinical record and immunization registry verification.

Phase 1: Qualitative Assessment

We will conduct in-depth interviews with adolescents (age: range 15-17 years; estimated number of participants: range 12-24; number of adolescent girls: range 6-12; number of adolescent boys: range 6-12) and with the guardians of adolescents (estimated number of guardians: range 6-12). The goal of these qualitative interviews is to explore knowledge, cultural considerations, beliefs, and barriers related to vaccination to inform intervention development. We will also conduct in-depth interviews with rural health providers to document inner and outer contexts—informed by the rigorous frameworks of implementation science—of vaccine acceptance and vaccine hesitancy (estimated number of health providers: range 8-12). We will use rapid qualitative analysis [21] and thematic coding and analysis methods [22] to elucidate ways in which the intervention needs to be crafted so that it is acceptable to adolescents, parents, and their health providers in rural Alabama.

Qualitative in-depth interviews will be audio-recorded by using digital recorders, and audio files will be uploaded to an encrypted server. Files will be transcribed into Microsoft Word files by an experienced transcriptionist. We will collect these data as the interviewers, with the assistance of a trained research assistant from the target population. Coding and analysis will be performed by using rapid qualitative analysis and a thematic analysis approach, in which a priori themes and subthemes from theory and literature are supplemented with emerging themes that are "grounded" [23] in data. The NVivo (QSR International) qualitative software will be used for coding and analysis.

Phase 2: Intervention Development

We will use intervention mapping [24] and the designing for dissemination [25] approach, which will be informed by data from the first phase, to develop the intervention. We chose the 4-step intervention mapping model to inform the development process [24]. Intervention mapping is a systematic, iterative process characterized by contextual evaluation, stakeholder feedback, and the use of theories and evidence, making it an excellent fit for implementation science trials in real-world settings [24]. Using intervention mapping will allow us to prioritize key targets while considering barriers to testing and prevention.

The tablet-based intervention will include 3 modules consisting of multiple subtopics, deliver tailored (ie, for youth and rural contexts) digital content in the clinic waiting room, include motivational interviewing [26] components that are effective in evoking behavior change while being acceptable to adolescents and parents, and include ongoing support through text reminders. The intervention will be designed to reduce health provider burden and to consider practice and environmental limitations. We anticipate drafting 2 to 3 versions of the intervention before finalizing a version for pilot-testing. Each version will be reviewed by a group of adolescents and clinical health providers (estimated number of reviewers per version: range 4-6).

Phase 3: Intervention Evaluation

We will conduct a pilot hybrid type 1 effectiveness-implementation cluster-randomized controlled trial [20] to assess intervention acceptability and feasibility (clinics: N=4; adolescents: N=120). The cluster-randomized controlled trial design minimizes the risk of contamination among participants in different arms and is ideal when settings are similar in terms of population characteristics. These trials are frequently used when interventions are to be carried out at the level of whole groups. Implementation science hybrid designs assess intervention effectiveness in real-world settings and document barriers and facilitators to delivery and sustainability [20]. Considering that our goal is to disseminate the intervention widely, we must understand the contexts that influence success and failure, so that we can plan for them and mitigate weaknesses accordingly.

We will enroll 120 adolescents across 4 clinics; 2 clinics will be randomized to implement the intervention condition, and 2 clinics will be randomized to a time-attention control. All African American patients unvaccinated for HPV (aged 15-26; all genders) will be approached to enroll in the study when they come in for a visit, regardless of the purpose of that clinical visit. After informed consent is collected from adolescents, we will collect preintervention, immediately postintervention, 2-month postintervention, and 6-month postintervention survey data related to the behavior change objectives -- increased knowledge of vaccines, reduced stigma, and increased motivation, which all result in improved vaccine confidence and higher vaccination rates — in addition to participant demographics and known potential associates of vaccination or vaccine hesitancy. We will collect design metrics to assess feasibility and acceptability, informed by the Bowen framework [27] (Figure 2).

Figure 2. Randomized controlled trial study flow (phase 3).
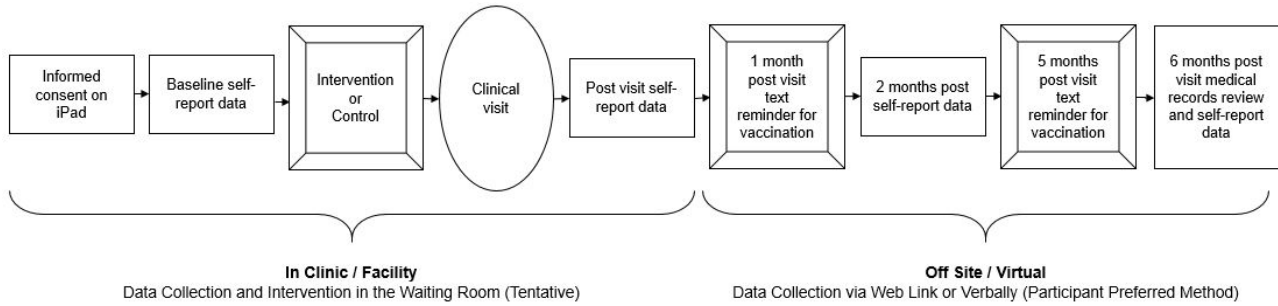
All participant data collection will occur electronically. Informed consent will be collected via Adobe Sign (Adobe Inc), and self-report data will be collected through a standardized Qualtrics (Qualtrics International Inc) survey. Pre- and postintervention data collection, which will occur in clinics, will be conducted with iPads (Apple Inc) that are dedicated to the study site. Data will be immediately uploaded to a secure database through wireless connectivity. Self-report data to be collected at 2 and 6 months post intervention will be captured by using the same standardized Qualtrics survey that will be used in clinics; the direct survey link will be shared via text or email, depending on the participants' preferences.

We will conduct exit interviews with clinic health providers to assess barriers and facilitators to implementation specifically to inform regional dissemination.

Effectiveness Data

Data on clinic-level vaccination rates and vaccination series completion rates will be collected prior to the start of the study

and once per year thereafter. Patient-specific data will be collected at the end of the 6-month study cycle.

Medical Records

We propose to collect data on vaccination from medical records at partner clinics. We will request records from partner clinics, and a member of each clinic will extract them for evaluation. The research team will review medical records for evidence that participants accepted vaccination during the 6-month study period, as well as evidence of whether the participants completed the vaccine series.

Feasibility Data (The Bowen Model [27])

Clinic staff will maintain logs on acceptances and refusals to study participation. We will use these data to assess if the study procedures and protocols are feasible and the intervention is acceptable (Table 1).

Table 1. Components of the Bowen model [27].

Component	Assessment focus	Sample outcomes
Demand	Documenting the use of the intervention	Fit within organizational culture and perceived effects and demand
Acceptability	Health providers' and patients' reactions to the intervention	Satisfaction, intent to continue use, and perceived appropriateness
Implementation	Extent to which the intervention is implemented as planned	Degree of execution and resources for implementation
Practicality	Extent to which intervention can be implemented in rural Alabama	Cost analysis factors affecting implementation
Adaptation	Modifications needed to accommodate the context	Degree to which outcomes are obtained with the mobile format
Integration	Level of system change for integrating the intervention	Perceived fit with infrastructure and perceived sustainability
Expansion	Potential success of the intervention in a different setting	Fit with the local goals and culture
Limited efficacy testing	Small-scale implementation	Effect size estimation and effects on key intermediate variables

Implementation Data

At 4 months after the start of the trial, we will solicit feedback from staff who were interviewed in the initial qualitative phase (estimated number of staff members: range 4-8). We will collect data on the inner and outer contexts affecting implementation and data on the policies, environments, funding, and social conditions that influenced intervention delivery; this interview

will take about 1 hour. We will also conduct in-depth exit interviews with a purposively selected group of adolescent participants on a rolling basis after they have concluded the 6-month study cycle (number of participants: range 6-12). The interviews will collect data on how the intervention was experienced and internalized. We will ask questions on how sociocultural nonintervention contexts affected the likelihood of vaccination and series completion. These data will provide

a direct look into real-world implementation considerations affecting African American adolescents.

Phase 3: Data Management and Quantitative Analysis

A descriptive analysis of all study feasibility and outcome variables will be summarized by using means and SDs for continuous measures and frequencies and percentages for categorical measures. Between-group differences will be compared by using standard 2-tailed cluster analyses. Further, 2-sample tests for proportions [28] will be used to compare initial vaccination acceptance, the indication of dose completion, and study dropout. An adjusted McNemar test [29] will be used to determine if the intervention group had any changes in vaccine knowledge post intervention. Similar analyses will be used in the control group, and the two groups' changes will be examined. For any continuous measure (eg, stigma), 2-sample *t* tests [30] will be used, and appropriate assumptions will be validated. Factors related to unexpected design or study implementation issues, such as systematic enrollment issues at clinics or differential times between patients' first visit and their follow-up resulting from issues beyond common follow-up issues, will be assessed. If it is determined that these issues require analysis adjustment, we will use generalized estimating equations to compare group differences in all measures while adjusting for these factors. Generalized estimating equations require all missing data to be missing completely at random; however, as our primary outcome relates to initial vaccination acceptance, we do not expect any missingness. Likewise, we will assume that study dropout is an indicator of incomplete dosing. Missing values for other outcomes will be examined, and if missingness at random can be assumed, multiple imputations [31] will be used.

Results

The study was funded at the end of December 2020. Approval from the University of Alabama at Birmingham Institutional Review Board was obtained in May 2021, and the qualitative data collection process outlined in the first phase of this project concluded in November 2021. The entire study is expected to be complete at the end of December 2023.

Discussion

Study Implications

Based on prior research with rural African American adolescents and their families and given the low rates of vaccination in rural Alabama, developing an intervention to promote vaccination among 15- to 26-year-old youth has the potential to make a notable public health impact. A novel feature of this study is its emphasis on adolescent decision-making and autonomy. This departure from prior studies that focused on changing parental or guardian behavior makes our protocol unique, and we hope that this increases its chances of making a strong impact. Furthermore, by developing this intervention, which leverages existing infrastructure, we increase the likelihood of this intervention being scalable to similar clinic settings across similar rural communities in Alabama and extending into other neighboring states, such as Mississippi and Tennessee.

Limitations

We note some important limitations to the study. Currently, the intervention focuses on adolescents and does not focus on parents. Because adolescents can consent for their own health care at 14 years of age in the state of Alabama, we opted to focus on them instead of their parents. During the qualitative phase, we may learn about clinic features that indicate a poor fit for such a research trial. If this occurs, as we have ample credibility with rural clinics across the state, we can recruit a replacement facility.

Conflicts of Interest

None declared.

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Abbreviations

HPV: human papillomavirus
IMB: Information-Motivation-Behavioral Skills

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Protocol

Stakeholder Perspectives on Clinical Decision Support Tools to Inform Clinical Artificial Intelligence Implementation: Protocol for a Framework Synthesis for Qualitative Evidence

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Abstract

Background: Quantitative systematic reviews have identified clinical artificial intelligence (AI)-enabled tools with adequate performance for real-world implementation. To our knowledge, no published report or protocol synthesizes the full breadth of stakeholder perspectives. The absence of such a rigorous foundation perpetuates the "AI chasm," which continues to delay patient benefit.

Objective: The aim of this research is to synthesize stakeholder perspectives of computerized clinical decision support tools in any health care setting. Synthesized findings will inform future research and the implementation of AI into health care services.

Methods: The search strategy will use MEDLINE (Ovid), Scopus, CINAHL (EBSCO), ACM Digital Library, and Science Citation Index (Web of Science). Following deduplication, title, abstract, and full text screening will be performed by 2 independent reviewers with a third topic expert arbitrating. The quality of included studies will be appraised to support interpretation. Best-fit framework synthesis will be performed, with line-by-line coding completed by 2 independent reviewers. Where appropriate, these findings will be assigned to 1 of 22 a priori themes defined by the Nonadoption, Abandonment, Scale-up, Spread, and Sustainability framework. New domains will be inductively generated for outlying findings. The placement of findings within themes will be reviewed iteratively by a study advisory group including patient and lay representatives.

Results: Study registration was obtained from PROSPERO (CRD42021256005) in May 2021. Final searches were executed in April, and screening is ongoing at the time of writing. Full text data analysis is due to be completed in October 2021. We anticipate that the study will be submitted for open-access publication in late 2021.

Conclusions: This paper describes the protocol for a qualitative evidence synthesis aiming to define barriers and facilitators to the implementation of computerized clinical decision support tools from all relevant stakeholders. The results of this study are intended to expedite the delivery of patient benefit from AI-enabled clinical tools.

Trial Registration: PROSPERO CRD42021256005; https://tinyurl.com/r4x3thvp

International Registered Report Identifier (IRRID): DERR1-10.2196/33145

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Introduction

Background

Clinical artificial intelligence (AI) is a fast-growing field, demonstrating exponential increases in academic publishing, but also in the frequency of market authorizations awarded to AI-enabled computerized decision support tools (CCDSTs) [1,2]. The concept of AI has been established for more than 70 years, and varying degrees of autonomy have been designated to CCDSTs for decades [3,4]. However, it is the leap in performance brought about by the combination of rising computational capacity and neural network technology that accounts for this most recent surge in interest from various health care stakeholders [5]. Despite interest and investment from academia, industry, and policy makers, a notable paucity of real-world applications of AI-enabled CCDSTs persists [6]. This is a mark of a translational gap known as the "AI chasm" [7].

To address this AI chasm, there is a need for contemporary evidence syntheses of clinical AI research, the quantitative aspects of which have already been satisfied [8-10]. However, syntheses of health care professional (HCP) perspectives on CCDSTs of any sort are either narrow or outdated [11,12]. Meanwhile, perspectives from patients are yet to be synthesized at all. This is problematic, as the efficacy of the tools themselves are important, but tells stakeholders little about the complexity of the surrounding contextual factors that will contribute heavily to the fate of the AI chasm [13].

Clarity on implementation issues from all stakeholders is required if technological progress is to be effectively translated into patient benefit. Tailored primary qualitative research is needed to build and implement any clinical AI-enabled tool, but to optimize the design of such work, the relevant qualitative evidence base must first be robustly synthesized.

The only completed attempt to provide a synthesis of HCP perspectives specific to "AI" found only 1 study, reflecting the infancy of real-world clinical AI applications [11]. In order to synthesize a meaningful number of studies, broader search terms will be required, which reflect fewer contemporary definitions of AI, but still describe automated contributions to health care. HCP perspectives on "clinical decision support systems" were most recently synthesized from 2000-2013 publications and require updating [12]. Other planned qualitative evidence syntheses promise more contemporary findings, but have focused criteria for population, phenomena of interest, and context eligibility. These reviews will be valuable, but they fall short of what is needed to support the complex process of implementation, as they do not synthesize the breadth of relevant perspectives.

A background search of existing published syntheses, protocols, and protocol registries including PROSPERO, MEDLINE (Ovid), the Cochrane Database of Systematic Reviews, and the Joanna Briggs Institute Database of Systematic Reviews and Implementation Reports identified no duplicate protocols or reviews. Literature from partly overlapping qualitative or mixed methods syntheses were identified and fell into one or more of the three following categories: (1) a more narrow definition of the population (ie, exclusion of patient or professional perspectives or exclusion of HCPs outside of a particular discipline) [1,4,14-16]; (2) a more narrow definition of the phenomenon of interest (ie, mobile health only or AI only) [14,17,18]; and (3) a more narrow definition of the context (ie, exclusion of primary or secondary care or focus on a single specialty) [4,14,17-19].

While the overlap between these syntheses may cumulatively sample the majority of the qualitative literature relevant to the proposed review question, these multiple reviews will not generate the holistic overview that a single synthesis of all stakeholder perspectives will produce. Many are also likely to be affected by the sparsity of AI-specific literature, which has limited the efficacy of prior qualitative evidence synthesis [11]. As such, without the proposed review, a clinically important research gap will remain, limiting the efficacy with which health care policy makers and providers can work to implement clinical AI-enabled tools.

This qualitative evidence synthesis aims to consolidate the pragmatic value of primary qualitative studies of relevant stakeholders' perspective on the implementation of CCDSTs in any health care context. In doing so, the review aims to holistically preserve the complexity of the interdependent factors that influence clinical AI implementation, supporting readers to make sense of transparent findings to address their unique implementation challenges.

Review Question

What are the perspectives of stakeholders on using computerized clinical decision support tools and how can they inform the implementation of clinical artificial intelligence-enabled tools?

Methods

The protocol of the proposed qualitative evidence synthesis has been registered on PROSPERO (ID 248025) and adheres to the PRISMA-P (preferred items for reporting systematic reviews and meta-analyses for protocols) 2015 checklist [20]. Best-fit framework synthesis will be conducted and reported according to ENTREQ (enhancing transparency in reporting the synthesis of qualitative research) guidelines [21,22].

Search Strategy

An initial limited search of MEDLINE (Ovid) informed by prior quantitative and qualitative synthesis search strings was undertaken to identify articles on the topic [4,10-12]. Evidence-based search strings for the identification of qualitative literature were also used [23]. The final search used terms and synonyms around professional or lay individuals, qualitative

research, CCDSTs, and health care. The text words contained in the titles and abstracts of relevant articles and the index terms used to describe the articles were used to develop a full search strategy for MEDLINE (Multimedia Appendix 1). The search strategy, including all identified keywords and index terms, was adapted for each included database. The reference list of all secondary research sources was identified and hand searched for additional studies before they themselves were excluded from synthesis. Similarly, published protocols were included at title and abstract screening to ensure published reports were captured. Where no report was identified, the corresponding authors of the protocols were contacted to ensure no report was available. Only studies indexed with an English language title and abstract were included as it is not feasible to adjust the search string for multiple languages. This is not anticipated to limit the scope of the review significantly. Studies where full text was not available in English language were translated using an automated text translation service prior to full-text screening and potential inclusion. Studies published since January 2014 were considered for inclusion, as 2014 saw the first market authorizations of clinical AI-enabled tools in Europe and America [1]. The final search was executed in April 2021, looking at studies between January 1, 2014, and April 30, 2021.

The research databases searched were MEDLINE (Ovid), Scopus, CINAHL (EBSCO), ACM Digital Library, and Science Citation Index (Web of Science). This constellation of databases was selected to support comprehensive coverage of medical, allied health professional, computer science, and grey literature, while minimizing the burden of search string translation and deduplication.

Study Selection

Following the research database search, all identified citations were collated and uploaded into Endnote x9.3.3 (Clarivate Analytics) and deduplicated. These citations were then uploaded to Rayyan (Rayyan Systems Inc) where titles and abstracts were screened by 2 independent reviewers (JH and MA) for assessment against the review's inclusion criteria. Potentially relevant studies were retrieved in full and assessed in detail against the inclusion criteria by 2 independent reviewers, with disagreements resolved by a third topic expert (GM). The reasons for exclusion of papers at full text that do not meet the inclusion criteria were recorded to be reported in the final report. Eligible full texts will be imported into NVivo Release 1.2.426 (QSR International) for coding. The results of the search and the study inclusion process will be reported in full in the final report and presented in a PRISMA flow diagram (Figure 1) [24].

Figure 1. PRISMA (preferred items for reporting systematic reviews and meta-analyses)-style diagram illustrating search strategy deployment in MEDLINE (Ovid), Scopus, CINAHL (EBSCO), ACM Digital Library, and Science Citation Index (Web of Science).
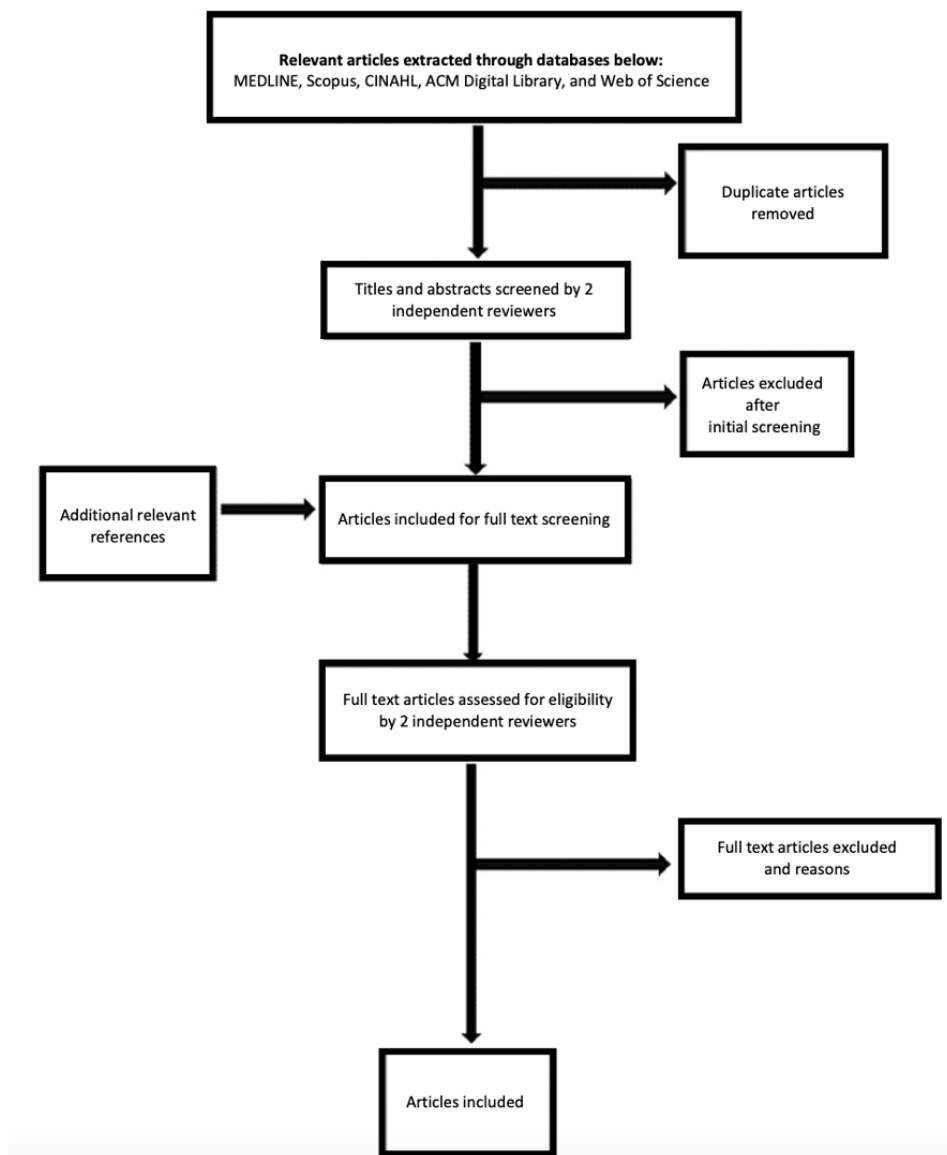
Inclusion Criteria

Participants

The participants included are patients, caregivers, or HCPs using or accessing fully or partly automated CCDSTs.

Phenomena of Interest

Of interest to this study are the stakeholders' perspectives of fully or partly automated CCDST implementation in a real-world or hypothetical setting.

Context

The context of this study will be all real-world, clinical trial, or hypothetical health care settings worldwide published during or after January 2014.

Types of Studies

This review will consider primary studies that focus on textual qualitative data, including but not limited to designs such as

phenomenology, grounded theory, ethnography, action research, and feminist research.

Exclusion Criteria

Phenomena of Interest

Articles that focus exclusively on computerized treatments, physical tools, information sharing, data storage, or data collection methods were not eligible. Such phenomena included computerized cognitive behavioral therapy, telemedicine applications, noninteractive decision aids, robot companions, nonautonomous robotic surgical instruments, electronic health records, and data collection smartphone apps. However, if articles consider these phenomena alongside a fully or partly automated CCDST and meet the other inclusion criteria, they were deemed eligible.

Assessment of Methodological Quality

Eligible primary studies will be critically appraised by 2 independent reviewers for methodological quality using the standard Joanna Briggs Institute Critical Appraisal Checklist

for Qualitative Research [25]. The authors of the papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer arbitrating if necessary. The results of critical appraisal will be reported in narrative form and in a table.

All included items, regardless of the results of their methodological quality, will undergo data extraction and synthesis, where possible. The results of critical appraisal will be used to describe the credibility of findings and to help interpret contradictions between the included studies.

Data Extraction

Data will be extracted from the studies included in the review by 2 independent reviewers (JH and MA) using NVivo Release 1.2.426. Data extraction will include publication date, study methods, health care context, population size and characteristics, phenomenon of interest, geographical location, and quality of each study. The findings and their illustrations, which relate to this review's phenomena of interest, will be extracted and assigned a level of credibility based on the strength of support offered by illustrations. A proportion of data collection will be performed in parallel by both reviewers in order to develop a consistent approach at the outset and to check that agreement is maintained throughout the process. Any disagreements that

arise between the reviewers will be resolved through discussion, or with input from topic (GM) and method (FB) experts where disagreements persist. The authors of the papers will be contacted to request missing or additional data, where required.

Data Synthesis

A total of 22 a priori themes established by the Nonadoption, Abandonment, and Challenges to the Scale-Up, Spread, and Sustainability (NASSS) framework will be used for this best-fit framework synthesis (Figure 2). The NASSS framework was considered as an appropriate framework as it outlines the interacting complexity of factors and related stakeholders at the policy, organizational, and practice level, shaping the implementation of digital innovations [13,26]. Two reviewers will carry out "line-by-line" coding in NVivo, to identify the findings from the included studies while associating them with the contributing study's descriptive data. Where these findings do not translate into the preexisting themes of NASSS, an inductive approach will be used by the reviewer to create an additional theme as per best-fit framework synthesis methodology [22]. Assigning findings to a priori themes and creating new themes will be performed by individual reviewers in the first instance. These decisions will then be critically reviewed through a series of meetings with all authors and 6 UK-based lay representatives with a range of health perspectives.

Figure 2. The Nonadoption, Abandonment, Spread, Scale-up and Sustainability (NASSS) model reproduced from the original open access publication.
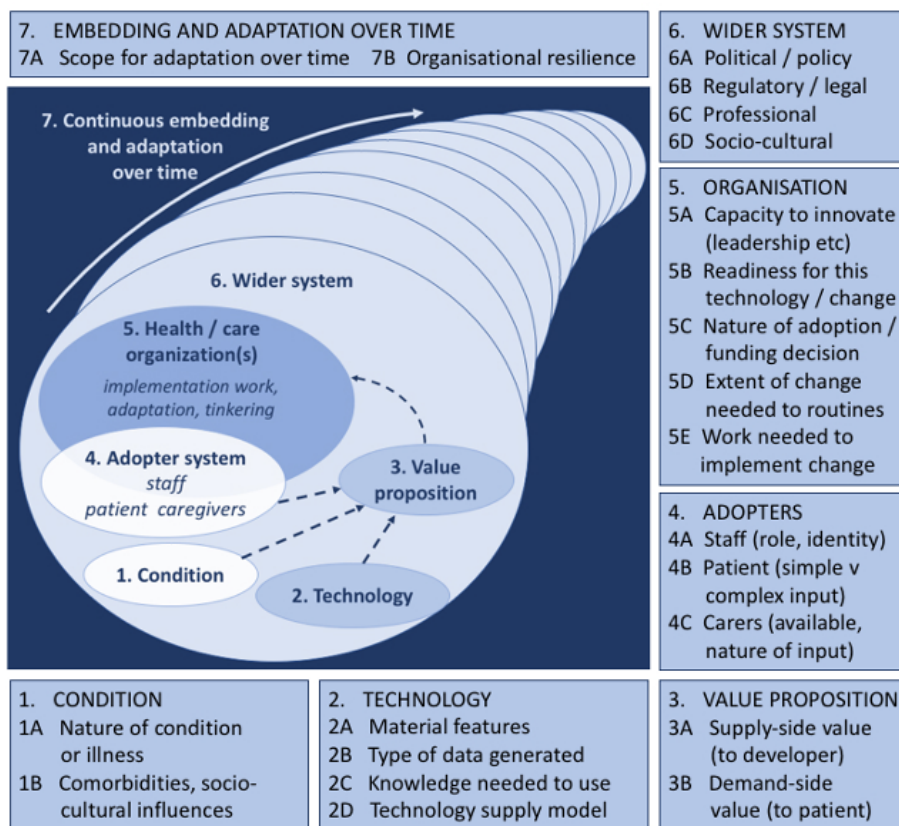
Assessing Confidence in the Findings

The transparent reporting of the critical appraisal method will support appraisal of the findings. A subjective assessment of the relevance of the synthesized findings to the population of

patients, caregivers, and health care professionals who it ultimately intends to serve will take place through discussion with health service stakeholders in a related subsequent primary qualitative research study.

Statistical Methods

Data concerning the final articles' characteristics including a quality score, the year and type of publication, source title and field, source impact factor, implementation context, theoretical approach use, study methods, and study participants will also be collected. These data will undergo the Kendell rank correlation coefficient testing and logistical regression analysis to identify trends and associations within eligible studies' characteristics.

Ethics Approval

This study has been granted ethical approval from the Health Research Authority (IRAS:280448).

Results

Study registration was obtained from PROSPERO (ID 248025) in May 2021. The search string was executed across the 5 databases in April 2021, yielding 4437 potentially eligible articles after initial deduplication. Abstract and full text screening is ongoing and due to be completed in late August 2021, with data extraction and quality appraisal set to commence following this stage. We expect to have completed full text data extraction by October 2021, with results expecting to be published in late 2021. We aim to publish the manuscript with open access in a peer-reviewed journal with conference presentations targeted to HCP, policy makers, and industry stakeholder groups. While the NASSS framework offers a powerful sense-making tool to analyze the breadth of data, it may not be immediately accessible to those without a background in social sciences. Consequently, the analysis will be centered on NASS, but the presentation of results will be categorized by the spheres of influence of stakeholder groups that arise from the data.

Discussion

Context

While publication regarding the efficacy of AI-enabled clinical tools has surged in the past 20 years, our pilot searches suggest a much more modest volume of literature exploring views of key stakeholders [2]. The qualitative research methods used in this literature offer a more sensitive tool to understand and manage the complexity surrounding CCDST implementation [27]. The proposed work aims to distil the practical value of the existing evidence base in order to make its value more accessible to implementation academics and practitioners working with AI. It will identify gaps in our understanding and help to inform meaningful future work, informing health care policy and future implementation of CCDSTs. Specifically, it will provide analysis of the potential barriers and facilitators to the implementation of AI-enabled CCDSTs across all health care settings, making a contribution with broad relevance. This is important given the strategic emphasis placed on AI-enabled clinical tools by health policy makers worldwide [28,29]. To the best of our knowledge, this is the first planned study that will synthesize the perspective of patients, HCPs, academics, and policy makers on CCDSTs.

Strengths and Limitations

One of the limitations of this review is finding the balance between accuracy through microlevel analysis and pragmatism from a macrolevel. We have attempted to minimize this by adopting the NASSS framework, which facilitates multilevel analysis and a full range of stakeholder perspectives, accepting that there will be some compromise in targeting this pragmatic goal. This is an intentional limitation, as it is only through considering the topic as a whole that we are able to meaningfully examine the complexity of implementation.

The proposed synthesis does not examine health, economic, or other quantitative data concerning CCDST. While such analyses are crucial to implementation, they are outside the scope of this protocol, which already covers an ambitious breadth of data. However, qualitative reflections of stakeholders' perceptions of cost and value that arise in the data will be analyzed.

Another limitation is the varied definitions of clinical AI used within the literature. We have taken a pragmatic approach in considering that the focus of clinical AI involves the partial or full surrender of autonomy from the practitioner. Consequently, we constructed eligibility criteria that included a priori rules based on CCDST, as well as "black box" CCDST, such as those using convolutional neural networks. Consequently, some of the perspectives raised may not relate directly to the implementation of contemporary definitions of clinical AI, but we will be transparent in reporting the characteristics of eligible articles in order to support readers' accurate interpretation.

Conclusions

This paper describes the protocol for a qualitative evidence synthesis aiming to consolidate the perspectives of stakeholders from all health care contexts on CCDST implementation. We hope the results of this study will influence the design of future research and health care policy to expedite patient benefit from AI-enabled clinical tools.

Conflicts of Interest

HDJH and PAK collaborate with DeepMind, a company involved in the development and application of clinical artificial intelligence-enabled tools. PAK has worked as a consultant for Roche, Novartis, Apellis, and BitFount and is an equity owner in Big Picture Medical. PAK has received speaker fees from Heidelberg Engineering, Topcon, Allergan, and Bayer. No other conflicts reported.

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Multimedia Appendix 1
Search strategy.
[DOCX File , 14 KB - resprot_v11i4e33145_app1.docx]

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Abbreviations

AI: artificial intelligence
CCDST: computerized clinical decision support tool
ENTREQ: enhancing transparency in reporting the synthesis of qualitative research
HCP: health care professional
NASSS: Nonadoption, Abandonment, and Challenges to the Scale-Up, Spread, and Sustainability
PRISMA-P: preferred items for reporting systematic reviews and meta-analyses for protocols

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<u>Protocol</u>

Evidence for Continuing Professional Development and Recency of Practice Standards for Regulated Health Professionals in Australia: Protocol for a Systematic Review

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Abstract

Background: Continuing professional development (CPD) and recency of practice (ROP) standards are components of health practitioner regulation in Australia. The CPD and ROP standards are currently under review, and an evidence base to assist the development of consistent standards is required. Preliminary searching was unable to find a recent systematic review of the literature to provide an evidence base to underpin the standards review.

Objective: This paper presents the protocol for a systematic review that aims to develop a current evidence base that will support the National Boards to develop more consistent, evidence-based, effective standards that are clear and easy to understand and operationalize.

Methods: Research questions were developed to support the planned review of CPD and ROP registration standards. Major databases and relevant journals were searched for articles published in English between 2015 and 2021, using key search terms based on previous unpublished reviews of the CPD and ROP registration standards. The quality of the articles retrieved will be assessed using an instrument suitable for use in the development of public policy. The findings will be published in a peer-reviewed journal.

Results: In September 2021, our search strategy identified 18,002 studies for the CPD-related research questions after removal of duplicates. Of these, 509 records were screened based on their title, and 66 full-text articles were assessed for eligibility based on their abstract, of which 31 met the inclusion criteria. A further 291 articles were identified as relevant to the ROP research questions. Of these, 87 records were screened based on their title, and 46 full-text articles were assessed for eligibility based on their abstract, of which 8 studies met our inclusion criteria.

Conclusions: This protocol outlines the scope and methodology that will be used to conduct a systematic review of evidence for CPD and ROP and inform a review of the standards for regulated health professionals in Australia. Previous research has shown that while CPD improves practitioner knowledge, the link to public safety is unclear. While there has been a greater focus on maintenance of certification and other quality assurance activities over the past 10 years, there remains great variability in CPD requirements across both professions and jurisdictions. ROP was found to be a poorly researched area with most research concentrating on medical practitioners, nurses, and midwives and no clear consensus about the optimal time period after which retraining or an assessment of competence should be introduced. As the CPD and ROP standards are currently under review, it is timely that a review of current evidence be undertaken.

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Introduction

Background

In July 2010, Australia introduced a national scheme for the regulation of health practitioners [1]. Initially, the National Registration and Accreditation Scheme (National Scheme) regulated 10 health professions (chiropractors, dental practitioners, medical practitioners, nurses and midwives, optometrists, osteopaths, pharmacists, physiotherapists, podiatrists, and psychologists). A further 4 professions (Aboriginal and Torres Strait Islander health practitioners, Chinese medicine practitioners, medical radiation practitioners, and occupational therapists) were brought into the scheme from July 2012, followed by paramedicine in December 2018.

The Health Practitioner Regulation National Law as in force in each state and territory established the Australian Health Practitioner Regulation Agency (Ahpra) to administer the National Scheme, working in partnership with the National Boards for the regulated professions. The National Boards and Ahpra protect the public by regulating health professionals who practice in Australia.

The National Law requires that National Boards must develop, consult on, and recommend certain registration standards to the Australian Health Workforce Ministerial Council. These core registration standards are generally reviewed every 5 years in line with good regulatory practice.

The registration standards for continuing professional development (CPD) and recency of practice (ROP) for health practitioners wishing to renew their registration for most National Boards are currently under review. Aspects of these standards are consistent while others are profession-specific, and there has been a trend toward more consistency over the life of the National Scheme. This systematic review will focus on all health professions regulated by Ahpra to provide an updated evidence base for registration standards for CPD for dental, medical radiation practice, nursing, midwifery, osteopathy, paramedicine, pharmacy, physiotherapy, podiatry, and psychology; and ROP for chiropractic, dental, medical radiation practice, optometry, paramedicine, pharmacy, physiotherapy, podiatry, and psychology.

Objective

This paper presents a protocol for a systematic review that aims to develop a current evidence base that will support the national boards to develop more consistent, evidence-based, effective standards that are clear and easy to understand and operationalize. It is designed to build on earlier research commissioned and/or undertaken by Ahpra for previous reviews of the CPD and ROP registration standards. The research report will include a summary of findings from earlier reviews and identify new research to provide a comprehensive, contemporary overview of the available evidence on CPD and ROP.

Review Questions

The overarching research question for the systematic review is as follows: How can the current registration standard requirements for [insert specific registration standard requirement] for Australian [insert health profession of interest] be as evidence-based and effective as possible in facilitating practitioners to practice safely and competently?

More detailed research questions for the systematic review and international benchmarking study are as follows:

1. What research has been conducted since the previous systematic review in 2015 regarding CPD and ROP for the [insert relevant health professions]?
2. How do the current Australian CPD and ROP standards for the [insert relevant health professions] benchmark against regulators in comparable jurisdictions?

CPD-specific questions are as follows:

1. Is there evidence to support an optimal quantity of CPD to maintain competence? Does the evidence suggest any benefit or disadvantage in requiring CPD to be completed over a particular period such as 1, 2, or 3 years? Is there a case for these to vary between health professions or to vary within the same health profession depending on differences in the scope of practice, practice division, and practice endorsement?
2. Does the evidence indicate that some types of CPD (including virtual) are more effective in improving practitioner competence and patient safety?
3. Is there evidence to suggest whether self-directed CPD or mandated CPD is more effective in promoting practitioners' competence and patient safety? Should some CPD be mandated? Is a mix of mandated and self-directed CPD more effective? If so, is there an optimal ratio of self-directed to mandated CPD?
4. Is there any evidence that CPD that has been accredited or subject to some quality assurance process is more effective in maintaining clinical competency and/or patient safety outcomes? What factors should be taken into consideration in accrediting CPD?
5. Under what circumstances could an exemption from CPD be justified? Is there evidence to suggest that a short gap in CPD (eg, 1 or 2 years) has a negative effect on professional competency, including any specific time frames for this effect to appear?
6. Is there any evidence to suggest a benefit or disadvantage to requiring CPD that is more focused on maintaining a practitioner's competence in their current scope of practice? What is the evidence on best practice in supporting CPD for practitioners who may wish to change their scope of practice? Is there any evidence to suggest that CPD contributes to other aspects of professional practice?
7. Is CPD more effective when it is based on a practitioner's assessment or reflection, and peer review or based on curricula to address their learning needs and skills gap, or

is CPD more effective when it is based on meeting an externally set requirement that is measured in hours or points?

8. Should practitioners who hold limited registration (or short-term temporary registration, through the pandemic subregister) be required to undertake CPD?

ROP-specific questions are as follows:

1. With regards to skills retention and skills fade, does the period of time vary between different health professions or at different stages of their career (eg, new graduate, early career, mature or advanced practitioners)?

2. Is there evidence regarding when competency assessment should be completed?

3. Is there any evidence for the minimum number of hours of practice over a set period of time needed to maintain competency? Does this vary across professions or scope of practice?

Methods

Eligibility Criteria

Studies and reports will be included in the systematic review if they meet the following criteria:

1. The focus of the article or report is on CPD and/or ROP for health professions regulated in Australia
2. Reviews, original research, reports, and theses
3. For research question 4: reviews, original reports or theses that compare different types of CPD
4. Published from January 1, 2015, onward
5. Written in the English language

Articles and reports will be excluded from the review if they are:

1. Focused on health and other professionals not regulated under the National Law
2. Focused on students, interns, or residents
3. Focused on regulatory standards other than CPD and/or ROP
4. Opinion pieces, newsletters, and conference presentations
5. Published before January 1, 2015
6. Not written in the English language

Information Sources

Databases to be searched for this review are as follows: the Allied and Complementary Medicine Database, MEDLINE, and PsycINFO (using the OVID platform), Better Evidence for Medical Education, CINAHL, the Campbell Collaboration of Systematic Reviews, the Cochrane Database of Systematic Reviews, Database of Abstracts and Reviews of Effects, Education Resources Information Centre, Embase, OTSeeker, Physiotherapy evidence, ProQuest Nursing and Allied Health, International Prospective Register of Systematic Reviews (PROSPERO), ScienceDirect, Web of Science, and Wiley Online Library.

These will be supplemented by hand searching relevant academic publications including but not limited to the *Aboriginal Health Worker*, the *Aboriginal and Islander Health*

Worker, *Academic Medicine*, *the American Journal of Occupational Therapy*, *Australian Health Review*, *Australian Journal of Chiropractic*, *Australian Occupational Therapy Journal*, *BMC Medical Education*, *the British Medical Journal*, *Chiropractic Journal of Australia*, *Clinical Teacher*, *Compendium of Continuing Education in Dentistry*, *Education Journal of Dental Education*, *Journal of Alternative and Complementary Medicine*, *Journal of the American Medical Association*, *Journal of Chiropractic Education*, *Journal of Continuing Education in the Health Professions*, *Journal of Continuing Education in Nursing*, *Journal of Medical Internet Research*, *JMIR mHealth and uHealth*, *Journal of Medical Regulation*, *Journal of Nursing Regulation*, *Medical Education*, *the Medical Journal of Australia*, *Nurse Education in Practice*, *Nurse Education Today*, *Pharmacy Education*, *Physical Therapy*, *Prehospital Emergency Care*, and *Professional Psychology*.

Gray literature will be sourced from the websites for each of the national boards, relevant international health professional regulatory bodies (eg, Health and Care Professions Council, the United Kingdom), health professional associations (eg, Australian Podiatry Association, the Association of Canadian Occupational Therapy), relevant government departments (eg, Australian Government Department of Health).

Reference lists of articles and reports of interest will be hand searched, and a forward citation search will be conducted using Google Scholar and Web of Science.

Search Strategy

Databases and other information sources will be searched for literature published between 2015 and 2021 in the English language. The search terms and sources of literature outlined below are based on our experience conducting a systematic review of the evidence for CPD and ROP standards for internal use based on journal articles and gray literature published between 1990 and 2014, and preliminary testing.

Medical Subject Headings (MeSH) by the National Library of Medicine will be used to search the databases outlined above, using all relevant root and hierarchical branches related to the terms. MeSH will also be explored to increase the ability to identify relevant publications where there are variations in the way articles are indexed. MeSH is a standardized hierarchically organized vocabulary developed by the National Library of Medicine to index, catalogue, and search biomedical- and health-related information.

MeSH terms related to health practitioner groups include "allied health occupations," "acupuncture," "chiropractic," "dentistry," "medicine," "emergency medical technicians," "medicine, traditional," "midwifery," "nurse-midwife," "nursing," "nursing, advanced practice," "nursing practical," "occupational therapists," "optometry," "osteopathic physicians," "osteopathic medicine," "pharmacy," "physical therapists," "physical therapy specialty," "physicians," "podiatry," "psychology, medical," and "radiologists."

MeSH terms related to the intervention include "competency based education," "education, continuing," "education, distance," "education, medical, continuing," "education, nursing,

continuing," "education, pharmacy, continuing," "learning," "peer review, health care," "return to work," "self-assessment," and "staff development."

MeSH terms related to the outcome include "career mobility," "competence, clinical," "competence, professional," "cultural competence," "inappropriate prescribing," "licensure," "malpractice," "mandatory programs," "mandatory reporting," "patient safety," "problem behavior," "professional practice," "professionalism," "quality of health care," "risk management," and "scope of practice."

Additional search terms related to each health practitioner group include "Aboriginal and Torres Strait Islander health practitioner," "Aboriginal and Torres Strait health worker," "Chinese medicine practitioner," "Chinese herbalist," "chiropodist," "medical radiation practitioner," "nuclear medicine technologist," "radiographers," "radiotherapists," "paramedics," "physiotherapists," "new graduate," "early

career," "mature practitioner," "mid-career," "late career," and "advanced practitioner."

Additional search terms related to the intervention or event of interest include "accreditation," "competency framework," "competency standards," "mentoring," "objective structured clinical exam," "on-line learning," "practice portfolio," "recency of practice," "re-entry program," "reflective practice," "refresher program," and "revalidation."

Search terms related to outcomes include "advanced practice," "authentic learning," "endorsement," "extended practice," "fitness to practice," "knowledge transfer," "impaired practice," "minimum practice hours," "non-medical prescribing," "registration standards," "skills decay," and "skills fade."

As outlined in the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol) guidelines [2], an illustrative search is presented in Table 1 for one database.

Table 1. Example search of MEDLINE to identify literature on continuing medical education and professional competence in physicians (search conducted September 14, 2020).

Search number	Topic	Search field	Search term	Results, n
1	Health profession	MeSH[a]	exp Physicians/	142,586
2	Health profession	MeSH	limit 1 to yr= "2015-current"	39,403
3	Intervention	MeSH	exp Education, Medical, Continuing	24,857
4	Intervention	MeSH	limit 3 to yr= "2015-current"	3005
5	Outcome	MeSH	exp Competence, Clinical	93,723
6	Outcome	MeSH	limit 5 to yr= "2015-current"	24,417
7	Outcome	MeSH	2 and 4 and 6	218
8	Outcome	MeSH	limit 7 to English language	206

[a]MeSH: Medical Subject Headings.

Study Records

Data Management

The search results will be imported into EndNote Software (version X9.3.3; Clarivate) [3], and duplicates will be removed using the Endnote "References/Find Duplicates" option. Full-text articles and reports will be stored in a secure location on our shared drive.

Selection Process

Titles listed in the search results will be checked, and the abstract will be consulted if the title appears relevant to any of the research questions. Articles and reports will be downloaded when the abstract gives the impression of being pertinent to the research questions and checked for inclusion in the review. As noted above, inclusion or exclusion and, where applicable, the reasons for exclusion, will be recorded.

Data Collection Process and Data Items

A Microsoft Excel (Microsoft Corp) spreadsheet will be used to record bibliographic information about each article or report (eg, author, date, title), the study population (eg, health profession, size, country), intervention (eg, type of CPD), main

findings, study type, National Health and Medical Research Council level of evidence [4], decisions as to inclusion or exclusion (including any reasons for exclusion), and the quality assessment.

Quality Appraisal

Where the full text of the article is assessed as relevant to the research questions, quality appraisal will be conducted by 2 people using the weighted evidence approach developed by the Evidence for Policy and Practice Information and Co-ordinating Centre at the Institute for Education in the University of London [5].

Briefly, this method provides an overall score to be derived for each study by assigning a score (high=1, medium=2, low=3) against each of the 3 criteria listed below and summing the scores.

1. The trustworthiness of the results judged by the quality of the study within the accepted norms for the particular research design used in the study (methodological quality)
2. The appropriateness of the study design for addressing the systematic review's research question (methodological relevance)

3. The appropriateness of the focus of the research for answering the review question (topic relevance)

The overall rating is derived by summing the scores assigned for each of the criteria. The overall weight of evidence would therefore be indicated as high (3,4), medium (5,6), or low (7-9).

Two reviewers will independently assess the weight of evidence of the included studies, and their assessment will be recorded on the spreadsheet.

Data Extraction and Reporting

Data extraction and quality assessment will be undertaken by the primary reviewer (PM). A second reviewer (SA) will confirm the accuracy of the data. Any disagreements will be resolved through discussion or third-party adjudication. Data extraction by a single reviewer results in considerable time saving and has little impact on the conclusions [6].

As meta-analysis is not feasible for this type of systematic review, the findings will be reported in narrative form with information about the included studies presented in tabular form and published in a peer-reviewed journal. The narrative will draw out the main themes of the systematic review and discuss their implications in the context of health practitioner regulation in Australia.

Results

Studies Relevant to the CPD Research Questions

In September 2021, our search strategy identified 18,791 studies through database searching, with an additional 96 records identified through other sources, resulting in 18,002 records after duplicates were removed. Of these, 509 records were screened based on their title, and 17,493 records were excluded. A total of 66 full-text articles were assessed for eligibility based on their abstract, of which 35 full-text articles were excluded because they did not meet the inclusion criteria. A total of 31 studies met the inclusion criteria.

Studies Relevant to the ROP Research Questions

Our search strategy identified 278 studies through database searching, with an additional 25 records identified through other sources, resulting in 291 records after duplicates were removed. Of these, 87 records were screened based on their title and 41 records were excluded. Forty-six full-text articles were assessed for eligibility based on their abstract, of which 38 were excluded, leaving 8 studies that met our inclusion criteria.

Discussion

This is the first systematic review completed by Ahpra and the National Boards of the evidence for CPD and ROP standards

that covers all health professions regulated by the National Scheme. As such, its focus is wider than that of the recently published protocol for a scoping review of ROP for nurses and midwives [7].

It is anticipated that this systematic review will provide a comprehensive evidence base for CPD and ROP requirements for professions regulated by Ahpra. Previous research has found that even though there is good evidence to show CPD is effective in increasing practitioner knowledge, there is less evidence supporting that CPD changes clinical practice, and even less evidence linking CPD to improved patient safety [8-10]. In 2010, an Institute of Medicine study in Washington found major flaws in the way in which CPD was conducted, financed, regulated, and evaluated [11], which led to a greater focus on strategies such as maintenance of certification and other quality assurance activities [12-15]. A CPD mapping exercise conducted in 2015 found considerable variance in CPD standards across European jurisdictions, with a trend toward increased mandatory requirements for CPD and revalidation [16]. ROP was found to be a poorly researched area with most research concentrating on medical practitioners, nurses, and midwives, with no clear consensus about the optimal time period after which retraining or an assessment of competence should be introduced [17,18].

This protocol has been designed to identify, summarize, and assess the quality of the evidence published to date for CPD and ROP registration standards for selected regulated health professions in Australia. As outlined above, a major strength of the method is that it covers a broad range of health professions. Other strengths include research questions that are designed to support the planned review of CPD and ROP standards in Australia, a comprehensive search strategy with clearly defined inclusion and exclusion criteria, and an appropriate instrument to assess the quality of the evidence for use in the development of public policy.

Potential limitations of the method include the following: there are differences in standards for health practitioners in jurisdictions where publications are found and those in Australia; there are likely to be fewer publications focusing on professions with lower numbers of registrants; and, due to the nature of the review, the authors are unable to correct study biases.

In conclusion, this protocol describes a detailed method for a systematic review of the evidence for CPD and ROP registration standards for health practitioners. This review will inform a multiprofession review of CPD and ROP standards in Australia. The findings will be of interest to regulators of health practitioners in other jurisdictions and may be used to inform international regulatory standards.

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Conflicts of Interest

None declared.

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Abbreviations

Ahpra: Australian Health Practitioner Regulation Agency
CPD: continuing professional development
MeSH: Medical Subject Headings
National Scheme: National Registration and Accreditation Scheme
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol
PROSPERO: International Prospective Register of Systematic Reviews
ROP: recency of practice

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Protocol

Cognitive Function, Mental Health, and Quality of Life in Siblings of Preterm Born Children: Protocol for a Systematic Review

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Abstract

Background: Children and adults born preterm are at increased risk of cognitive impairments, mental health disorders, and poorer quality of life. Epidemiological studies have shown that the impact of preterm birth extends to the immediate family members; however, existing research have focused on parents, and little attention has been given to siblings.

Objective: The aim of the systematic review described in this protocol is to synthesize currently available evidence on the impact of exposure to preterm birth (ie, having a sibling born preterm) on cognition, mental health, and quality of life of term born siblings (index child) of preterm born children, and to critically appraise the evidence.

Methods: This protocol outlines a systematic review designed in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist. We will include all studies that assess outcomes in siblings of children born preterm. Quantitative and qualitative studies will be eligible for the systematic review, and only studies in English will be included. Firstly, search will be conducted electronically on PubMed, Scopus, Embase, Mednar, and opengrey.eu databases and, secondly, manually in Google Scholar and reference lists. The search strategy will include keywords and synonyms, Boolean operators, and text words (ie, within title and abstract). The team of reviewers will screen the search results, extract data from eligible studies, and critically appraise the studies. Analysis will involve both descriptive and quantitative approaches. Meta-analysis will be conducted if appropriate.

Results: This systematic review was registered on PROSPERO (International Prospective Register of Systematic Reviews) on December 18, 2020, and it is currently in progress. The findings will be synthesized to determine the effect of preterm birth on full-term siblings and the quality of the available evidence.

Conclusions: The evidence derived from this study will shed light on gaps and limitations in the field of preterm birth, more specifically, the effect of preterm birth on full-term siblings. In addition, we hope that understanding the impact of preterm birth on family members will inform targeted interventions and policies for those identified at high risk and how to mitigate health risks.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42021222887; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021222887

International Registered Report Identifier (IRRID):   DERR1-10.2196/34987

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Introduction

Global estimates show that 1 in 10 babies are born preterm, and approximately 1 million children die due to complications related to preterm birth every year [1]. Although low- and middle-income countries account for more than half of the world's preterm births, several high-income countries have experienced an increase of preterm birth rate in the last decades [2].

Preterm birth is defined as infants born alive before 37 completed weeks of gestation or fewer than 259 days from the first date of a woman's last menstrual period [1,3]. The World Health Organization classifies preterm birth in three subcategories according to gestational age: babies born before 28 completed weeks of gestation are classified as extremely preterm; those born from 28 to 32 weeks are very preterm; and moderate-to-late preterm refer to those born between 32 and 37 weeks of gestation [1]. Prematurity has been associated to risks in neuropsychological functions, such as lower language skills [4], learning disabilities and academic challenges [5], and poor psychiatric and social well-being [6-8]. Research looking at children born moderate and late preterm suggests that when compared with their term-born peers, moderate and late preterm children have poorer social-emotional competence and higher developmental delays and have 3 times higher odds of language impairment [9]. Similarly, extremely preterm children are found to have significantly lower academic attainment [10], lower health-related quality of life [11], and greater risk of having behavioral problems compared with their peers [12].

It has been well reported in the literature, however, that the impact of preterm birth reaches beyond the adverse health outcomes of the preterm child, also affecting the immediate family members. Epidemiological studies have suggested that the poor health outcomes of the family members result from strains posed by preterm birth [13-15]. The adverse effects may differ in time points, according to gender and role in the family, severity of prematurity, the socioeconomic status of the family, and the support made available according to social structures. However, the focus has been placed on the impact of preterm birth on parents and associated environmental stressors [16-21], and little attention has been given to the full-term born sibling of the preterm born child.

Siblings, the first peer group experience, are a bridge to building experiences, which are believed to be pillars for identity development, and traits that will be fundamental to creating relationships and life course experiences outside the family nucleus [22]. In families experiencing crisis or periods of stress, the sibling role is redefined [23]. While there may be opportunities for growth and positive experiences in such environment, there is also a possibility that family dynamics will increase the full-term child's responsibilities, inhibit their sense of self, and surface health challenges [23]. The association between family dynamics—such as parental stress and depression, interaction, attention, and nurturing—has been recognized to play a crucial role in determining basic cognitive capacities [24], mental health [25], and quality of life [26] in early years and to contribute to adverse health outcomes during childhood and adulthood [26].

Our hypothesis is that siblings of preterm born infants are at risk of poor cognitive, mental health, and quality of life outcomes; that the adverse effects will be more prominent in early life (ie, primary school years); and that its intensity will attenuate into adulthood. A study looking at families with disabled children have reported that internalizing behavior problems are most prevalent among siblings of children with disabilities, compared to control [24]. The study further reported that siblings in families with lower socioeconomic status were more exposed to stressful environments, and consequently at higher risk of adjustment problems [24]. However, little is known about the impact of preterm birth on term born siblings. The existing research investigating the association between preterm birth and the health of siblings has approached this issue mainly in two ways: qualitatively [27-31] and within a familial analysis with focus on parents [28,30-33]. Two qualitative longitudinal studies conducted in Brazil used the perspective of the parents to investigate the impact of preterm birth on term born siblings, during the period of stay at the Neonatal Intensive Care Unit (NICU) [28,34] and up to 36 months of life of the preterm child [34]. Both studies reported an impact on mothers and index children's relationship as a consequence of the imposed separation resulting from the mother's need to stay with the preterm newborn at the hospital and placing the siblings under the care of their social support network. In addition, the studies reported that the changes in family dynamics often led to feelings of jealousy, uncertainty, and anxiety conveyed through questions around the preterm born's health. Another study used direct observation and play to sketch behavioral profiles of 10 children aged between 20 months to 6 years with siblings in the NICU [27]. The author of the study described the term born siblings' phantasies, defenses, and anxieties during the stay of the preterm sibling in the NICU as accompanied by ambiguous feelings and actions [27]. In their longitudinal study, Saigal et al [33] briefly discussed the impact of preterm birth on siblings, attributing the observed negative impact to reduced parental attention. Similar conclusions were drawn in a phenomenological study by Gaal et al [29], which investigated the experience of 28 term born adults, aged between 17 and 35 years, who grew up with a preterm born sibling. The conclusions were supported by theories arguing that differences in parent-child relationships within families can originate from parents' different treatment, but also can arise from differences in children's attributes [35]. In addition to the differentiation treatment, the full-term born siblings also reported feelings of loyalty and responsibility toward their preterm born siblings, despite acknowledgment that preterm siblings disrupted their lives [29].

In synthesis, although the above studies constitute an invaluable contribution to the subject, they suffer from two main limitations. First, they focus on parental reports of sibling health,

which provides a potentially subjective and colored depiction of the siblings' experience. Second, their focus on experiences delimits the conclusions on power and effect of exposure. For example, although the current research suggests that the sibling effect may be important, it is not clear how important the effect may be. It is crucial to understand the degrees to which preterm birth and the different levels of impairment and disability of the preterm born child act as risk factors to the full-term sibling.

Therefore, the purpose of the systematic review will be to synthesize the available evidence investigating and reporting cognition, mental health, and quality of life outcomes of the index child exposed to preterm birth, from early years to adulthood. In addition, we are interested in investigating the effect of outcomes in different ages, and we will critically appraise the evidence. Understanding the impact of preterm birth on term born children may pave the way to targeted, participatory interventions and policies for those identified at high risk and allow for health risks to be mitigated.

Methods

Protocol Registration

The protocol is based on the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist. The review protocol has been registered in PROSPERO (International Prospective Register of Systematic Reviews) database (registration CRD42021222887). The review team are 2 PhD candidates (WS and EV), 1 clinician (EK), and 1 epidemiologist (SS). The team offers a multidisciplinary background in maternal and child health, pediatrics, and life-course epidemiology.

Eligibility Criteria

The traditional systematic review approach based on the Population, Intervention, Comparator, and Outcome framework was used in this protocol to outline the eligibility criteria.

We will include studies in which study the population comprises the index children and their preterm born siblings. Studies where preterm population information on gestational age and birth weight is provided will be included; however, those studies providing only birth weight will only be included when the reported birth weight is lower than 1500 gr. Studies whose population is solely preterm children with major neurodevelopmental impairment (ie, cerebral palsy and mental retardation) will be included, and sensitivity analysis will be conducted where possible. In addition, studies investigating or reporting cognitive outcomes, mental health outcomes, and quality of life outcomes of the index children will be included. Studies including survivor and nonsurvivor preterm siblings will also be included. We are interested in research studies using school records, health professional and parental reports, and reports by the index children. Finally, only studies in English will be included, for reproducibility and to allow both reviewers to contribute equally to the review process.

Studies reporting only the preterm sibling outcomes with term-born siblings as controls will be excluded, and studies defining preterm birth as birth weight of lower than 2500 gr, but without indication of gestational age, will also be excluded.

Outcomes

The outcomes of the review will be grouped under the following headings: (1) cognitive outcomes, which include cognitive test scores, rates of cognitive impairment, reported learning difficulties, and related traits; (2) mental health outcomes, which include psychiatric diagnoses, subthreshold symptoms, and behavioral traits predicting mental health disorders; and (3) quality of life outcomes, which include standardized quality of life questionnaires on life events such as education, occupation, or starting a family.

Information Sources

Studies will be identified using two approaches. First, electronic searches will be conducted on PubMed, Scopus, and Embase electronic databases. For grey literature, we will be using opengrey.eu and Mednar databases. Second, we will conduct manual searches on Google Scholar and on reference lists of the relevant articles obtained on electronic databases, to retrieve additional relevant articles. The search will be conducted by 2 reviewers, WS and EV, in consultation with an expert librarian.

Search Strategies

The search strategy includes keywords (ie, MeSH [Medical Subject Headings] terms), a set of synonyms for the keywords, and text words (ie, within title and abstract) which will be combined, as illustrated in Multimedia Appendices 1 and 2. These search terms will be entered into the databases and will be truncated as appropriate recurring to use of Boolean operators.

Study Selection

Literature search results will be transferred to a reference management software and screened for duplicates. The review of the studies will be conducted by WS and EV in two stages using the review's eligibility criteria. The first phase of the selection process consists of the screening of titles and abstracts. The second phase will involve examination of the full text for compliance of studies with eligibility criteria. In case of disagreement at any of the above stages, a third reviewer will be brought in for a decision. In case of insufficient information in the articles, WS will contact the authors for clarification. There will be given 2 weeks to receive a reply before the article is excluded for lack of reply and insufficient information. The data will be recorded in a Microsoft Excel spreadsheet that is shared between the reviewers and supervisory team. Records of all searches in the different databases will be kept, and the search process will be presented in a PRISMA flow chart to show the details of the selection process.

Data Extraction

Two reviewers will conduct data extraction in order to minimize bias and reduce error. For all records, the following details will be recorded: title, authors, publication date, study design, country, population characteristics (including number of participants, birth subcategories, and weight), methods, outcome data, and time point of measurements (Table 1). Data will be organized in a way that will support and enable interpretation of results in the data synthesis stage. A standardized data

extraction form will be created for use among reviewers. The   data extraction form will be piloted by EK and SS.

Table 1. Data extraction variables.

Variables	Content
Study	- Authors - Title - Publication status - Publication date - Study aims - Study design - Country
Classifications	- Prematurity subcategory model used - Prematurity subcategories description - Birth weight measure used
Age	Age of preterm children at time of study
Population characteristics	- Population type - Population size
Time point	Time point of measurement
Outcomes	Outcomes reported
Results	Significance of evidence (statistical)

Critical Appraisal

All selected studies will be fully evaluated for quality. Critical appraisal will be conducted by WS and EV. A quality assessment tool based on the Critical Appraisal Skills Programme and the Joanna Briggs Institute Critical Appraisal tool will be used to assess the quality and conduct the validity of the selected studies. The tool has been tailored to allow evaluation of studies using different methodologies. The studies will be assessed for internal and external validity and bias.

Data Synthesis

Data synthesis will be conducted using both quantitative and qualitative methods. A summary table of all included studies will be provided, and interpretation of findings will include a summary of inclusion and exclusion criteria. This will be accompanied by a flow diagram including the number of unique records identified by the searches, records excluded after preliminary screening, records retrieved in full text, studies excluded after assessment of the full text, and studies meeting the eligibility criteria for the review. Methods and design of the studies will also be analyzed, and the potential study bias discussed. Evidence will be graded using the GRADE (grading of recommendations, assessment, development, and evaluation) system, and a summary of findings table presented.

Quantitative Data Synthesis

If 3 or more studies are available for analysis, meta-analysis will be conducted to generate a more precise estimate of the magnitude of effect on health outcomes of parents and full-term siblings, using R statistical software (The R Foundation). The most appropriate statistical analysis will be chosen and used, considering type of studies and heterogeneity of the final studies. If appropriate, subgroup analysis will be carried out to explore differences between preterm subcategories, provided the data presented on literature allow such examination.

Qualitative Data Synthesis

Qualitative evidence will be analyzed using the metastudy methodology [36]. This approach is conducted in two stages, which are the following: (1) analysis stage, which involves analyzing theory (metatheory), methods (metamethod), and findings (metadata analysis) of the primary studies; and (2) meta-synthesis stage, which involves an in-depth interpretation of the results to create an understanding of the topic being studied [36,37].

The metamethod and metatheory analysis will be guided by our aim to critically appraise the available evidence on cognition, mental health, and quality of life outcomes of the index child exposed to preterm birth. In addition, we will evaluate the theoretical framework used in the qualitative study, how these theories support the methods used, and the conclusions achieved in each study. As part of the metadata analysis, we will critically interpret the results and find similarities and discrepancies between the included studies [36].

Amendments

Any protocol amendments will be properly documented by the authors, including date of changes, description of the changes, and rationale for changes.

Ethics and Dissemination

Ethical approval is not needed for this systematic review because primary data will not be collected. The systematic review will be published in a peer-reviewed journal.

Patient and Public Involvement in Research

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of this protocol and respective systematic review.

Results

This systematic review was registered on PROSPERO on December 18, 2020, and it is currently in progress. The findings will be synthesized to determine the effect of preterm birth on full-term siblings and the quality of the available evidence.

Discussion

Our systematic review aims to synthesize the best available evidence on the long-term trajectory of the impact of preterm birth on health outcomes of index children and offer a detailed appraisal of the methodological quality of the research. This review is the first attempt to synthesize and critically appraise evidence on the impact of exposure to preterm birth on full-term born siblings, to the best of our knowledge. In doing so, we reinforce the importance of recognizing extended familial factors when considering preterm birth. This systematic review will follow PRISMA guidelines, and we aim to follow high-standard quality; however, we recognize the ever-existing risk of bias and that this may represent a study limitation. We will implement several strategies to minimize risk of bias, such as blinded review, as well as discussions between reviewers and within the review team at each stage of the review and validate data to ensure reliability. It is expected that a critical evaluation of the existing literature will provide an insight into the gaps and limitations of the longitudinal study of preterm birth and inform future works in this field.

Data Availability

All data relevant to the study are included in the article or uploaded as supplementary information.

Authors' Contributions

WS led the development of the protocol, wrote the first draft of the manuscript, and integrated the comments from coauthors. EK and SS provided mentorship and supervision to WS, critically revised successive drafts of the manuscript, provided important intellectual input, and approved the final version for publication. EV critically revised the final draft of the manuscript, provided important intellectual input, and approved the final version for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Pubmed search.
[PDF File (Adobe PDF File), 103 KB - resprot_v11i4e34987_app1.pdf]

Multimedia Appendix 2
Scopus search.
[PDF File (Adobe PDF File), 81 KB - resprot_v11i4e34987_app2.pdf]

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Abbreviations

GRADE: grading of recommendations, assessment, development, and evaluation
MeSH: Medical Subject Headings
NICU: Neonatal Intensive Care Unit
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

Frailty Factors and Outcomes in Patients Undergoing Orthopedic Surgery: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: Frailty is an aggregate expression of susceptibility to adverse health outcomes because of age- and disease-related deficits that accumulate across multiple domains. Previous studies have found the presence of preoperative frailty is associated with an increased risk of adverse outcomes. The number of older adults undergoing orthopedic surgery is rapidly increasing. However, there has been no evidence-based study on the relationship between frailty and outcomes in patients undergoing orthopedic surgery.

Objective: The aims of this study are to investigate the association between frailty and outcomes in patients who underwent orthopedic surgery as well as patient factors associated with frailty.

Methods: The methods to be used for this systematic review are reported according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-analysis Protocols) 2015 checklist. An extensive search will be conducted in PubMed, Embase, the Cochrane Library, and other mainstream databases. Any study where patients undergoing orthopedic surgery were assessed using a defined or validated measure of frailty and the association of frailty with patient factors and/or outcomes was reported will be included. A total of 2 researchers will independently screen articles for inclusion, with disagreements resolved by a third reviewer. We will perform a narrative synthesis of the factors associated with frailty, prevalence of frailty, effect of frailty on patient outcomes, and interventions for patients who are frail. A meta-analysis focusing on individual factors associated with frailty and the effect of frailty on patient outcomes will be performed, if applicable. The risk of bias will be evaluated. A subgroup analysis and sensitivity analysis will be performed.

Results: Literature searches were conducted in September 2021 and the review is anticipated to be completed by the end of July 2022.

Conclusions: This systematic review and meta-analysis will provide an overview of frailty and investigate the relationship between frailty and patient outcomes as well as the relationship between patient factors and frailty in patients undergoing orthopedic surgery. This study could potentially increase patients' awareness of the outcomes associated with frailty, compel clinical specialties to further acknowledge the concept of frailty, and enhance the development of assessment instruments and tools for frailty.

Trial Registration: PROSPERO CRD42020181846; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=181846

International Registered Report Identifier (IRRID): DERR1-10.2196/28338

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Introduction

Frailty is characterized by a decline in function across multiple physiological systems, accompanied by an increased vulnerability to stressors [1-3]. It occurs in adults at any age but is more prevalent in older adults. Furthermore, 2 studies have separately shown that the weighted average estimate of frailty is 9.9% and 11%, and that frailty is more prevalent among women than men [4,5]. However, for individuals ages 85 years and older, the prevalence of frailty is 39.1% for men and 45.1% for women [6]. Due to the aging population, the prevalence of frailty is increasing and the condition is gaining global attention [5].

Evidence-based studies have confirmed the association between frailty and increased mortality, hospitalization, falls, and admission to long-term care among the general population [7]. Moreover, robust meta-analyses have concluded that patients with frailty who undergo surgery such as vascular [8,9], cardiac [10,11], and general surgery [12,13] are at a higher risk of short- and medium-term mortality and postoperative complications. Therefore, numerous clinical specialties have taken the concept of frailty into consideration. Assessment instruments and tools, such as the Frailty Index [14], have been developed and modified to be specific to the condition and to various specialties.

Frailty is always associated with sarcopenia. Sarcopenia, which can be assessed by cross-sectional imaging, is defined as a progressive and generalized skeletal muscle disorder and is also associated with increased adverse outcomes [15]. More and more studies about older adults are focusing on sarcopenia. Additionally, sarcopenia has been used as a proxy measure of frailty [16].

Patients undergoing orthopedic surgery represent a distinct population in terms of demographic parameters, comorbidities, and other factors. Although orthopedic surgeons are treating an aging population, there remains a lack of vigilance in identifying patients who are frail. Also, to the best of our knowledge, there is no robust evidence-based study on the relationship between frailty and outcomes in patients undergoing orthopedic surgery [4]. Therefore, this systematic review and meta-analysis aims to investigate the association between frailty and patient outcomes and to recognize factors associated with frailty in patients undergoing orthopedic surgery.

Methods

Protocol Registration

The methods of this systematic review are reported according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-analysis Protocols) 2015 checklist [17,18]. The review protocol was registered with PROSPERO (the International Prospective Register of Systematic Reviews; CRD42020181846). Any amendments to this protocol will be updated on PROSPERO and documented accordingly.

Participants

This systematic review will include studies reporting on patients with symptomatic or suprathreshold (for treatment) orthopedic pathologies. Patients undergoing orthopedic procedures will be included for meta-analysis, if applicable. Orthopedic pathologies will include, but are not limited to, arthritis, bone fractures, intervertebral disc herniation, and sports injuries. Orthopedic procedures will include, but are not limited to, arthroplasty, amputation, internal fixation, spinal canal decompression, and spinal fusion. Included patients should have their frailty status measured using a defined or previously validated measure of frailty. Those whose frailty was only measured after intervention or who were defined as prefrail will be excluded.

Exposure

Studies where frailty was measured by research-based assessment tools will comprise the "exposure group."

Controls

Studies where nonfrailty was measured by research-based assessment tools will be used as controls.

Outcome Measures

This study will include 2 main outcome measures in accordance with our aims. The first is factors (such as demographic and social factors, clinical factors, lifestyle factors, and biological factors) associated with frailty in patients undergoing orthopedic surgery. The second is outcomes which include short- and long-term mortality, postoperative complications, and readmission.

Search Strategy

The search strategies have been devised by the senior authors and accurately and repeatedly modified according to the analysis of the results after several tentative literature retrievals. A total of 2 independent reviewers will tentatively retrieve the studies in PubMed (MEDLINE) to ensure accurate retrieval. If their results are the same, an extensive search will be conducted in PubMed, Embase, the Cochrane Library, CINAHL, PsyclNFO, Scopus, and Web of Science. The literature search results will be saved and managed using EndNote X9 (Clarivate PLC). Detailed search strategies will be included in the first table of the paper reporting the study's results.

Inclusion Criteria

Studies will be included according to the following criteria:

1. Involving patients undergoing orthopedic surgery who were assessed using a defined or previously validated measure of frailty.
2. Reporting on the association of frailty with patient factors and/or outcomes.
3. Reporting on comparisons between frail and nonfrail patients undergoing orthopedic surgery as a separate subgroup.

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Exclusion Criteria

Studies will be excluded according to the following criteria:

1. Studies that only included patients undergoing orthopedic surgery who had asymptomatic disease, disease below the threshold for treatment, or disease treated with conservative management.
2. Studies where frailty was only measured post intervention or measured with continuous scores, without applying a defined "frailty threshold" to dichotomize the study population into frail and nonfrail groups.
3. Studies that did not report the methods used for measuring frailty.
4. Studies that did not include patients who were not frail.
5. Review articles, case reports, editorials or comments, or studies where the full text was not available.
6. Nonhuman studies

Selection Process

The studies retrieved from the databases will be screened by 2 independent reviewers (PY and DW) according to their titles and abstracts. Studies will be marked as Y (yes), M (maybe), or N (no) by reviewers. If a study is marked as Y/Y or Y/M, it will advance to the next step of the review. If a study is marked as Y/N, M/M, or M/N, it will be considered a conflicted study and will be reviewed by the lead author and resolved through team discussion. If a study is marked as N/N, it will be excluded. The full texts of potentially eligible studies will be reviewed again by 2 independent reviewers (PY and DW) according to the inclusion and exclusion criteria.

Before the formal selection process, 100 studies will be chosen at random and 2 independent reviewers will perform an exercise according to the previously mentioned process. If sufficient agreement has been reached, the 2 independent reviewers will screen the full texts of the papers; otherwise, a second exercise will be performed until there is sufficient agreement between the reviewers.

Quality Assessment

A quality assessment of the included studies will be performed by 2 independent reviewers (PY and DW). The Newcastle-Ottawa Scale (NOS) will be used to assess cohort studies and case-control studies [19]. An adapted version of the NOS will also be used to assess cross-sectional studies. In the subsequent meta-analysis, Version 2 of the Cochrane Risk of Bias tool and the ROBINS-E (Risk of Bias in Nonrandomized Studies of Exposures) tool will be used to assess the risk of bias of included studies where applicable.

Quality of Evidence

The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system will be used to assess the quality of the evidence presented by the studies [20].

Data Extraction

A data extraction form will be developed and piloted on no less than 5 included studies. The feedback from this will be used to guide the modification of the form. Then, 2 independent reviewers, (PY and DW), will abstract the data from included studies using the new version of the form. The main content of the extracted data will include basic information on the study, methodology for frailty measurement, patient frailty factors, assessment of quality, and outcomes. Any disagreements will be discussed and resolved with the lead reviewer. All extracted data will be stored in a Microsoft Excel (Microsoft Corp) spreadsheet. Detailed data extraction tools will be found in the second table of the paper publishing the results of this study.

Data Synthesis

We will perform a narrative synthesis of the factors associated with frailty, prevalence of frailty in patients with various orthopedic pathologies, effect of frailty on the outcomes of the patients, and interventions to address frailty. After that, we will evaluate the homogeneity of the included studies. There may be an opportunity to conduct a meta-analysis focusing on individual factors associated with frailty and the effect of frailty on patient outcomes if 3 or more studies meet the requirements for the meta-analysis.

Assessment of Heterogeneity

We will examine each included study to identify and assess the potential statistical, clinical, and methodological heterogeneity. The *P* value and I-squared statistic will be calculated to estimate the existence and magnitude of heterogeneity.

If the I-squared statistic is >50%, there would be extensive statistical heterogeneity. The judgement of clinical or methodological heterogeneity mainly depends on the authors' clinical and methodological expertise. If the heterogeneity is strong, we will perform a systematic review in the place of a meta-analysis.

Subgroup Analysis

To explore the source of the clinical or methodological heterogeneity, we will identify subgroups according to age, gender, frailty assessment tools, orthopedic diseases, and orthopedic operations. A narrative synthesis focusing on the subgroups will be performed. After that, meta-analyses will also be conducted for these same subgroups if we obtain sufficient data for the proposed groups.

Sensitivity Analysis

Sensitivity analyses will be performed to test which study is the source of heterogeneity or whether the findings are robust. We will exclude low-quality studies if the studies selected have a wide range of quality. We will also perform a sensitivity analysis, restricting the meta-analysis to frequently used studies.

Meta-regression

To further investigate the sources of clinical heterogeneity, a meta-regression will be performed if we obtain sufficient data. The metareg function in R (R Foundation for Statistical Computing) will be used to conduct the meta-regression with log-risk estimates. The standard error will be determined from 95% CIs for the log-risk estimates.

Ethics Approval

Due to the nature of the study, there are no ethical concerns and informed consent will not be required.

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Results

The systematic review and meta-analysis are ongoing. The literature searches began in September 2021. Data abstraction and synthesis are expected to be completed at the end of April 2022. The review and analysis are anticipated to be finished by the end of July 2022. We plan to disseminate the results in a peer-reviewed journal.

Discussion

Necessity and Objective

Frailty is an emerging global health burden, with major implications for clinical practice and public health [4], The prevalence of frailty is expected to rise alongside population aging [5]. The identification of frailty is the first challenge facing health care providers. In the past decades, many frailty measurement instruments have been developed based on questionnaires, performance measures, electronic health record data, or a combination of these [4]. However, no consensus has been reached globally on how frailty should be measured [4]. Among prior research-based instruments, measurements based on electronic medical records seem to be more accepted and easily to be translated to clinical practice [21-23]. However, patients with different pathologies may have heterogeneous features and physicians in different specialties may evaluate their patients with their own focuses. Therefore, evidence-based research in the development and validation of frailty measurement tools for each specialty or even each pathology is required. The orthopedic specialist is increasingly challenged with treating older adults, a population with a higher prevalence of frailty and with multisystem disease and concomitant physical or cognitive impairments [24]. However, vigilance in frailty recognition and research on the association between frailty and patient outcomes is only recently beginning to emerge. Therefore, this systematic review will employ a rigorous methodology to summarize the existing data on patients undergoing orthopedic surgery who are frail. Our main objectives are to describe the characterization and measurement of frailty along with the associated outcomes, estimate the prevalence of frailty among patients undergoing orthopedic surgery, investigate patient factors associated with frailty in patients undergoing orthopedic surgery, and provide robust evidence on the associations of frailty with clinical outcomes.

Outlook

We believe the results of this review will inform clinicians, patients, and health care providers of the best available evidence about the impact of frailty in patients undergoing orthopedic procedures. We also expect that our findings will fill certain gaps as well as trigger further research to enhance clinical decision-making with a focus on patient-important outcomes.

Strengths

To the best of our knowledge, this review is anticipated to be the first to (1) describe and critique the tools which are used to assess the frailty in patients undergoing orthopedic surgery and the quality of evidence for their use, (2) investigate the association between frailty and patient outcomes, and (3) recognize patient factors associated with frailty in patients undergoing orthopedic surgery. The strength of our study lies in the nature of systematic review and meta-analysis study types, which adhere to established eligibility criteria, predefine outcomes, and incorporate multiple independent reviewers to minimize bias and increase reproducibility.

Limitations

The conclusions of this study will be limited by the number and quality of studies included. There may be heterogeneity caused by differences in the study populations, interventions, and outcome measures.

Conclusions

This systematic review and meta-analysis will provide an overview of frailty and investigate the relationship between frailty and outcomes and the relationship between patient factors and frailty in patients undergoing orthopedic surgery. This study could potentially increase patients' awareness of the outcomes associated with frailty, compel clinical specialties to embrace the concept of frailty, and enhance the development of assessment instruments and tools.

Authors' Contributions

All authors contributed to the conception of the study. The search strategy and manuscript and data extraction tool were devised by DW and revised by PY.

Conflicts of Interest

None declared.

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Abbreviations

GRADE: Grading of Recommendations Assessment, Development, and Evaluation
NOS: Newcastle-Ottawa Scale
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-analysis Protocols
PROSPERO: Prospective Register of Systematic Reviews
ROBINS-E: Risk of Bias in Nonrandomized Studies of Exposures

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Protocol

Lymph Node Yield in Gastrointestinal Cancer Surgery With or Without Prior Neoadjuvant Therapy: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: Lymph node yield is the number of lymph nodes retrieved during oncological resection and histopathologically identified in the resection specimen. It is an important surrogate parameter for assessing the oncological radicality of the resection of gastrointestinal carcinomas, as well as a prognostic factor in these diseases. It remains unclear if and to what extent neoadjuvant chemotherapy, radiotherapy, or chemoradiotherapy, which have become established treatments for carcinoma of the esophagus, stomach, and rectum and are increasingly used in pancreatic carcinoma, affect the lymph node yield.

Objective: This systematic review with meta-analysis is conducted with the aim of summarizing the available evidence regarding the lymph node yield, an oncological surrogate marker, in patients with gastrointestinal carcinomas undergoing surgery after neoadjuvant therapy compared to those undergoing surgery without neoadjuvant therapy.

Methods: Randomized and nonrandomized studies comparing oncological resection of esophageal, stomach, pancreatic, and rectal carcinoma with and without prior neoadjuvant therapy are eligible for inclusion regardless of study design. Publications will be identified with a defined search strategy in 2 electronic databases: PubMed and Cochrane Library. The primary endpoint of the analysis is the number of lymph nodes identified in the resected specimen. Secondary endpoints include the number of harvested metastatic lymph nodes, operation time, postoperative complications, pathological TNM staging, and overall and recurrence-free survival time. Using suitable statistical methods, the endpoints between patients with and without neoadjuvant therapy, as well as in defined subgroups (neoadjuvant chemotherapy, radiotherapy, or chemoradiotherapy; and patients with esophageal, gastric, pancreatic, or rectal cancer), will be compared.

Results: The literature search and data collection started in October 2021. Results are expected to be published in mid-2022.

Conclusions: This meta-analysis will provide the most up-to-date and complete summary of the evidence on an association between neoadjuvant therapy and lymph node yield in gastrointestinal cancer surgery. The underlying hypothesis is that neoadjuvant therapy decreases the number and size of lymph nodes through lymphocyte depletion and radiation-induced fibrosis, thus leading to a lower possible lymph node yield. The findings of the meta-analysis will show if this hypothesis is supported by evidence.

Trial Registration: PROSPERO CRD218459; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021218459

International Registered Report Identifier (IRRID):   DERR1-10.2196/35243

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Introduction

Background

The TNM system for the classification and staging of malignant tumors in its current, eighth edition allows for prognostic statements about malignant tumor diseases depending on, among other things, the extent of lymph node involvement [1]. The N category in the TNM classification of gastrointestinal carcinomas is defined by the number of regional lymph nodes with histologically confirmed tumor invasion. Lymphadenectomy—the systematic resection of the regional lymphatic tissue and lymph nodes—is used for both therapeutic and staging purposes. Lymph node yield is the number of lymph nodes retrieved during oncological resection and histopathologically identified in the resection specimen. To allow for a valid statement about the number of affected lymph nodes, it is crucial that the lymph node yield is high—that is, that all regional lymph nodes are removed and identified in the subsequent histopathological examination. Therefore, treatment guidelines often stipulate a minimum number of lymph nodes to be removed and histopathologically analyzed. For example, regarding the surgical treatment of colorectal cancer, the current German S3 guideline specifies that 12 or more lymph nodes be removed and examined [2]. This is supported by the European Society for Medical Oncology Clinical Practice Guidelines for diagnosis, treatment and follow-up of rectal cancer [3] and the American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Treatment of Colon Cancer [4].

However, some studies suggest that neoadjuvant chemotherapy, radiotherapy, or chemoradiotherapy, which have become established treatments for carcinoma of the esophagus, stomach, and rectum, and are increasingly used in pancreatic carcinoma, lower the lymph node yield in the case of colorectal cancer [5-9]. The mechanisms of this lower lymph node yield after neoadjuvant therapy could be based on lymphocyte depletion and radiation-induced fibrosis of the stroma, which lead to a reduction in the size of the lymph nodes and thus complicate their surgical and histopathological identification. Moreover, the occurrence of stromal atrophy and adipocytic replacement during therapy makes lymph node identification more difficult

and can also contribute to a lower lymph node yield [10,11]. This mechanism has been shown in particular for radiotherapy and less so for chemotherapy [6]. Lastly, although there is no higher-level evidence supporting this hypothesis, differences in the surgeon's approach for lymph node dissection of patients with or without prior neoadjuvant therapy—either more or less aggressive—may be of importance [7].

Differences in the lymph node yield could possibly lead to understaging of the N category in the TNM classification. This can affect the expected prognosis of the disease and thus have consequences for the decision for or against adjuvant therapy.

Objective

Based on these considerations, it has become clear that the lymph node yield should play a major role in decisions regarding the therapy of malignant tumor diseases. The existing evidence on the effect of neoadjuvant therapy on the lymph node yield will be summarized in this systematic review with meta-analysis. The primary aim is to compare the lymph node yield of resections in esophageal, gastric, pancreatic, and rectal carcinoma after neoadjuvant chemotherapy, radiotherapy, or chemoradiotherapy with the lymph node yield after upfront resection. The secondary aim is to compare the lymph node yield in defined subgroups of patients (neoadjuvant chemotherapy, radiotherapy, or chemoradiotherapy; and patients with carcinoma of the esophagus, stomach, pancreas, or rectum) and to assess secondary outcomes such as the number of metastatic lymph nodes, the lymph node ratio, the incidence of postoperative complications, and postoperative survival time.

This report contains the protocol of the review.

Methods

This protocol is reported according to the recommendations of the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 statement [12]. The pertinent checklist can be found in Multimedia Appendix 1.

Eligibility Criteria

The eligibility criteria for studies to be included in the systematic review and meta-analysis are shown in Textbox 1.

Textbox 1. Eligibility criteria.

- The study includes patients in whom a carcinoma of the esophagus, stomach, pancreas, or rectum was resected oncologically (ie, with systematic lymphadenectomy).

- The study includes at least one group of patients who underwent neoadjuvant therapy (chemotherapy, radiotherapy, or chemoradiotherapy) prior to surgery and one group of patients who underwent upfront surgery (surgery without prior neoadjuvant therapy).

- The study reports the lymph node yield (the number of resected lymph nodes) for study participants.

- There is no limitation regarding study design if the above criteria are met.

- The abstract and full text of the study are available in English, German, Russian, Italian, Spanish, or French.

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Information Sources and Search Strategy

The electronic literature databases PubMed and Cochrane Library will be searched through their respective online search engines using a defined search strategy (Multimedia Appendix 2). The search will be performed on studies published between the databases' inception and the cutoff date (October 8, 2020). Moreover, the reference lists of included articles will be manually searched.

Data Management

The abstracts of the publications identified by the search strategy will be uploaded to the web application Rayyan QCRI (Rayyan Systems Inc) [13] to perform the study selection. Data extracted from the single studies will be stored in a standardized spreadsheet and will subsequently be transferred into the review software RevMan (version 5.3; The Cochrane Collaboration) [14].

Selection Process

The abstracts of the studies identified by the literature search will be read by two independent reviewers to determine whether the studies meet the eligibility criteria. If a final assessment is not possible based on the abstract alone, the assessment will be based on the full text of the publication. A study is included or excluded from the systematic review based on a unanimous decision from both reviewers. If no agreement can be reached between the two reviewers, a third independent reviewer will act as an arbiter in the selection process. Duplicates and multiple reports of the same study will be identified and either excluded or collated so that each study, rather than each report, will be the unit of interest in the review. The record selection process will be recorded in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

Data Collection Process

A standardized data collection form will be used for the collection of study characteristics and outcome data. The form will be piloted on at least one study included in the review. A review author will independently extract the study characteristics and results from the selected studies.

Data Items

From the full texts of the selected publications, the data shown in Textbox 2 will be collected for the overall study population and the defined subgroups, if available.

Textbox 2. Data to be collected from selected publications.

- General information on the publication: title, author(s), date of publication, status of publication, journal in which the manuscript was published, language of the publication, funding of the study

- Study design

- Disease for which the study participants were treated (carcinoma of the esophagus, stomach, pancreas, or rectum)

- Patient characteristics: sex, age, American Society of Anesthesiologists (ASA) physical status [15], Eastern Cooperative Oncology Group (ECOG) Performance Status [16]

- Pretherapeutic clinical TNM stage

- Description of the surgical approach(es)

- Possible neoadjuvant therapy:

  - Chemotherapy

  - Radiotherapy

  - Chemoradiotherapy

- Lymph node yield during resection (the total number of histopathologically identified lymph nodes in the resection specimen)

- Positive lymph nodes (the number of lymph nodes in the resection specimen with histopathological confirmation of tumor invasion)

- Lymph node ratio (the number of positive lymph nodes divided by the lymph node yield)

- Duration of the operation

- Postoperative complications (if available, according to the Clavien-Dindo classification [17])

- Pathological TNM stage (from resection specimen)

- Overall survival time (using the maximum available follow-up from the single studies)

- Disease-free survival time (using the maximum available follow-up from the single studies)

Outcomes and Prioritization

A meta-analysis will be conducted for the primary and secondary outcomes shown in Textbox 3.

Textbox 3. Primary and secondary outcomes for meta-analysis.

Primary outcome
• Lymph node yield during resection
Secondary outcomes
• Positive lymph nodes
• Lymph node ratio
• Duration of the operation
• Postoperative complications (if available, according to the Clavien-Dindo classification [17])
• Pathological TNM stage
• Overall survival time
• Disease-free survival time

Risk of Bias in Individual Studies

The risk of bias of the individual studies will be estimated according to their respective study design. For nonrandomized studies, the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I; The Cochrane Collaboration) tool will be used. Prior to assessment, an emulated ideal randomized controlled trial aiming to answer the research question will be conceived. This trial will serve as a risk of bias reference against which the selected studies will be compared. For randomized trials, the Risk of Bias tool for randomized trials (RoB 2; The Cochrane Collaboration) will be used. A full description of these tools can be found in the Cochrane Handbook for Systematic Reviews of Interventions [18,19]. The domains of bias considered for each study design are shown in Textboxes 4-5.

Specifically for this meta-analysis, the following confounding domains will be addressed: pretherapeutic tumor stage, pretherapeutic physical status, and age. These domains are used to decide whether a study participant undergoes neoadjuvant therapy or not. A specific cointervention to be considered as a potential source of confounding bias is the surgical approach, which could be related to the intervention received and is, at the same time, prognostic for the outcome of interest.

For each domain, the tools foresee "signaling questions" with response options of "yes," "probably yes," "probably no," "no," and "no information." Based on the responses, the risk of bias for each domain will be judged as "low," "moderate," "serious," "critical," or "no information" in ROBINS-I and "low risk of bias," "some concerns," or "high risk of bias" in RoB 2. The risk of bias for the single domains will then be used to ascertain an overall risk of bias for the study according to Table 1.

Textbox 4. Domains of bias considered for nonrandomized studies.

Preintervention domains
• Bias due to confounding
• Bias in selection of participants into the study
At-intervention domain
• Bias in classification of interventions
Postintervention domains
• Bias due to deviations from intended interventions
• Bias due to missing data
• Bias in measurement of the outcome
• Bias in selection of the reported result

Textbox 5. Domains of bias considered for randomized trials.

• Bias arising from the randomization process
• Bias due to deviations from intended interventions
• Bias due to missing outcome data
• Bias in measurement of the outcome
• Bias in selection of the reported result

Table 1. Risk of bias judgment according to the ROBINS-I and RoB 2 tool.

Overall risk of bias judgment	Interpretation	Criterion for nonrandomized studies according to the ROBINS-I[a] tool	Criterion for randomized trials according to the RoB 2[b] tool
Low risk of bias	The study is comparable to a well-performed randomized trial.	The study is judged to be at low risk of bias for all domains for this result.	The trial is judged to be at low risk of bias for all domains for this result.
Moderate risk of bias (ROBINS-I)/some concerns (RoB 2)	The study appears to provide sound evidence for a nonrandomized study but cannot be considered comparable to a well-performed randomized trial.	The study is judged to be at low or moderate risk of bias for all domains.	The trial is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
Serious risk of bias (ROBINS-I)/high risk of bias(RoB 2)	The study has one or more important problems.	The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain.	The trial is judged to be at high risk of bias in at least one domain for this result. OR The trial is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.
Critical risk of bias (only ROBINS-I)	The study is too problematic to provide any useful evidence and should not be included in any synthesis.	The study is judged to be at critical risk of bias in at least one domain.	N/A[c]
No information (only ROBINS-I)	No information on which to base a judgement about risk of bias.	There is no clear indication that the study is at serious or critical risk of bias and there is a lack of information in one or more key domains of bias (a judgement is required for this).	N/A

[a]ROBINS-I: Risk of Bias in Nonrandomized Studies of Interventions.

[b]RoB 2: Risk of Bias tool for randomized trials.

[c]N/A: not applicable.

Data Synthesis

The primary outcome (lymph node yield) will be reported separately for the intervention group (neoadjuvant therapy) and control group (upfront surgery) as a weighted mean with standard deviation. The groups will be compared using the weighted mean difference (and relative difference of standard deviation), for which 95% CIs will be calculated. A forest plot will be drawn. The same analysis will be done for the defined subgroups: patients who underwent neoadjuvant chemotherapy, neoadjuvant radiotherapy, or neoadjuvant chemoradiotherapy and patients with esophageal, gastric, pancreatic, or rectal cancer.

The secondary outcomes number of positive lymph nodes, lymph node ratio, and duration of the operation will be assessed in the same way. The secondary outcome postoperative complications will be dichotomized (grade 1 and 2 vs grade 3a and higher, according to the Clavien-Dindo classification [17]). The incidence of severe complications (grade 3a and higher) per group will be determined and compared using the chi-square test and a forest plot. The rates for the secondary outcomes overall and disease-free survival at 1, 3, and 5 years will be compared using weighted rates and a forest plot. The histopathological tumor stage (pathological TNM) will be qualitatively described for the groups.

Sensitivity analyses will be conducted according to ascertained risk of bias as described above. For these, all studies with a high or serious risk of bias will be excluded and the analyses of the primary outcome, as described above, will be conducted.

The I^2 statistic, the P value from the chi-square test, and the between-study heterogeneity (τ^2) will be used to assess heterogeneity among the studies in each analysis. If substantial heterogeneity (greater than 50%) is identified, reasons for this will be sought by performing subgroup analyses considering the specified subgroups and the causes of heterogeneity. Heterogeneity will also be assessed by evaluating whether there is good overlap of the confidence intervals. Any statistical heterogeneity will be taken into account when interpreting the results.

To assess possible publication bias, if the number of included studies is sufficient, we will create a funnel plot using the primary outcome and evaluate funnel asymmetry with Begg and Egger tests for continuous data [20,21] or Peters test for binary data [22].

Assessing the Strength of the Body of Evidence

A "summary of findings" table will be created using the 5 Grading of Recommendations, Assessment, Development and Evaluations considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence—based on the studies that contributed data to the meta-analyses for each outcome—classifying it as high, moderate, low, or very low. The methods and recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions will be used [23].

Ethical Considerations

The ethical committee of the Medical Faculty of the Martin-Luther University Halle-Wittenberg waived this study from the need for ethical approval because no data from individual patients will be used (reference number: 2021-003).

Results

The literature search and data collection started in October 2021. Results are expected to be published in mid-2022.

Discussion

Aim and Hypothesis

This systematic review with meta-analysis is conducted with the aim of summarizing all available evidence regarding the lymph node yield, an oncological surrogate marker, in patients with esophageal, gastric, pancreatic, and rectal carcinoma undergoing surgery after neoadjuvant therapy compared to those undergoing surgery without prior neoadjuvant therapy. One hypothesis is that neoadjuvant therapy decreases the number and size of lymph nodes through lymphocyte depletion and radiation-induced fibrosis, thus leading to a lower possible lymph node yield. The findings of the meta-analysis will show if this hypothesis is supported by evidence.

Comparison to Prior Work

This meta-analysis will provide the most up-to-date and complete summary of the evidence on an association between neoadjuvant therapy and lymph node yield in gastrointestinal cancer surgery. Numerous single studies have been published on the topic, but they have shown heterogeneous results. To date, a comprehensive analysis of all the available evidence has not been completed.

Limitations

This review is limited by the available publications at the time of the search of the literature databases (PubMed and Cochrane Library). The search was performed on studies published between the databases' inception and the cutoff date (October 8, 2020) and is therefore limited. There is the possibility of publication bias. Moreover, the literature search is expected to identify mostly nonrandomized single studies for inclusion into the meta-analysis, which might cause bias in the results. Treatment protocols regarding neoadjuvant therapy and surgery will most likely vary between the single studies, which might lead to heterogeneous results.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[PDF File (Adobe PDF File), 370 KB - resprot_v11i4e35243_app1.pdf]

Multimedia Appendix 2
Search strategy.
[DOCX File , 13 KB - resprot_v11i4e35243_app2.docx]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RoB 2: Risk of Bias tool for randomized trials
ROBINS-I: Risk of Bias in Nonrandomized Studies of Interventions

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Protocol

Stigma Toward Bariatric Surgery in the Netherlands, France, and the United Kingdom: Protocol for a Cross-cultural Mixed Methods Study

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Abstract

Background: Bariatric surgery is an effective procedure for the treatment of obesity. Despite this, only 0.1% to 2% of eligible individuals undergo surgery worldwide. The stigma surrounding surgery might be a reason for this. Thus far, no research has systematically studied the nature and implications of bariatric surgery stigma. The limited studies on bariatric surgery stigma are often conducted from the perspective of the public or health care professions and either use small and nonrepresentative samples or fail to capture the full essence and implications of the stigma altogether, including attitudes toward patients and perpetrators of the stigma. In addition, studies from patients' perspectives are limited and tend to address bariatric surgery stigma superficially or implicitly. Finally, the extent to which cultural factors shape and facilitate this stigma and the experiences of patients have not yet been researched.

Objective: This study aimed to explore the perceptions, experiences, and consequences of bariatric surgery stigma from the perspective of the public, health care professionals, and patients before and after bariatric surgery. Furthermore, although the concept of stigma is universal, every society has specific cultural norms and values that define acceptable attributes and behaviors for its members. Therefore, this study also aimed to explore the extent to which cultural factors influence bariatric surgery stigma by comparing the Netherlands, France, and the United Kingdom.

Methods: This paper describes the protocol for a multiphase mixed methods research design. In the first part, we will conduct a scoping review to determine the current knowledge on bariatric surgery stigma and identify knowledge gaps. In the second part, semistructured interviews among patients before and after bariatric surgery will be conducted to explore their experiences and consequences of bariatric surgery stigma. In the third part, surveys will be conducted among both the public and health care professionals to determine the prevalence, nature, and impact of bariatric surgery stigma. Surveys and interviews will be conducted in the Netherlands, France, and the United Kingdom. Finally, data integration will be conducted at the interpretation and reporting levels.

Results: The study began in September 2020 and will continue through September 2025. With the results of the review, we will create an overview of the current knowledge regarding bariatric surgery stigma from patients' perspectives. Qualitative data will provide insights into patients' experiences with bariatric surgery stigma. Quantitative data will provide information related to the prevalence and nature of bariatric surgery stigma from the perspective of the public and health care professionals. Both qualitative and quantitative data will be compared for each country.

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Conclusions: The findings from this study will lead to new insights that can be used to develop strategies to reduce bariatric surgery stigma and improve access, use, and outcomes of bariatric surgery.

Introduction

Background

Obesity (BMI ≥30 kg/m^2) has become a major health issue worldwide. People with obesity are at risk for several conditions, including cardiovascular disease, diabetes, hypertension, infertility, arthritis, and certain types of cancer [1]. More severe forms of obesity are associated with lower quality of life and higher chances of morbidity and mortality [2]. For people with severe obesity (BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with ≥1 obesity-related condition), bariatric surgery is considered the only effective treatment when diet, exercise, or pharmacological interventions do not result in sufficient or permanent weight loss [3-5]. There are numerous types of bariatric surgery; however, essentially, all involve the surgical alteration of the stomach or intestines to restrict the intake or absorption of food [6]. People with severe obesity undergoing bariatric surgery lose an average of approximately 45% to 58% of their excess body weight, depending on the type of procedure performed, and maintain this weight loss in the long term [7]. In addition to sustained weight loss, there is increasing evidence that bariatric surgery leads to improvement in obesity-related comorbidities such as type 2 diabetes and hypertension [3-5,8], thereby reducing the risk of mortality [5].

Despite the effectiveness of bariatric surgery, worldwide, only 0.1% to 2% of people with obesity who are eligible for bariatric surgery undergo surgery [9]. Underuse of bariatric surgery is largely related to unequal access to care, misconceptions about the safety and efficacy of surgery, and cultural and social bias and stigma [10,11]. Similar to obesity, bariatric surgery is highly stigmatized, with surgery being viewed as a *last resort* and an *easy way out* method to lose weight [11]. In addition, people with obesity who choose or have bariatric surgery are stigmatized and perceived by others as *lazy*, *sloppy*, *less competent*, and *lacking in self-discipline* compared with people with obesity who lose weight through diet and exercise [12-17]. The negative attitudes toward the procedure and patients of bariatric surgery stem from the assumptions about personal responsibility in obesity and the misconceptions about surgery being an *easy fix* and *low-effort* method of losing weight [9,13,16].

There are numerous potential consequences of the prevailing negative attitudes toward bariatric surgery and patients [11,18]. For example, people who are eligible for surgery may not be referred by health care professionals because of the stigma surrounding the procedure [19,20]. People with obesity who internalize and agree with stigmatizing beliefs may be discouraged from considering surgery [12,15,21] out of fear of being judged by others as taking the *easy way out*. This fear of judgment may also withhold those who are considering or have undergone surgery from disclosing their surgery status [11,13,15,22-24], which can limit opportunities for social support. After surgery, stigma may hamper patients' ability to adhere to necessary postsurgical dietary and behavioral recommendations [25,26] and therefore decrease surgery success.

Currently, numerous studies have documented obesity stigma (stigma toward people with obesity) in many countries and diverse populations [14,16,18,27-35]; however, research on bariatric surgery stigma is limited and often conducted from the perspective of the public [12,14,16,17,29,30,32,36-42] and health care professionals [20,36,43-46]. These studies provide valuable insights into the prevalence and nature of bariatric surgery stigma. However, they have several limitations. First, many studies on bariatric surgery stigma have focused on attitudes toward the procedure itself rather than on attitudes and behaviors toward people who are considering or have undergone bariatric surgery. Stigma is a term used to describe the negative way in which we think about, feel, and act toward individuals who are different from us, as these individuals possess certain socially unacceptable characteristics or attributes [47]. Therefore, to fully capture the prevalence and nature of bariatric surgery stigma, research needs to address not only the stigma attached to the procedure but also the stigma attached to the person who is considering or has undergone bariatric surgery. Thus far, only 4 studies have investigated attitudes toward patients of bariatric surgery, all of which were conducted among the public. However, all of these 4 studies included small sample sizes [14,16,17,39], and 3 used nonrepresentative samples (eg, undergraduate or psychology students) [14,16,39], limiting their generalizability.

Second, although the stigma toward the procedure has been researched extensively, how this stigma is conceptualized and measured differs significantly between studies. For instance, most studies addressing stigma toward bariatric surgery measure stigma in terms of *belief in public versus private funding* [12,41,42], *willingness to recommend or undergo surgery* [20,29,32,36-38,43,45,46], *perception of surgery as medical or cosmetic* [12,37], and *agreement with easy way out* [12,20,40]. This lack of clear conceptualization and the various ways of measuring stigma make it difficult to compare the results of different studies and hinder the accumulation of knowledge about bariatric surgery stigma and its consequences. In addition, many studies that claim to measure stigma toward bariatric surgery actually measure individual-level factors that trigger the occurrence and perpetuation of the stigma, such as knowledge about and perceived effectiveness of surgery

[20,29,30,32,37,45,46], rather than the actual stigma. This is often the case for studies among health care professionals. Although these studies provide valuable information regarding the factors that cause and perpetuate the stigma, important aspects of the stigma, stereotypes, and prejudice remain underexamined. Understanding what stereotypes and prejudices are associated with bariatric surgery, and thus how bariatric surgery is framed, is important as it influences how people think about, feel, and act toward patients of bariatric surgery. In addition, acquiring this knowledge is a key step in intervening and tackling negative stereotypes, prejudices, and behaviors toward patients of bariatric surgery.

Third, most research into bariatric surgery stigma thus far has focused on the stigma from the perspective of stigmatizers. Although these studies among the public [12,14,16,17,29,30, 32,36-42] and health care professionals [20,36,43-46] provide evidence that stigma toward patients of bariatric surgery exists, they provide no knowledge regarding the actual experiences of patients with the stigma and the consequences thereof. The importance of understanding the perspectives of patients of bariatric surgery is reflected in the number of studies published over the past years [21,48,49]. These studies highlight the impact of bariatric surgery on many different aspects of patients' lives and the challenges patients face after surgery. However, they provide limited information regarding patients' experiences with bariatric surgery stigma. Existing studies among patients of bariatric surgery mostly focus on weight stigma and the implications thereof and tend to address bariatric surgery stigma superficially or implicitly, presenting a limited snapshot of the actual stigmatizing experiences of patients [21,48]. Studies from patients' perspectives are vital to obtaining a better understanding of the extent to which patients of bariatric surgery perceive, experience, and internalize bariatric surgery stigma; how they respond to this stigma; and how this stigma affects patients' everyday lives [13,24].

Finally, existing studies on bariatric surgery stigma have documented the presence of this stigma in several parts of the world, varying from Western countries (eg, Germany, the United Kingdom, the United States, and Australia) [29,32,36] to less westernized countries (eg, Saudi Arabia and China) [37,44]. Despite this, we know relatively little about whether and to what extent cultural factors such as social, beauty, and gendered norms shape people's attitudes, behaviors, and experiences of stigma. Stigma is a social construction influenced by cultural, historical, and situational factors and is constantly evolving within social interactions, norms, context, and values [50]. Individual characteristics may be stigmatized at one historical moment but not at another or in one specific place or context but not in another within the same period [51]. Hence, although the concept of stigma is universal, every society has specific cultural norms, values, and structures that define acceptable attributes and behaviors for its members. Consequently, the perception of what constitutes stigma may vary from one society to another [34,51]. Cultures emphasizing fashion, luxury, and a slender body as a reflection of the ideal feminine beauty, such as in France, might promote obesity stigmatization, particularly among women [52]. However, it is unclear whether these norms would also facilitate the stigmatization and experiences of

patients of bariatric surgery. This illustrates the fundamentally social nature of stigma and the need for research into the cultural factors that shape and facilitate the occurrence of bariatric surgery stigma and the experiences of patients.

Aims and Objectives

Currently, no studies have systematically explored bariatric surgery stigma. Consequently, our understanding of the prevalence, nature, and implications of bariatric surgery stigma remains limited. Many studies aiming to increase the understanding of bariatric surgery stigma have been conducted from the perspective of the public or health care professionals and tend to focus mostly on the stigma associated with the procedure rather than the stigma toward patients. Studies that investigate public attitudes toward patients of bariatric surgery use small and nonrepresentative samples and different ways of conceptualizing and measuring stigma, limiting the generalizability of and comparability between studies. Moreover, many studies from the perspective of the public and health care professionals actually measure factors that cause or perpetuate bariatric surgery stigma. Therefore, our understanding of what the stigma related to bariatric surgery entails, both for the procedure and toward patients, remains limited. In addition, our knowledge of patients' experiences is limited as many studies among patients of bariatric surgery tend to address it implicitly. Finally, the extent to which cultural factors shape and facilitate bariatric surgery stigma and the experiences of patients has not yet been researched.

Given the limited knowledge and lack of systematic research on the prevalence, nature, and consequences of bariatric surgery stigma, the overall aim of this study is to explore the perceptions, experiences, and consequences of bariatric surgery stigma from the perspective of (1) people with obesity who are considering or about to undergo surgery (patients before bariatric surgery), (2) people who have undergone surgery (patients after bariatric surgery), (3) the general public, and (4) health care professionals. In addition, this study aims to explore the extent to which bariatric surgery stigma is shaped by cultural factors by comparing three European countries: the Netherlands, France, and the United Kingdom. These countries were chosen as they are geographically and socioeconomically close but differ significantly in their views toward and approaches to tackling obesity. In addition, to date, no research has been conducted on the prevalence, nature, and consequences of bariatric surgery stigma in the Netherlands and France.

The objectives of the research are as follows:

1. To determine the current knowledge on stigma toward bariatric surgery and its consequences from the perspective of patients of bariatric surgery and identify possible knowledge gaps
2. To explore the experiences and consequences of bariatric surgery stigma from the perspective of patients of bariatric surgery
3. To determine the prevalence and nature of bariatric surgery stigma in the general public and among health care professionals

4. To assess the extent to which bariatric surgery stigma is culture dependent by comparing the Netherlands, France, and the United Kingdom.

Methods

Theoretical Framework

The theoretical framework guiding this study is the Health Stigma and Discrimination Framework (HSDF) developed by Stangl et al [53] (Multimedia Appendix 1). The HSDF is a multilevel theoretical framework that "articulates the stigmatization process as it unfolds across the socio-ecological spectrum in the context of health" [53]. This framework comprises several domains, including drivers and facilitators of stigma, stigma markings, and stigma manifestations, which, in turn, influence the main outcomes (eg, coping, adherence to treatment, and accessibility to quality health care) and, ultimately, health and quality of life among the stigmatized group. Drivers and facilitators of stigma determine the occurrence and perpetuation of stigma (stigma markings). Drivers (individual-level factors) are inherently negative and include, for example, blame and attributions of responsibility and control. Drivers of stigma may originate from, for example, lack of knowledge. Facilitators (social-level factors), on the other hand, may be positive or negative and include cultural and gender norms and (institutional) laws, policies, and regulations.

Within this framework, stigma can manifest itself in terms of stigma practices and stigma experiences. Stigma practices are defined from the perspective of *those who stigmatize* and include stereotypes (ie, labels and beliefs about the characteristics of a group), prejudice (ie, endorsement of beliefs and negative evaluations), and stigmatizing behavior and discrimination (ie, unfair treatment and social rejection) [53]. Stigma experiences are defined from the perspective of people who are stigmatized and include actual experiences of stigmatizing acts and discrimination (experienced stigma; eg, negative comments from friends), perceptions of stigma (perceived stigma; eg, "People think I cheated by having surgery"), anticipation or expectation of discrimination or social rejection if one's condition becomes known (anticipated stigma; eg, "I'm afraid of how my friends would react if they found out I had surgery"), and the internalization of stigma (internalized stigma; eg, "It

was the surgery, not me that made me lose weight and I felt ashamed").

We will apply the HSDF to data analysis (ie, the development of data extraction forms and coding categories; details are provided in the following sections). Furthermore, we will use this framework to highlight how and at what levels bariatric surgery stigma operates and affects individuals who are considering or have undergone surgery. In addition, the framework will also be used to highlight the similarities and differences between countries. Finally, we will use the HSDF to help identify which multiple-level interventions are needed to meaningfully intervene and combat bariatric surgery stigma.

Study Design

This study uses a multiphase mixed methods research design with an exploratory sequential and convergent component (Figure 1) [54,55]. This type of research design examines a topic or problem through a series of phases or separate studies. Although each phase stands on its own (convergent component), these phases are connected sequentially (exploratory sequential components). This study will be conducted in 4 parts, each addressing the corresponding objectives. The first part addresses research *objective 1* through a literature review. The results of this part will also be used to inform the development of interview guides, surveys, and analyses. The second part, the qualitative phase, is directed toward achieving research *objectives 2 and 4*. In this part, patients of bariatric surgery will be interviewed regarding their experiences with bariatric surgery stigma and the consequences of this stigma before and after surgery. We will use the findings from baseline qualitative interviews to further inform the development of the surveys (eg, identify additional domains, language use, and wording of items) [54]. The third part, the quantitative phase, addresses research *objectives 3 and 4*. We will conduct surveys among the public and health care professionals to determine the prevalence and nature of bariatric surgery stigma. Although the findings of the interviews will be used to inform the development of the surveys, each method will address a specific research objective. Consequently, both qualitative and quantitative data collection can occur concurrently [54,55]. The findings of the interviews and surveys, each analyzed and synthesized individually, will be combined afterward to create a better and holistic understanding of the research topic and draw valid conclusions (part 4) [54,55]. The research, methods, and activities for each part are explained in more detail in the following sections.

Figure 1. Multiphase mixed methods research design comprising 4 parts.
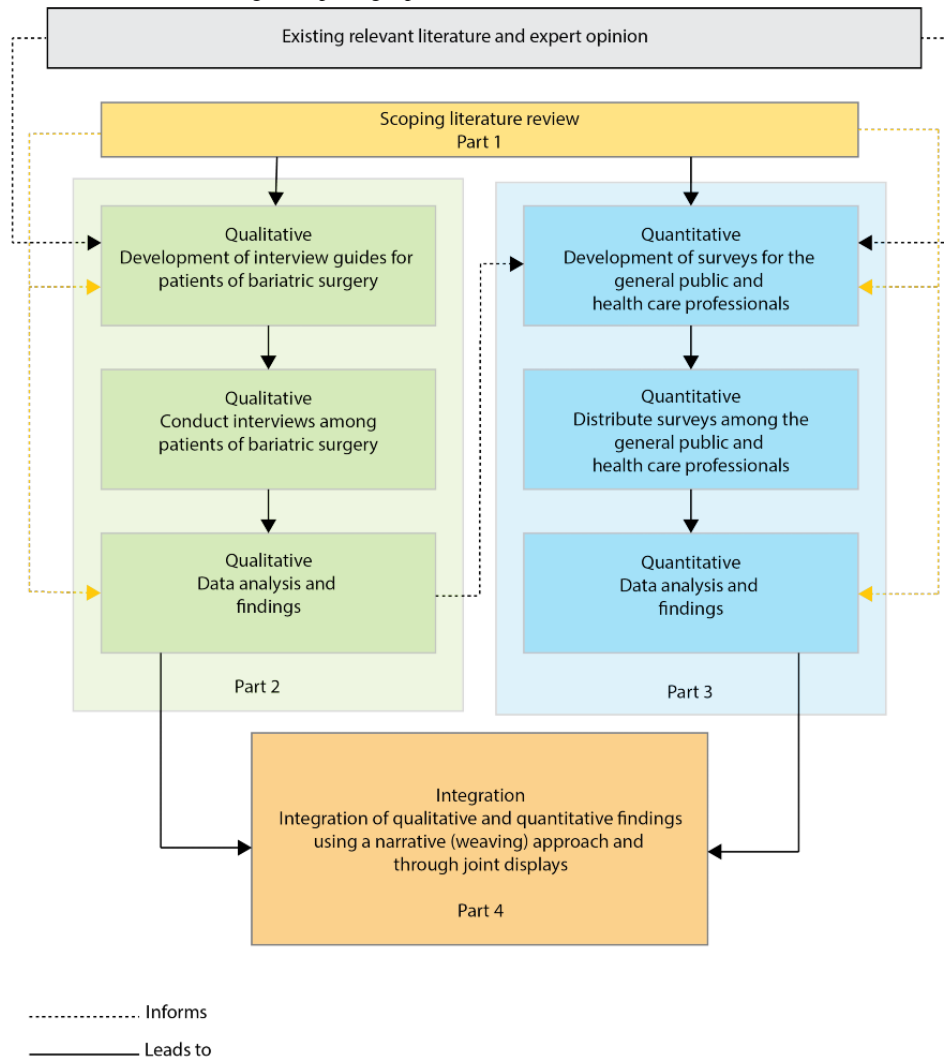
Study Setting and Study Population

We will collect data from the Netherlands, France, and the United Kingdom. Although these countries are geographically and socioeconomically close [56], the way their health care systems are organized [57-59] and their views of and approaches to tackle obesity [60-65], as well as their organization of, access to, and rates of bariatric surgery, differ significantly [65].

The study population comprises 4 different groups:

1. Patients before bariatric surgery, comprising people with severe obesity (BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with ≥1 obesity-related condition) considering, awaiting, scheduled, or about to undergo bariatric surgery
2. Patients after bariatric surgery, comprising people who have undergone bariatric surgery
3. The general public
4. Health care professionals involved in the bariatric surgery care pathway [60-65]

Part 1: Literature Review

To determine the current knowledge on stigma toward bariatric surgery from the perspective of patients of bariatric surgery and identify knowledge gaps (objective 1), we will conduct a scoping literature review adhering to the PRISMA-ScR (Preferred

Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [66]. A total of four electronic databases will be searched: PubMed, Web of Science, PsycINFO, and MEDLINE. The search terms will include 2 main keywords, *stigma* and *bariatric surgery*, and will be expanded with synonyms and Medical Subject Heading terms. Both qualitative and quantitative studies addressing the experiences and perceptions of stigma for patients before and after bariatric surgery will be considered for inclusion. A data extraction form developed iteratively using the HSDF and piloted by a minimum of 2 reviewers will be used to extract data from all relevant papers and include information on study characteristics (eg, author, year of publication, and country), sample characteristics (eg, gender, age, type, and time of surgery), and stigma-related findings.

Part 2: Qualitative Phase—Interviews

Data Collection: Semistructured Interviews

Semistructured interviews will be conducted to explore the experiences and consequences of bariatric surgery (objective 2) from the perspective of patients before and after bariatric surgery and assess the extent to which this experienced stigma is culture dependent (objective 4). We developed a preliminary interview guide based on relevant literature [23,67], the results

from the scoping literature review, and consultations with experts in the field of bariatric surgery (eg, bariatric surgeons). Iterative changes to the interview guides will be made if needed. The interview guides will be initially developed in English and forward and backward translated into the Dutch and French languages by independent translators. For both patients before and after bariatric surgery, the interview guides will broadly explore the following themes: (1) personal, public, and health care professionals' views of bariatric surgery; (2) motivation and decision-making for bariatric surgery; (3) disclosure of bariatric surgery and stigma experiences; and (4) expected changes after surgery or changes since surgery.

Sampling and Recruitment

Participants aged ≥18 years considering, awaiting, scheduled, about to undergo, or have undergone bariatric surgery and living in the Netherlands, France, or the United Kingdom will be recruited for interviews. The main criterion for patients before bariatric surgery is that participants need to fulfill the BMI criteria to undergo bariatric surgery (BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with ≥1 obesity-related condition). Purposive sampling will be used to recruit patients both before and after bariatric surgery. Purposive sampling is a cost-efficient sampling method that is useful for qualitative research as it allows the researcher to intentionally select participants according to predetermined criteria relevant to a particular research objective [68-70]. To provide a wide range of perspectives, we aim to include patients from different age groups, genders, and socioeconomic statuses. Therefore, participants for the interview will be recruited via health care professionals, (digital) posters and (digital) flyers at clinics and hospitals, social media (eg, web-based community and associations on Facebook, Twitter, or Instagram), forums, and in person during events for people who are about to or have undergone bariatric surgery. Participants who express interest will be screened for eligibility, provided with information about the study, and scheduled for an interview at their desired location. We will interview the participants only after they have provided their informed consent. On the basis of previous studies, we anticipate that the interviews would last between 30 and 90 minutes [71-74].

Data collection will stop when data saturation is reached. Data saturation occurs when no new information is obtained [69,70], typically by 12 interviews in qualitative studies. To ensure data saturation, we will conduct a minimum of 24 interviews (12 before and 12 after bariatric surgery) in each country.

Part 3: Quantitative Phase—Surveys

Data Collection: Surveys

Surveys will be used to determine the prevalence and nature of bariatric surgery stigma (objective 3) from the perspective of the general public and health care professionals and assess the extent to which this stigma is context and culture dependent (objective 4). We developed a preliminary version of the survey based on existing relevant literature [13,30,32,36-38,43-46, 75-78], expert opinions, and the preliminary results of the scoping literature review. The survey is segmented into several parts: the first part assesses whether respondents meet the eligibility criteria for the survey and includes 3 questions that

can be answered with either *yes* or *no*: "Are you 18 years or older?"; "Do you live in the Netherlands, France, or the United Kingdom?"; and "Are you able to read and understand English, Dutch, or French?" Only respondents who answer *yes* to all 3 questions and provide informed consent will be allowed to continue with the remainder of the survey. The second part of the survey collects information on knowledge and attitudes toward obesity and its treatment. The third part collects information on knowledge and attitudes toward bariatric surgery. We will measure both positive and negative attitudes toward bariatric surgery. As recommended by Rattray and Jones [79], to engage respondents, the final part of the survey collects demographic information such as age, gender, self-reported height and weight, country of residence, ethnicity, educational level, marital status, and occupation. For health care professionals, information such as type of specialization, years of experience, and experience working with people with obesity will also be assessed. The surveys comprise both closed- and open-ended questions (eg, "Have you ever heard positive comments about people who have had bariatric surgery?...If yes—What positive comments have you heard?").

The surveys will be developed in English, tested by experts, and translated into Dutch and French. To test the readability of the survey items and ensure conceptual and semantic equivalence, the surveys will be forward and backward translated by independent translators fluent in both English and the language of the translated survey [80]. Once conceptual and semantic equivalence is ensured, the survey will be piloted by a small group of respondents in their native language to verify whether respondents can understand and answer all the questions [81]. Once the surveys are revised and corrected for errors, if needed, the final version of the survey will be placed on the web to collect data for the study.

We will distribute a link to the web-based surveys via national and international professional organizations, national and international panels, and personal networks of health care professionals in the bariatric surgery pathway. Respondents will be asked to complete the survey within a 6-week time frame. After 3 weeks, a reminder will be sent to increase the response rate.

Recruitment and Sampling

We will use probability and nonprobability sampling methods to recruit members of the general public and health care professionals in each country.

Members of the general public will be recruited via paid web-based panels. The inclusion criteria for the general public are adults aged ≥18 years and living in the Netherlands, France, or the United Kingdom, who can communicate in the country's national language (Dutch, French, or English) and give informed consent.

Health care professionals will be recruited via associations for the study of obesity (surgery; eg, the European Association for the Study of Obesity), general surgery societies (eg, the Dutch Association of Surgeons), and national and international web-based panels and hospitals in the 3 countries. For each country, we will strive to include a representative sample of

health care professionals involved in the bariatric surgery care pathway, including (primary) general practitioners, practice nurses, endocrinologists, internists (internal medicine), general surgeons, bariatric surgeons, psychologists, and registered dietitians. The inclusion criteria for health care professionals are adults aged ≥18 years involved in the bariatric surgery care pathway and living in the Netherlands, France, or the United Kingdom, who can communicate in the country's national language (Dutch, French, or English) and give informed consent.

To generalize the study findings and avoid sampling errors or biases, the minimum sample size required for the survey study among the general public is 1155 respondents (385 respondents per country). The sample size was calculated by using Raosoft Sample Size Calculator [82], assuming a CI of 95%, a margin of error of 5%, and a 50% chance of agreeing to take part in the study [82,83]. For health care professionals, the minimum sample size required was calculated assuming an unlimited population size [82]. This resulted in a minimum sample size of 1155 health care professionals (385 respondents per country). To ensure that the minimum sample size for both the general public and health care professionals is obtained, we will increase the sample size by 50%, distributing the surveys to a minimum of 1733 respondents (578 respondents per country) in the general public and a minimum of 1733 health care professionals (578 respondents per country) [83].

Data Analysis

Quantitative Data Analysis

Quantitative data analysis will be conducted using SPSS (version 27; IBM Corp). To prepare the survey for analysis, data will first be imported to SPSS and cleaned (eg, checked for missing values, recording, and computing variables). Descriptive statistics will be reported in absolute and relative values using the measures of frequency (count and percentage), central tendency (mean), and variation (SD, minimum, maximum, and range) for all quantitative data, where applicable. Inferential statistics (chi-square tests, t tests, and ANOVA) will be performed to analyze the differences and associations between demographic groups and countries. The significance level will be set at $\alpha=.05$.

Qualitative Data Analysis

Interviews will be audio recorded and transcribed in full, with all personal identifiable information removed. The transcripts will then be imported into a qualitative data analysis software package (eg, Atlas.ti Scientific Software Development GmbH) for coding and analysis. The data will be analyzed using both deductive (theory-driven) and inductive (data-driven) thematic analysis approaches [84,85]. Thematic analysis is a method for identifying, analyzing, and interpreting patterns of meaning in qualitative data [84,85]. Quotations from the participants, derived from the English interviews and original Dutch and French interviews translated into English, will be used to illustrate the findings and allow readers to assess the accuracy of the analysis [86,87].

Data Integration of Part 2 and Part 3

According to a study by Fetter et al [54], the findings of mixed methods studies can be integrated into the design, method, and interpretation and reporting levels of research. Given the aim and multiphase design of this study, the integration will occur at 2 levels: the methods level and the interpretation and reporting level. Integration at the methods level will occur by building using findings from the scoping literature review and qualitative interviews to inform the development of the surveys. Integration at the interpretation and reporting level will be implemented by connecting the qualitative findings from part 2 of the study with the quantitative findings from part 3 of the study using a staged approach in which the results of each part (survey vs interviews) are reported in stages as the data are analyzed and published separately [54]. The findings of the quantitative and qualitative data analyses will then be brought together using a narrative (weaving) approach describing the quantitative and qualitative findings on a theme-by-theme basis using the HSDF as a guiding framework [54]. Finally, the qualitative and quantitative findings will be integrated through joint displays. Joint displays bring data together through visual means (eg, tables, graphs, figures, and matrices) and help to draw out new insights beyond the information gained from separate qualitative and quantitative findings [54].

Ethics Approval

The Medical Research Involving Human Subjects Act does not apply to this study in the Netherlands, as confirmed in September 2021 by the Medical Research Ethics Committee of Utrecht. On January 22, 2022, the Social Science Ethical Committee of the University of Wageningen approved the qualitative part of this study. We will submit the quantitative part of the study separately for ethics approval. The study will also be submitted for review by the Medical Research Ethics Committee in France (Comité de Protection des Personne) and the United Kingdom (Research Ethics Committee).

Participation in this study is voluntary. Before the start of the survey and interviews, we will provide participants with information about the purpose and scope of the study, the length of the survey and interview, their personal rights, and data protection regulations. Data will only be collected after participants have provided informed consent. Interview participants will have the opportunity to ask questions before giving informed consent and signing the relevant consent forms. The survey participants can contact the researchers for any additional information or further questions regarding the study. All participants will be informed that they can withdraw from the interview or stop with the surveys at any time without providing any form of explanation.

Participants in both surveys and interviews will be assured of confidentiality and anonymity. Survey data will be collected anonymously using a certified web-based survey tool that complies with the European Union's General Data Protection Regulation [88]. Interview data will be audio recorded and transcribed afterward. Once transcribed, audio recordings will be erased. All written transcriptions will be deidentified by removing names and changing any identifying data that can be linked back to the participant. All collected data will be securely stored in an encrypted password-protected folder with restricted access.

There is no major risk anticipated with filling in the survey and participating in the interviews. However, survey respondents might feel uncomfortable sharing their views on obesity and bariatric surgery. To reduce this risk, survey respondents will be informed about the potential risks and benefits of the study during the consent process so that they can choose whether to participate [89]. In addition, potential survey respondents will be informed that if they choose to participate, they can choose to skip questions or stop with the survey at any time without providing a reason [89]. The same principles apply to the interview participants. Interview participants may also feel distressed or discomfort when discussing their experiences with stigma; in this situation, participants will be asked whether they are fine and whether they would like to take a short break and continue with the remainder of the interview later on. Toward the end of the interview, we will encourage participants to contact the researcher if they experience continued discomfort or distress as a consequence of participating in the interview.

Results

The research study started in September 2020 and will continue through September 2025. The Research and Assessment Committee from the Wageningen School of Social Sciences reviewed this study (Multimedia Appendix 2 [25,26,90,91]). We will conduct a scoping review to create an overview of the current knowledge related to the experiences and consequences of stigma for patients before and after bariatric surgery. We will also use this information to identify knowledge gaps and further inform the research methods and analyses. Data collected using quantitative methods will provide information on the prevalence and nature of bariatric surgery stigma and will be used to assess the extent to which stigma is culturally dependent. Finally, the qualitative aspect of the study is designed to generate rich information on the lived experiences of patients before and after bariatric surgery, taking into account the experiences and impact of stigma. We will compare quantitative and qualitative findings from all the 3 countries to discuss the similarities and differences between each country.

Discussion

Principal Findings

Obesity is becoming a major health issue in today's society. One way of combating obesity and related diseases is through bariatric surgery. However, the widespread stigma surrounding bariatric surgery may restrict access to this procedure and influence the well-being of patients before and after bariatric surgery, in turn generating health disparities, as people who meet the criteria for bariatric surgery are often economically disadvantaged, have lower levels of education, have less access to health care, and come from racial or ethnic minorities [92,93]. Therefore, it is critically important to conduct research on the nature, experiences, and impacts of stigma. If bariatric surgery stigmatization withholds individuals with obesity from undertaking bariatric surgery or decreases the well-being of patients of bariatric surgery, it is important to alter these negative attitudes in both the general population and health care professionals.

This will be the first study to investigate bariatric surgery stigma from multiple perspectives and in multiple countries. This study is expected to lead to new knowledge and a better understanding of bariatric surgery stigma in several ways. First, although previous research predominantly focused on weight bias and obesity stigmatization, this study will lead to in-depth knowledge on bariatric surgery stigmatization as it uncovers the nature and prevalence of bariatric surgery stigma and how it is perceived and experienced by patients of bariatric surgery. Second, the research will study bariatric surgery stigma from the perspective of both the stigmatized (eg, patients before and after bariatric surgery) and the potential stigmatizer (eg, the general public and health care professionals), which will foster a more comprehensive picture of the topic. Understanding bariatric surgery stigma from the general public, health care professionals, and patients' perspectives might help with decreasing negative attitudes. More knowledge regarding the prevalence and nature of bariatric surgery stigma and hearing about the experiences of patients of bariatric surgery may help reduce the bias and negative attitudes held by the public and health care professionals and help prepare future patients for surgery.

Third, the research will be unique in combining quantitative survey data with in-depth qualitative data to gain a full understanding of the topic. Surveys and interviews will be used as complementary methods to explore different perspectives on stigma. Although mixed methods designs generally require more time, resources, and skills in different research methods, they are valuable as they contribute to a better understanding of the problem than quantitative or qualitative research methods alone [55].

In addition, the research will compare 3 European countries (the Netherlands, France, and the United Kingdom), which will provide insights into how bariatric surgery stigmatization is constructed and maintained by its societal and cultural context. A cross-cultural study of bariatric surgery stigma will help us understand how the drivers and facilitators of stigma, stigma experiences, and discrimination are similar or different across cultures, thereby highlighting how stigma is influenced by culture. Furthermore, this study will be guided by the HSDF to help understand how bariatric surgery stigma operates at different levels and help identify what interventions are needed to combat this stigma. Finally, the topic of bariatric surgery stigma will be approached from an interdisciplinary perspective: contributions from sociology, psychology, ethics, public health, medicine, and health care will be used to document and analyze the topic.

Limitations

In this mixed methods research, data will be collected in the national language of the country. This poses challenges for (1) the translation of surveys and interviews and (2) data analysis, as translation to a common language is time consuming and expensive, and the meaning can easily be distorted or lost in the process of translation [94]. For example, in some languages, words can have several meanings depending on the context in which they are spoken. In addition, some words or phrases (eg, *Gezellig* in Dutch and *Ras-le-bol* in French) cannot literately

be translated into other languages. The accuracy and validity of the data might be compromised because of translation.

To help ensure the accuracy of the data collected and the validity of the results reported so that local meaning and cultural connotations are not lost, we will pay particular attention to the development and testing of surveys and interview topic guides and the analysis and reporting of data [80,94]. Surveys and interviews will be forward and backward translated by independent translators who have good proficiency in the language and then piloted by native speakers. To minimize the risk of misinterpretation, misunderstanding, and loss of respondents' intended meaning and thus maintain the *conceptual equivalence*, qualitative data derived from the interviews will be analyzed in the language in which it was obtained, using an iterative coding framework with common labels. Participants interested in the study results will receive a summarized version in both English and the language of origin (Dutch or French).

For the interviews, because of time constraints and the geographical spread of hospitals and clinics that perform bariatric surgery in the Netherlands, France, and the United Kingdom, it is not possible to include participants from all regions within these countries. Consequently, not all types of patients of bariatric surgery will be represented in this study. In addition, in qualitative studies, it is often difficult to assess whether the sample is representative of the population. To ensure that a wide range of patient perspectives is included in the study, we will interview patients from different age groups, genders, and socioeconomic statuses. In addition, interviews will be conducted until data saturation is reached and, thus, no new information is discovered [69,70].

Conclusions

This protocol outlines the rationale and design of a cross-cultural mixed methods study focused on understanding the prevalence, nature, and impact of bariatric surgery stigma from the perspective of the public, health care professionals, and patients of bariatric surgery in the Netherlands, France, and the United Kingdom. We expect the results of this study to be relevant for people with obesity who are considering bariatric surgery, people who have undergone surgery, and health care professionals involved in the care of people with obesity and patients of bariatric surgery. The findings of this study have several practical implications. It can be used to educate the general public regarding patients' experiences, in the education of health care professionals who work with patients of bariatric surgery, by health care professionals to generate discussions with patients and raise awareness of the issue, and to develop interventions that can be used to educate patients of bariatric surgery before surgery about the potential experiences and implications of stigma to prepare them for life afterward. In turn, bariatric surgery access, use, and outcomes, including the quality of life of patients, may be improved.

Acknowledgments

Authors' Contributions

FKG and KTV were responsible for the conceptualization of the study. KTV, BCM, MAK, and EJH were involved in the implementation of the study. FKG was responsible for the writing and further revision of the first draft of the manuscript. KTV, EJV, BCM, MAK, and EJH were responsible for reviewing and commenting on the draft versions of the manuscript. EJV was affiliated with Rural Sociology, Department of Social Sciences, at Wageningen University at the time the draft versions were written and is currently affiliated with the Almere University of Applied Sciences in Almere, the Netherlands. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Health Stigma and Discrimination Framework.
[PDF File (Adobe PDF File), 312 KB - resprot_v11i4e36753_app1.pdf]

Multimedia Appendix 2
Peer-review report from the Wageningen School of Social Sciences.
[PDF File (Adobe PDF File), 361 KB - resprot_v11i4e36753_app2.pdf]

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Abbreviations

HSDF: Health Stigma and Discrimination Framework

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Review

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Protocol

Telemedicine for Adults With Cochlear Implants in the United Kingdom (CHOICE): Protocol for a Prospective Interventional Multisite Study

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Abstract

Background: Cochlear implants provide hearing to approximately 750,000 people with deafness worldwide; these patients require lifelong follow-up. Care for adults with implants in the United Kingdom occurs at one of 19 centers, which may be far from the patients' homes. In a previous randomized controlled trial, we successfully introduced person-centered care. We designed, implemented, and evaluated the following remote care pathway: a personalized web-based support tool, home hearing check, self–device adjustment, and upgrading of sound processors at home rather than in the clinic. The remote care group had a significant increase in empowerment after using the tools, and the patients and clinicians were keen to continue. We would now like to scale up these improvements as an option for >12,000 UK adults using implants; we are commissioning an independent evaluation of this intervention and rollout to establish if it achieves its aims of more empowered and confident patients; more accessible and equitable care; stable hearing; more efficient, person-centered, and scalable service; and more satisfied and engaged patients and clinicians.

Objective: This study aims to evaluate the impact and rollout of a person-centered clinical care pathway via telemedicine for adults with cochlear implants in the United Kingdom, using both outcomes and process evaluation.

Methods: This project will scale up and evaluate a person-centered long-term follow-up pathway for adults using cochlear implants through a personalized website, including a home hearing check, uploading photos of cochlear implant site, listening in noise and music practice, ordering of spares, questionnaires, and other resources. Both quantitative and qualitative analyses will be conducted, and they will be both an outcome and process evaluation.

Results: As of July 2021, the trial is closed, and all data collection is complete. The evaluation report is expected to be published in December 2021, and the research data have not yet been analyzed.

Conclusions: This project will present the results of the first scaling up of a remote care pathway for adults with cochlear implants in the United Kingdom.

Trial Registration: International Standard Randomized Controlled Trial Number ISRCTN51668922; https://www.isrctn.com/ISRCTN51668922

International Registered Report Identifier (IRRID):   DERR1-10.2196/27207

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Introduction

Background

Cochlear implants are the most successful of all neural prostheses [1]; they can provide hearing to people with severe to profound deafness. Approximately 1600 people receive cochlear implants in the United Kingdom (UK) each year [2]. The total number of people with implants is approximately 20,000 in the UK (estimated from [2]) and approximately 0.75 million worldwide (estimated from [3-5]). Numbers are likely to increase rapidly, with only approximately 5% of eligible people in the UK and worldwide having received an implant [4,6]. The number of people of retirement age is projected to increase by 28% by 2035 [7], indicating a further increase in the number of people with hearing impairment. Adult cochlear implant care in the United Kingdom is provided at one of 19 tertiary centers involving assessment, surgery, and a resource-intensive acute phase of device adjustment and rehabilitation. When a patient attends a long-term follow-up appointment, the following tasks may be performed: speech recognition testing, device adjustment, rehabilitation, equipment check and troubleshooting, and the provision of replacement or upgraded equipment. Currently, UK implant centers review patients on a clinic-led schedule, which means review appointments that provide little benefit to the patient can occur. Conversely, when some patients attend routine appointments, there is hearing deterioration that the patient had not noticed. This is often remedied by replacing equipment, which the patient could have done at home.

Cochlear implant centers may be several hours away from the patient's home, necessitating travel expenses, time off work, and family disruption; distance to care is a significant barrier to hearing care worldwide [8]. Making this care pathway person centered instead may provide a more efficient and effective service and allow more timely identification of issues; evidence suggests that person-centered care can improve a range of factors, including patient experience, care quality, and health outcomes, and may help clinics manage a growing number of people with long-term conditions [9].

We previously designed and implemented a remote care pathway for adults with cochlear implants to enable them to perform some of the follow-up tasks themselves at home. We ran a 6-month clinical trial with 60 people randomized to either a telemedicine remote care pathway or a control group who followed their usual appointment schedule [10]. The main outcome evaluated was patient empowerment, which has been shown to be strongly linked to better outcomes in people with long-term conditions. We found that only the remote care group had a significant increase in their cochlear implant empowerment after using remote care tools. The quality of life remained unchanged in the 2 groups. The hearing check results in the clinic improved in the remote care group, although they

did not notice a change. However, the control group felt that their hearing had become slightly worse. This may suggest that the remote care group was better able to take action to keep their hearing stable during the trial, or, perhaps, the control group felt they were missing out on a desirable opportunity to take a more active role in their hearing health care.

Discontinuing routine appointments and attending the clinic only when there is a clinical need may provide the following benefits for patients using cochlear implants:

- More stable hearing (problems identified and resolved quicker)
- Better hearing (ability to fine-tune when away from the clinic)
- Convenience of not traveling for routine appointments
- Reduction of travel costs and time, time off work, and disruption to family life
- Increased confidence in managing one's own hearing
- Greater equality in service delivery (same level of service regardless of distance from the clinic)

It may also mean that the clinic has greater resources (time, money, and space) to see both patients with more complex needs and an expanding population of new patients. People using cochlear implants and their families generally like to take a more active role in their care and welcome the use of technology to assist self-care [11,12]. The National Health Service (NHS) has a strong commitment to promoting self-care and self-management [13] for people with long-term conditions [14], with "the vision of a citizen-centred, digitally-enabled, health and social care system" [15]. Evidence shows a significant improvement in outcomes when patients use self-management tools [16], and those who are activated and involved in their care tend to have better health outcomes [17,18]. We are now ready to scale up successful remote care interventions for many more people with cochlear implants in the United Kingdom.

Objective

This study aims to evaluate the impact and rollout of a person-centered clinical care pathway via telemedicine for adults with cochlear implants in the United Kingdom, using both outcomes and process evaluation.

Methods

Project Design and Setting

This is a prospective, interventional, multisite, quality improvement project led and sponsored by the University of Southampton. All research measures will be self-administered on the web or by a paper questionnaire at the patient's home or other locations of their choice. The staff will complete the measures at work or at a location of their choice. Data collection began when the first site opened on June 11, 2019, and continued

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until January 31, 2021. Clinics will join the study when appropriate local approvals are obtained; therefore, it is likely that the follow-up at each clinic will be for different durations.

Intervention

This project introduced a remote care pathway option for adults using cochlear implants: cochlear implant home care (CHOICE). We built a personalized, scalable, and responsive web app (not a native application but accessible from any internet browser) based on our previously trialed CIRCA (Cochlear Implant Remote Care website; built in LifeGuide [19]). The app incorporated a home hearing check based on the triple digit test [20], personalized reminders (eg, change microphone cover), rehabilitation exercises (listening in noise, music, and telephone practice), uploading a photo of the cochlear implant surgery site (behind the ear) for review by the clinical care team, information and training, logging the number of hours patients used their cochlear implant (optional and self-reported only), evaluation measures, ordering replacement parts for their cochlear implant, emotional support resources, and questionnaires (Figure 1). The home hearing check provides a screen for whether the patient should come to the clinic based on comparison with a baseline check. Speech perception in noise testing using spoken digits (eg, *one*) has the advantage of digits being highly familiar stimuli usually known by people with even limited language skills. Digit testing requires a closed, set response and is, thus, suitable for self-testing over the telephone or internet [21,22] and has a minimal learning effect [23]. The test correlates well with speech recognition in noise with sentences in people using cochlear implants [24-27].

It is vital that patients remain vigilant in preventing medical issues related to their cochlear implants. This mainly involves appropriate action for ear infections (following the center's protocol) and checking the site of the implant and skin under the coil magnet. The CHOICE website advises patients to contact their clinical care center with any medical concerns. The web app has the functionality to upload and store photos of the patient's implant site. Patients will be asked to take a baseline photograph at an early stage to provide a comparison with later images.

The patient's clinician at their cochlear implant center will have access to their results and web app use in the CHOICE web-based clinician dashboard. Cochlear implant center clinic appointments will be given if required, requested, or indicated by the outputs of the remote care tools. Otherwise, the patients in this pathway will continue with remote care. Participants may access the web app tools as often as they wish.

Automated flagging by email and website notifications will be the cornerstone of the remote care pathway. This will ensure that the patient's problems are not missed and will provide the most efficient use of clinician time. Some patient flagging situations are as follows: no interaction with CHOICE for 3 months; hearing deterioration; patients who indicate that they need help on the general check-up questionnaire; each time a photo is uploaded, clinicians need to review it; replacement stock items are required; patient reports their daily sound processor use is <6 hours; request to leave CHOICE; and freedom of information request.

When an alert is received, the patient's clinician will decide whether further action is required; for example, an in-center appointment.

The CHOICE website conforms to the following specifications: risk management (ISO 14971:2007) and software life cycle (BS EN 62304:2006) and complies with the requirements of the European Union directive 93/42/ECC for medical devices. It is Conformitè Europëenne marked and registered with the Medicines and Healthcare products Regulatory Agency as a Class 1 medical device.

Figure 1. Cochlear implant home care (CHOICE) web app patient dashboard.
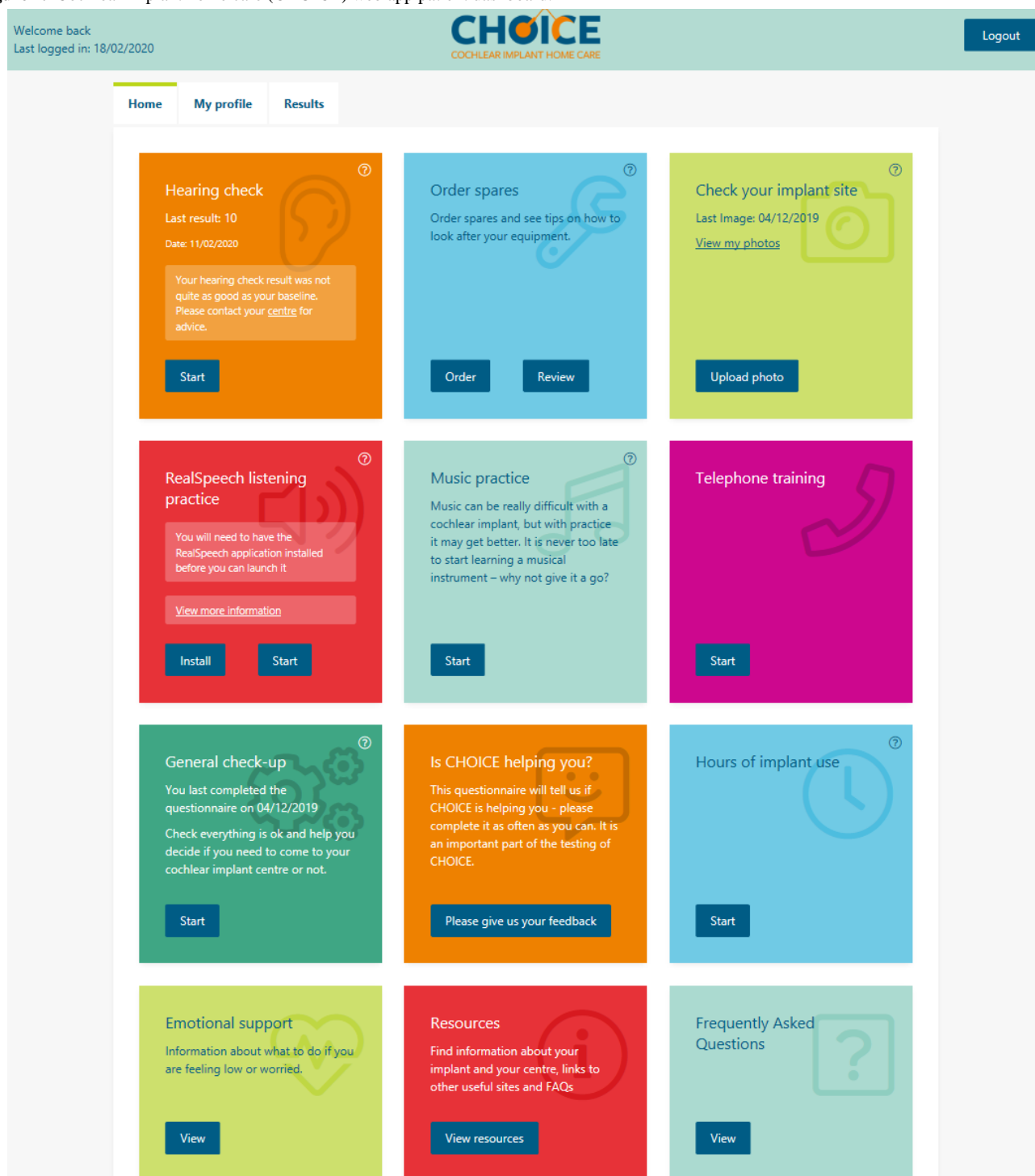
Participants

Overview

The following 7 UK centers will offer CHOICE to their patients:

1. St Thomas' Hospital Hearing Implant Center, London
2. University of Southampton Auditory Implant Service
3. Royal National Throat Nose and Ear Hospital, London
4. Nottingham Auditory Implant Program
5. North East Regional Cochlear Implant Program, Middlesbrough
6. The Richard Ramsden Center for Hearing Implants, Manchester
7. Emmeline Center, Cambridge

All adult sites were contacted about CHOICE and its evaluation; these sites wanted to be involved. CHOICE is currently an intervention for adults only. Initially, scaling up to only 7 of the adult sites will allow for detailed evaluation. Depending on the evaluation results, CHOICE may be offered to all sites in the future.

Proposed Sample Size

We do not yet know what proportion of patients will choose to follow this pathway, as the previous study was a single-center randomized controlled trial involving a limited number of patients [10]. However, 7 centers care for approximately one-third of the approximately 12,000 adults [28] with cochlear implants in the United Kingdom. At the early stages of project planning, we estimated that if 40% of patients enrolled, this may involve approximately 1700 patients. We expect this to be the upper limit for recruitment. Scaling up a digital health tool for people with cochlear implants has not been done before; thus, we cannot predict the uptake. We anticipate that up to 10 members of staff per will be involved per site (total 70). As the aim of the project was not to formally test a hypothesis, a sample size calculation was not conducted.

Recruitment

We recommend shared decision-making among the patient, their family, and their clinician to decide who should be on a remote care pathway [29]. Factors that need to be considered include the patient's care needs; routine maintenance of equipment; access to technology; mobility; literacy; dexterity; any comorbidities (eg, visual impairment); and other factors, such as do they live alone and do they have transport. All patients who meet the inclusion criteria and, after discussing with their clinician as needed, choose the remote care pathway will be invited to participate in the study. Only those who consent to the study will be able to continue with remote care at this stage. As patients' circumstances and abilities change, we recommend service delivery flexibility, with easy transfer to a clinic-based care model, if required. Staff at participating centers will be invited to take part and sign a consent form for their data to be included in the evaluation. Participant

recruitment commenced on June 11, 2019, and continued until January 31, 2021.

Patient Inclusion Criteria

The inclusion criteria for patients are as follows:

1. Using a cochlear implant (any device—unilateral or bilateral)
2. Living in the United Kingdom
3. Aged ≥18 years
4. Able to give informed consent to data sharing
5. Access to a computer or device with internet access
6. Willing and able to comply with CHOICE pathway
7. Willing and able to comply with the evaluation

Health Professional Inclusion Criterion

The inclusion criterion for health professionals was being a staff member at participating cochlear implant centers.

Evaluation and Research Outcomes

Overview

The Wessex Academic Health Science Network (AHSN) will perform an independent evaluation to assess the impact and success of the care pathway on patients, staff, and services and understand the process of implementing CHOICE using a concurrent triangulation mixed methods design. It will be both an outcome and process evaluation. The evaluation was commissioned in September 2017 and is informed by a growing research base on the challenges associated with the adoption and spread of digital programs. The research team will collect the clinical outcome measures. All the outcomes, methods, and measures corresponding to the research questions are listed in Table 1.

Table 1. Outcomes, methods, and measures collected from patients, staff, and services.

Outcome	Research question	Method	Measures	Time point
Patients				
Patient impact (engagement)	1	Quantitative	CHOICE[a] web app data: number of log-ins, time spent on CHOICE, uses of self–device adjustment (if appropriate), and uses of home hearing check	All data
Patient impact (quality)	1	Quantitative	Number of errors in CHOICE, adverse events, and missed issues	All data
Patient impact	1	Quantitative	Survey about use of follow-up care (consequences for travel cost, time, hours off work, and child care [including accompanying person])	Once at patient focus group or interview
Patient impact	1	Quantitative	NHS[b] Friends and Family Test	Minimum of twice: baseline (on registration) and after using CHOICE for several months
Patient impact	1	Qualitative	Focus groups	Once: planned but unable to happen because of the COVID-19 pandemic
Patient impact	1	Qualitative	One-on-one interviews	Once: for patients who prefer one-on-one interviews or if focus groups cannot occur; toward the end of the project
Patient empowerment	2	Quantitative	PAM[c] questionnaire and CI-EMP[d] questionnaire	Baseline (on registration) and 6 months following registration or end of the project—whichever comes sooner
Patient hearing	2	Quantitative	Home hearing check results	All data
Patient change in empowerment, hearing, and quality of life	2	Quantitative	Global ratings of change questionnaire	Baseline (on registration) and 6 months following registration or end of the project—whichever comes sooner
Patient health-related quality of life, including hearing	2	Quantitative	HUI3[e] questionnaire	Baseline (on registration) and 6 months following registration or end of the project—whichever comes sooner
Patient health-related quality of life	2	Quantitative	EQ-5D-5L[f] questionnaire	Baseline (on registration) and 6 months following registration or end of the project—whichever comes sooner
Patient preference of service delivery	2	Quantitative	Discrete Choice Experiment questionnaire	Baseline (on registration) and 6 months following registration or end of the project—whichever comes sooner
Patient confidence and experience	4 and 5	Quantitative	R-Outcomes surveys	Baseline (on registration) and every 6 months; some participants may choose to complete an optional, shorter questions set more often
Staff				
Staff impact (engagement)	1	Quantitative	CHOICE web app data from clinician dashboard: number and type of log-ins	All data
Staff impact	1	Quantitative	NHS Friends and Family Test	Minimum of twice: baseline (on registration) and after using CHOICE for several months
Staff behavior	1	Quantitative	NoMAD[g] questionnaire	At interview or by email and by email request toward the end of the evaluation
Staff impact	1 and 9	Qualitative	Focus groups (staff)	Once: planned but unable to happen because of the COVID-19 pandemic
Staff impact	1 and 9	Qualitative	One-on-one interviews (staff)	Once for key staff who are not available for the on-site focus group; toward the end of the project

Outcome	Research question	Method	Measures	Time point
Staff experience	7	Quantitative	R-Outcomes surveys	Baseline (on registration) and every 6 months
Services				
Spread, equity of access, and resource use	3, 4, and 8	Quantitative	Clinic activity information	See Multimedia Appendix 1 for more details

[a]CHOICE: cochlear implant home care.

[b]NHS: National Health Service.

[c]PAM: Patient Activation Measure.

[d]CI-EMP: Cochlear Implant Empowerment Scale.

[e]EQ-5D-5L: EuroQol 5-Dimension 5-Level.

[f]HUI3: Health Utilities Index Mark 3.

[g]NoMAD: Normalization Measure Development.

Primary Research Questions

This study attempts to answer the following primary research questions:

1. Evaluation: What is the impact of the rollout of the new care pathway on users of the program (people with cochlear implants and the staff)?

2. Research: Does the new care pathway increase empowerment for people with cochlear implants while having no detrimental effect on their hearing and quality of life?

Secondary Research Questions

This study attempts to answer the secondary research questions provided in Textbox 1.

Textbox 1. Secondary research questions.

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3. What is the extent of the spread of the new care pathway?

- What has facilitated the adoption of the new care pathway?

- What has hindered the adoption of the new care pathway?

4. Does the new care model improve patients' confidence to self-manage their cochlear implant as measured by patient-reported outcomes of health confidence, health status, and personal well-being?

- Do patients initiate review appointments with the service rather than rely on or wait for appointments scheduled by the service?

5. Does the new care model improve patients' experience of follow-up care?

- Do patients engage with the technology as measured by patient-reported outcomes of digital confidence and perceived value of the tool?

6. Does the new care model improve equity of access to follow-up care?

7. Does the new model of care improve the experience of staff working in the service, as measured by staff-reported outcomes of job confidence and work well-being?

- Do staff have confidence in the new care model, as measured by staff-reported outcomes of digital confidence and perceived value of the tool?

- Do they recommend it?

8. Does the new care model improve the use of resources by reducing the need for follow-up appointments and enabling the service to be delivered by a different skill mix?

9. What lessons can be learned from the implementation process that will benefit the spread and adoption of this model?

Patient Outcomes

Quantitative Measures

All data will be downloaded from the CHOICE web app, and patient use of all elements of CHOICE, including the hearing check, will be assessed. Errors in CHOICE, adverse events, and missed patient issues will be collected during the study period. Patients who take part in the focus group or interview will be asked to complete a short survey about the cost implications of switching to remote care (eg, impact on travel costs and need for childcare).

Quantitative data about patients' use of CHOICE will be collected using the R-Outcomes survey tool [30]. These measures share a common framework with 4 items and 4 responses suitable for use on a mobile device and are validated, short, and have a lower reading age than other measures. R-Outcomes are incorporated into CHOICE and will assess the patients' health, well-being, health confidence, digital readiness,

and user experience. The NHS Friends and Family Test was also incorporated into the CHOICE web app, asking the question, "How likely are you to recommend this service to friends and family if they need similar care or treatment?" with 6 response options ranging from *extremely likely* to *extremely unlikely* [31].

We will use the following measures to assess empowerment, health-related quality of life, hearing, and patient care pathway preference: Patient Activation Measure (PAM), Cochlear Implant Empowerment Scale (CI-EMP), EuroQoL 5-Dimension 5-Level (EQ-5D-5L) questionnaire, Health Utilities Index Mark 3 (HUI3), a global change rating, and a discrete choice experiment (DCE). PAM is a well-validated generic measure of patient activation that evaluates the knowledge, skills, beliefs, and behaviors that patients have for self-management of their long-term condition [32,33]. The CI-EMP is a questionnaire specifically designed to measure how empowered people are to manage their own cochlear implant care [34]. The EQ-5D-5L is a standardized health outcome measure comprising five dimensions: mobility, self-care, usual activities, pain or

discomfort, and anxiety or depression [35]. The HUI3 is a multi-attribute health status classification system that evaluates eight domains: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain [36].

The global rating of change scales will be used to capture whether patients perceive a change in their hearing, empowerment, and quality of life to determine whether any changes observed in the PAM, CI-EMP, HUI3, or EQ-5D-5L are meaningful; that is, whether they were perceived by patients.

We designed a DCE to assess the effects of the following five care pathway attributes on the preferences of the participants for remote care (Figure 2):

1. Who decides when the next clinic appointment will be?
2. When is the ability to understand speech monitored?
3. Who can fine-tune the cochlear implant?
4. Where can patients get rehabilitation and troubleshooting information that is personalized to their needs?
5. How are upgrades to sound processors provided?

Figure 2. The 5 elements of the discrete choice experiment.
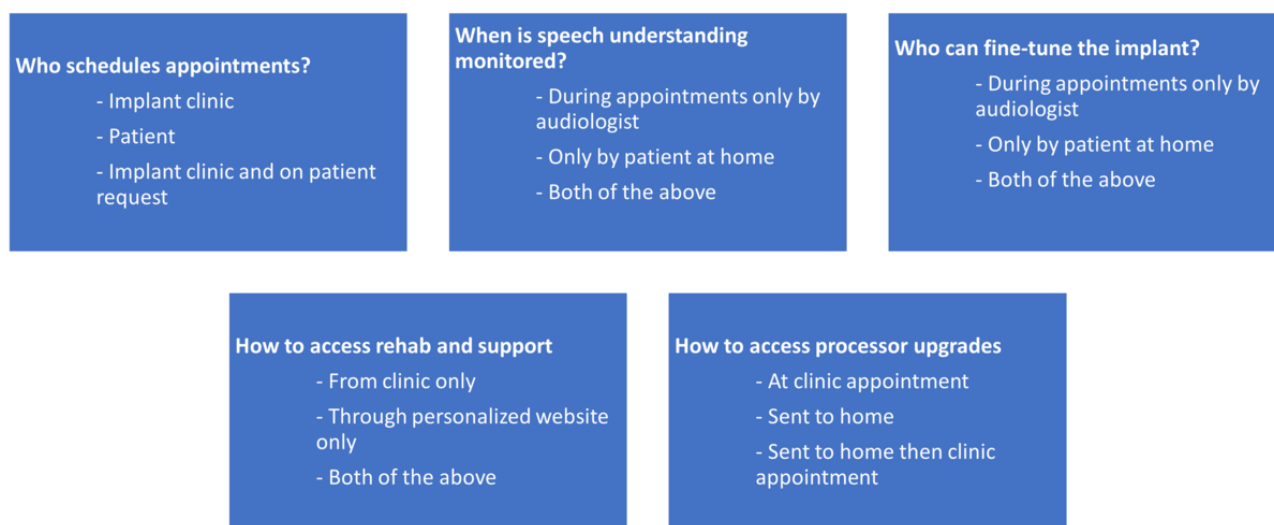
Each attribute had 3 levels that described different approaches and degrees of remote care; for example, the choices for who decides when the next clinic appointment will be *the implant clinic*, *the patient,* or *the implant clinic (however, the patient can request appointments when required)*. The experiment was constructed using the mix and match design method [37], as implemented in the *support.CEs* package for the R statistical environment [38]. The experimental design was organized into 2 blocks to reduce the number of questions each participant had to complete, and patients will be randomly assigned to complete either block 1 or block 2. The design requirements of 5 attributes per alternative, 2 alternatives per choice question, and 2 experimental blocks resulted in the allocation of 9 discrete choices per block. The role of the DCE is to help us learn about

how the different elements of the care pathway interact to shape participant preferences for remote care compared with the usual pathway. It is possible that the preferences that patients have for remote care could relate to their outcomes, and we will explore these relationships using exploratory correlational analyses.

Qualitative Measures

Although the qualitative fieldwork was initially planned as focus groups of patients and staff at each site, because of the COVID-19 pandemic, this changed to telephone or web-based interviews. Up to 20 patients per site will be recruited. The interviews will be audio recorded, transcribed, and managed

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using NVivo (version 12; QSR International); 2 Wessex AHSN qualitative evaluators will conduct all interviews.

Staff Outcomes

Quantitative Measures

CHOICE web app data about staff use of the clinician dashboard will be downloaded and analyzed. The staff will also be asked to complete the NHS Friends and Family Test and R-Outcomes (with additional measures of work well-being and innovation adoption) within the CHOICE clinician dashboard.

Qualitative Measures

As for patients, focus groups were planned but changed to telephone or web-based interviews because of the COVID-19 pandemic; up to 10 staff per site will be recruited for one-on-one interviews.

Services Outcomes: Quantitative Measures

Local service-level activity data will be collected at all sites with a view to assessing resource use and the workforce (Multimedia Appendix 1). We aim to obtain data from all clinic patients to maximize the sample size. A cohort of patients will also be identified for comparison. This will comprise patients registered with clinics but who have not yet been offered the new care model. We will look at the aggregated clinical activity before and after the introduction of the tool (eg, numbers of outpatient appointments and DNAs in the inclusion group). There will not be a control group of patients undergoing the same measures as the intervention group. We will also analyze the centers' previously collected service-level data to evaluate the current pathway.

Process Evaluation

This part of the evaluation will assess what lessons can be learned from the implementation process and what *key ingredients* are replicable to other clinical settings.

Evaluation of the Behaviors of Staff Involved in Implementation of CHOICE

The evaluation design is informed by the Normalization Process Theory [39], which provides a pragmatic framework for collecting and analyzing what the staff does in response to changes in the model of care, and the nonadoption, abandonment, scale-up, spread, and sustainability (NASSS) framework [40] will inform the design of the staff interviews. In addition, the Normalization Measure Development questionnaire [41] will be administered to the staff early on in the rollout and later by email at the end of the data collection period.

Evaluation of the Factors That Have Facilitated or Hindered the Adoption of CHOICE

An analysis of the findings from the qualitative data sources will be compared with factors known to be important for spread and adoption [40]. This will enable us to understand the factors that facilitate or inhibit the embedding of CHOICE in the care pathway.

Assessment of Resource Use and Workforce

As this model is scaled up, it will offer important learnings on how it can be delivered most efficiently and whether the anticipated changes in clinic activity and type (as a consequence of remote care options) have any implications for the clinic workforce. For example, if the reason for clinic attendance is known in advance, as it is requested by the patient, the patient may not need to be seen by a senior audiologist. Data on the workforce at each site, as well as any changes during the project, will be collected and analyzed.

We will examine the economic impact on the clinic activity of implementing the new care model. We will also apply predictive modeling to understand the impact of scaling up the model beyond a target cohort of several thousand patients. The costs associated with the delivery of follow-up activities will be sourced from each site to understand the impact of uptake of remote care.

Data Analysis

All data analyses aim to answer the 9 primary and secondary research questions. Statistical analyses will be performed using the SPSS Statistics package (version 26; IBM Corp).

Quantitative

Descriptive statistics and graphs will be used to present the data. Data will be displayed visually wherever possible to facilitate sharing with various stakeholders. The significance value will be set at $P=.05$, including Bonferroni corrections for multiple comparisons where appropriate. All repeated-measures data will be compared at baseline and follow-up using analysis of variance to examine any changes in empowerment, hearing, and quality of life in the participants. Surveys will be analyzed at the baseline and follow-up time points using inferential statistical analyses. The choices of participants in the DCE will be subjected to conditional logit model analysis using the *survival* package of the R programming language.

Qualitative

The qualitative data from the patient interviews, staff interviews, and case studies will be thematically analyzed separately but brought together in the triangulation phase using synthesis meetings with different involved investigators. To address the evaluation questions, qualitative findings will be synthesized with the quantitative findings. Both theoretical frameworks applied to this evaluation (NASSS and Normalization Process Theory) will be used to facilitate an understanding of the findings. Qualitative interview data will be coded by 2 qualitative evaluators (Wessex AHSN) using a coding framework based on the NASSS framework. A small sample of transcripts will test and refine the framework with an agreement between the coders. The coding framework and coding of transcripts will use NVivo software. Higher order codes and themes will be presented for scrutiny and sensemaking to the wider evaluation team.

Missing Data

We anticipate significant missing data because of the large number of outcomes measured and the clinical population. We expect that data will mostly be missing not at random, as those

who discontinue the use of CHOICE or drop out are likely to be those who find it less helpful. This may lead to significant bias. There is likely to be a selection bias, as patients who agree to follow a remote care pathway may not be representative of the population. The same will apply to clinicians: those who want to be involved in implementing CHOICE are likely to be more invested in remote care than their colleagues. Following recommendations [42], when data are ready to be analyzed, inspection will suggest whether statistical methods should be used to handle missing data. As this is an outcome and process evaluation, the extent and pattern of missing data will in itself be significant, with nonresponse bias expected. It is also possible that reporting bias may occur; people with cochlear implants are often so grateful for their treatment that they may provide answers in the direction they perceive that the researchers want.

Monitoring

Steering Group

The CHOICE steering group (SG) meets every 4 months and comprises the CHOICE chief investigator; project manager (PM); 2 patients; coordinators of 2 other cochlear implant centers; the lead of the independent evaluation team; and senior representatives from the NHS Specialist Commissioning, The Ear Foundation, and the National Cochlear Implant Users Association. The purpose is to advise and guide the project by reflecting differing stakeholder needs to maximize success and ensure the long-term sustainability of the project. The SG acts as a sounding board for the project, particularly in relation to key project risks (including time, cost, quality, commercial, legal, and ethical risks). The SG also deals with safety monitoring, adverse events, data monitoring, deviations from and breaches of protocol, and major project changes.

Evaluation Advisory Group

The evaluation advisory group (EAG) is a requirement of the project funder and its remit relates to the independent evaluation of CHOICE. The EAG meets every 3 months and comprises the Wessex AHSN's Director of Insight (chair), Associate Director of Insight (evaluation lead), program manager, and data analyst; the CHOICE chief investigator and PM; a strategic advisor from Consilium Partners Ltd; the Director of R-Outcomes Ltd; the RUBIS.Qi evaluation lead (coaching organization provided by the funder); and a patient. The CHOICE team does not take decisions on the evaluation but collaborate and provide input as required. The EAG also provides a forum for reflecting on the findings of the evaluation during the course of the project and enable improvements in the scaling up of CHOICE via formative learning.

Industry Advisory Group

The industry advisory group was formed to ensure 2-way dialog with the device manufacturers of cochlear implants. This stakeholder group is purposefully separate from the SG so that CHOICE continues its ethos of being patient centric, charity funded, and agnostic of individual industry parties. The industry advisory group meets every 6 months and comprises the chief investigator and PM and 1 representative from each of the 4 cochlear implant companies: Advanced Bionics UK Ltd, Cochlear Europe Ltd, MED-EL UK Ltd, and Oticon Medical Ltd.

We have not established an independent data monitoring committee, as this is not a clinical trial, and it is not a requirement of the funder. The funder may observe, monitor, and inspect the delivery of the project and reserves the right to externally evaluate any aspect of the project and its outputs. The funder may need to allow members of The Health Foundation Research Directorate to inspect anonymized records and data, including recordings and transcripts of interviews with patients and others.

Patient and Public Involvement

The project team has a strong commitment to patient and public involvement, and a member of the project team is a service user (CR). Local and national publicity (through the website, Twitter, presentations to National Cochlear Implant Users' Association, newsletter articles, letters, emails, and Yahoo group) has already invited help in designing the project. Several people using cochlear implants have trialed the CHOICE website and the hearing check before its release and have provided feedback in writing and focus groups.

A risk assessment was approved by the University of Southampton Faculty of Engineering and the Environment on May 15, 2018 (FEERA 15927).

Data Management

The data will be managed according to the University of Southampton Research Data Management Policy. The study's data management plan and data protection impact assessment are available upon request. Deidentified data will be kept at the University of Southampton for at least 10 years. If patients decide to stop using CHOICE, we will keep the information we have collected thus far unless participants request that it be deleted. It will not be possible to delete data if they have already been anonymized. Individual cochlear implant centers will retain their own clinical patient data according to local policies.

Regarding evaluation data, only deidentified data will be provided to the independent evaluator, who will handle and store this in accordance with the agreements that are put in place at each site. Wessex AHSN will ensure that the data are handled in line with NHS standards, including data collection, code of practice, and information governance. The AHSN computer network is a private cloud-based system compliant with ISO 27001 and approved under the NHS Information Governance Toolkit. The cloud servers are based in the United Kingdom.

The retention schedule for data collected by Wessex AHSN is as follows:

- Audio recordings will be kept until the publication of the evaluation report (July 2021) and then destroyed.
- All other data, including transcriptions of the audio recordings, will be kept until 12 months after publication of the evaluation report (July 2022) and then securely transferred to the University of Southampton (under the control of the chief investigator) to be retained until 10 years after the study conclusion.

Ethics and Dissemination

Ethical approval was received in November 2018 from the South Central–Hampshire A research ethics committee (REC reference 18/SC/0658; IRAS project ID 242575), Health Research Authority, and Health and Care Research Wales.

Confidentiality

Personal and sensitive personal data will be entered into the web app by the patient. The patient will consent to data sharing. The data will be encrypted before transfer. At the close of the project or before, the data will be deidentified (personal data removed). We cannot guarantee anonymity as adults with cochlear implants are still rare in the general population (approximately 0.01% of the UK population or approximately 1 in 10,000 people).

Interviews (with staff and patients) will be audio recorded using an encrypted dictaphone and transcribed. Any used names will be removed after transcription. Data relating to individuals will not be linked together; that is, individual interviews and individual R-Outcomes data will not be linked. The findings will be linked through a synthesis process at the aggregate level. Safety monitoring and reporting of adverse events will occur according to the requirements of the local and national ethics committees, with full support from the sponsor.

Dissemination

The results will be presented locally, nationally, and internationally. Dissemination will include but not be limited to peer-reviewed publications both on the web and in print, conference and meeting presentations, posters, newsletter articles, website reports, and social media. To inform people with cochlear implants of the results, information will be sent to the National Cochlear Implant Users' Association and other patient groups and the University of Southampton Auditory Implant Service patient newsletter. We have budgeted for our academic publication of clinical results to be gold open access. The results of this evaluation will be published in a report by Wessex AHSN.

Results

As of July 2021, the trial is closed, and all data collection is complete. The evaluation report is expected to be published in December 2021, and the research data have not yet been analyzed.

Discussion

Limitations

A total of 7 sites agreed to participate in the implementation and evaluation of CHOICE. These sites are mostly larger adult cochlear implant centers in England. Sites were self-selected: those participating were the centers that expressed interest in taking part. This means that it is unlikely that these centers are representative of all UK adult cochlear implant centers; they are likely to be more willing to innovate. Given that data collection will commence as soon as centers and patients join CHOICE, there will be variable periods of follow-up.

We expect significant effect modification in subgroups (eg, by age, gender, cochlear implant center, and other demographic factors). Assessing and reporting effect modifications may help identify a subset of patients who would not benefit from remote care. We attempted to control for confounding factors by collecting the demographic and digital readiness data. However, it is possible that there are confounders that remain unaccounted for; for example, we will not collect data on mental health and social support or the impact of the COVID-19 pandemic. It is likely that the concurrent COVID-19 pandemic will be the largest confounding factor in the data. In addition, the coincidental launch of a manufacturer-led remote care pathway (Cochlear Remote Check) for patients with some devices is likely to confound the results. The nature of recruitment for this study (cochlear implant center choosing to be involved and patient choosing to take part) means that there is likely to be a significant bias. Patients who choose to take part in a trial of remote care may not be representative of the broader population of people with cochlear implants. As recruitment is performed via patient and clinic choice, it is not valid to have a control group of people who do not follow a remote care pathway.

We are aiming for 6 months of follow-up data. This may be insufficient to highlight the benefits and limitations of remote care, especially in the climate of change because of the COVID-19 pandemic. In addition, as patients are encouraged to register for CHOICE at any point, there may only be a very short experience of using CHOICE by the end of data collection for many people.

The PAM may not be very sensitive to changes in the empowerment of people using cochlear implants because of its medical perspective. Given that this is the first time there has been a large-scale rollout of a remote care model for cochlear implants, we do not know how many people will participate. Low patient numbers and dropouts are likely to affect the quality of the results, although reporting them will provide important information on the success of the implementation. Patients who discontinue the use of CHOICE will be asked to provide a reason for their withdrawal.

Conclusions

This project will present the results and learnings from the first scale up of a remote care pathway for adults with cochlear implants in the United Kingdom.

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Authors' Contributions

The clinical conception and design for the study were done by HC and PK. The evaluation conception and design were completed by PD and AS. All the authors contributed to the drafting of the protocol, critical revision of the manuscript, and obtaining funding.

Conflicts of Interest

Authors HC, PK, TF, KG, CR, MW, and D-MW were involved in the development of the CHOICE web app but have no financial interest in the web app. All authors received grant funding from the Health Foundation for this study. HC performed private consultancy work for Cochlear (one of the cochlear implant manufacturers) from 2011 to 2017. HC has received travel grants from all 4 cochlear implant manufacturers unrelated to this study. PK received grant funding from Cochlear to conduct unrelated research within the same topic (cochlear implants). PD and AS received a separate grant from the Health Foundation for a rapid insight program from 2020 to 2021. Wessex Academic Health Science Network is funded by National Health Service England, National Health Service Improvement, and the Office for Life Sciences to support innovators under the contract. Some innovations include self-management applications for other conditions.

Multimedia Appendix 1
Specification for quantitative activity information and source of data (services). Column 2 relates each outcome to a research question.
[DOC File , 64 KB - resprot_v11i4e27207_app1.doc]

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Abbreviations

AHSN: Academic Health Science Network
CHOICE: cochlear implant home care
CI-EMP: Cochlear Implant Empowerment Scale
DCE: discrete choice experiment
EAG: evaluation advisory group
EQ-5D-5L: EuroQoL 5-Dimension 5-Level
HUI3: Health Utilities Index Mark 3
NASSS: nonadoption, abandonment, scale-up, spread, and sustainability
NHS: National Health Service
PAM: Patient Activation Measure
PM: project manager
SG: steering group
UK: United Kingdom

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An E–Mental Health Solution to Prevent and Manage Posttraumatic Stress Injuries Among First Responders in Alberta: Protocol for the Implementation and Evaluation of Text Messaging Services (Text4PTSI and Text4Wellbeing)

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Abstract

Background: First responders are confronted with traumatic events in their work that has a substantial toll on their psychological health and may contribute to or result in posttraumatic stress injuries (PTSIs) for many responders. Persons with a PTSI usually seek management therapies. Evidence indicates that digital delivery of these therapies is an innovative, efficient, and effective way to improve PTSI symptoms as an adjunct to in-person delivery.

Objective: This project aims to implement and provide accessible, convenient, and economical SMS text messaging services, known as Text4PTSI and Text4Wellbeing, to first responders in Alberta, Canada; to prevent and improve the symptoms of PTSI among first responders; and to improve their overall quality of life. We will evaluate posttraumatic symptoms and the impact of Text4PTSI and Text4Wellbeing on stress, anxiety, and depression in relation to the correspondents' demographic backgrounds.

Methods: First responders who subscribe to Text4PTSI or Text4Wellbeing receive daily supportive and psychoeducational SMS text messages for 6 months. The SMS text messages are preprogrammed into an online software program that delivers messages to subscribers. Baseline and follow-up data are collected through online questionnaires using validated scales at

enrollment, 6 weeks, 12 weeks, and 24 weeks (end point). In-depth interviews will be conducted to assess satisfaction with the text-based intervention.

Results: We hypothesize that participants who enroll in this program will have improved PTSI symptoms; increased or improved quality of life; and significant reduction in associated stress, depression, and anxiety symptoms, among other psychological concerns. Improvement will be determined in comparison to established baseline parameters.

Conclusions: This research will be beneficial for practitioners and will inform policy-making and decision-making regarding psychological interventions for PTSI. Lessons from this study will inform the scale-up of the intervention, a cost-effective, zero contact therapeutic option to manage PTSI.

International Registered Report Identifier (IRRID): PRR1-10.2196/30680

Introduction

Background

First responders are personnel with specialized training to render care to patients who experience traumatic events (eg, acute illness, accidents, natural disasters, and terrorism) as the first point of contact. These personnel typically include firefighters, police officers, paramedics, corrections officers, and emergency health care workers, who often attend to persons in critical situations or conditions [1-3].

Posttraumatic stress injury (PTSI) is a mental health condition that first responders may experience at some point in their careers [2]. Some potentially traumatic events include motor vehicle accidents, fires, sexual assault, floods, and situations involving unexpected death, among others. These events can bring about injury and stress-related traumas that influence emotional well-being and prosperity [4]. Most first responders report experiencing multiple traumatic events in their lives [2,4,5]. Approximately 6.8% of people develop PTSI over their lifetime [6]. PTSI symptoms may affect the general well-being of the individuals; alter mood; and contribute to insomnia, irritability, and traumatic flashbacks [2].

PTSI is closely related to posttraumatic stress disorder (PTSD). Both share similar symptoms and are sometimes used interchangeably across the literature. Differences are subject to debate among various schools of thought. Whereas PTSD refers to a psychiatric disorder, PTSI, as defined by the Global PTSI Foundation, refers to biological injury associated with physical changes in the nervous system [7]. Psychiatrists and military officers have suggested that relinquishing the word "disorder" in favor of "injury" will minimize the stigma that prevents troops from seeking treatment. Thus, changing the name from PTSD to PTSI would change people's perception of the condition [8].

PTSI rates are high among first responders ranging from one-third to more than half of those exposed to potentially traumatic events [9]. Globally, it is estimated that 10% to 35% of first responders experience psychological conditions, including PTSI [3,10]. A meta-analysis examining mental disorders among ambulance personnel estimated prevalence rates of 11% for PTSD, 15% for depression, 15% for anxiety, and 27% for general psychological distress [11,12]. Another

study revealed that 80% of rescue, firefighter, medical, and police personnel who cared for victims of an apartment building explosion reported at least a symptom of PTSD [13]. Surprisingly, the prevalence rate of PTSD in these groups were found to widely range from 0% to 46% [14,15]. First responders experiencing PTSI may decrease productivity, increase risk of suicide, and show poor social interaction [16].

The most common co-occurring diagnosis with PTSI is depression, with about 36% to 55% of patients with PTSI experiencing concurrent depression [4,17]. A study conducted among first responders showed an increased risk of PTSI of 25.6% and 16.7% at 7 and 13 months, respectively, with a depression rate of 16%, after exposure to a traumatic event [18]. A proportion of first responders who are exposed to traumatic events seek psychological support or treatment [6,19]. There is no doubt that PTSI is a substantial mental health concern, especially among first responders, and contributes to a substantial overall cost for mental health. It is estimated that there are 69,000 police personnel; 110,000 firefighters; 30,000 paramedics; 17,000 correctional services personnel; over 7000 border services personnel; and 18,000 volunteer search and rescue personnel who serve as first responders in Canada [18]. About 2.5 million Canadian adults and 70,000 first responders have experienced PTSI in their lifetimes [9].

Psychological treatment to address PTSI may be unavailable due to access considerations such as location or lengthy waitlist, among others [1]. This informs the need for a service that will improve access and prevent and manage PTSI digitally. Narrative synthesis indicates that the digital delivery of these therapies might be as powerful as in-person delivery [20,21]. Additionally, these means may also lessen stigma and price while providing a remedy [22,23]. Evidence has shown that about one-third of persons with PTSI never recover due to inadequate and high-cost care; hence, cost-effective management is required [22]. Because of PTSI and its impact on first responders and their families, governments and other policy-making bodies, including the Canadian Workers' Compensation Boards, initiated a guide for the rehabilitation of PTSI with a structured legislature to accept PTSI claims [23-25].

Mobile/smartphone technology can support and improve patient outcomes in psychological care [26,27]. An acceptable way to

provide psychological interventions to the public and to those with mental health conditions is supportive SMS text messaging. Considering it is comparatively affordable, available, and efficient, text-based messaging can be delivered to many users at the same time, which may reduce the mental health treatment gap [26]. Mobile/smartphone messaging can prevent and manage health conditions and provide individuals with supportive and customized messages pertaining to their unique health conditions [26,28,29]. Supportive SMS text messaging can reduce hospitalizations and improve health behavior [30,31]. Research has demonstrated that, overall, an individual's mental health improves upon receiving supportive SMS text messages [32-34]. Early provision of psychoeducation is effective in the prevention and management of PTSI [35]. About 80% of subscribers reported high satisfaction with the service and improved mental health status in studies conducted in Alberta [36]. A global survey conducted in 2015 revealed the median of access to the internet, with 87% having access to the internet and 68% of people own a smartphone. Among western countries, Canada is in a high-use group, with 90% of Canadians using the internet and 67% owning a smartphone [37]. These messages will effectively support patients who are attending individual or group treatment at Alberta Mental Health Centres.

Adjunct supportive text message therapy for psychological conditions has been tested on mood disorders among other psychological conditions [26]. However, to our knowledge, this innovation has not yet been conducted with PTSI and with first responders specifically. To address this gap, we propose an innovative program for first responders that seek to prevent and manage PTSI among this cohort with an evidence-based supportive SMS text messaging program developed using the concept of cognitive behavioral therapy.

Objectives

This project will implement a structured daily SMS text messaging service known as Text4PTSI and Text4Wellbeing, which aims to prevent and reduce the occurrence of PTSI and to manage PTSI symptoms among first responders. We will evaluate posttraumatic symptoms; correspondent's demography; and Text4PTSI's and Text4Wellbeing's impact on stress, anxiety, and depression.

We propose the following research questions:

- Will Text4PTSI and Text4Wellbeing prevent/improve the symptoms of PTSI among Alberta's First Responders (eg, firefighters, police officers, paramedics, sheriffs, corrections officers, and emergency health care workers)?
- Will Text4PTSI and Text4Wellbeing improve the quality of life in the community of first responders experiencing PTSI symptoms by reducing symptom burden?
- How satisfied are subscribers with Text4PTSI and Text4Wellbeing programs (technical care, access, and utility)?

Methods

Study Design

The mixed methods study design will engage both quantitative and qualitative approaches [38]. Both approaches will be used independently as well as together and triangulated using the theoretical framework.

Theoretical Framework

Outcomes have been defined as the change in health status directly attributable to the efforts or success of the health care experience [39-41]. Thus, successful treatment is associated with the efficacy of the provided care [42-45]. However, this study, as with many mental health impact evaluations, is subjective [46], given that it applies self-reported assessments by the participants. However, as suggested by the desire-fulfillment theory, outcomes possess a predominately positive association with satisfaction [47,48]. This is because the underlying rationale for seeking care is often to alleviate some form of functional impairment [49]. Comparing evidence on the difference (and similarities) between the need for health as perceived by the patient and the need for health care (as defined by the physician through scientific means) provides an opportunity for research. Consequently, this study will contribute to closing this gap by triangulating evidence from standardized psychological evaluation with evidence of patient satisfaction. Batbaatar and colleagues [50] identified nine determinants of variations in satisfaction with health care services: technical care, interpersonal care, physical environment, access (accessibility, availability, and finances), organizational characteristics, continuity of care, and outcome of care (Table 1). Our study will be guided by this framework and adapted for our e–mental health intervention (Table 2).

Table 1. Theoretical framework guided by Batbaatar et al's [50] determinants of patients' satisfaction.

Determinants	Batbaatar et al's [50] definition	Text4PTSI/Text4Wellbeing adaptation
Technical care	The extent to which the services adhere to standards and norms of clinical diagnoses and treatments	Perception of the extent to which the services adhere to standards and norms of clinical diagnoses and treatments
Interpersonal care	The amount of caring for patients through noticing, participating, sharing, active listening, companioning, complimenting, comforting, hoping, forgiving, and accepting.	Not directly applicable
Physical environment	Pleasantness of the atmosphere, room comfort, bedding, cleanliness, noise level, temperature convenience, lighting convenience, food service, bathroom comfort, clarity of sign and directions, arrangement of equipment and facilities, and parking.	Not directly applicable
Access	Health service access is a multidimensional determinant measured by how (1) organizational issues (accessibility), (2) service resources (availability), and (3) personal barriers (affordability) prevent populations from access to health services.	(1) Ease of use of technology (text messaging services) and (2) personal barriers
Organizational characteristics	Reputation and image of the hospitals	Not directly applicable
Continuity of care	Uninterruptedness of health service process from the same hospital, location, or provider and in which the patient and the physician are cooperatively involved in ongoing health care management toward the goal of high quality, cost-effective medical care	(1) Continued use of intervention throughout the study period and (2) perceived complementary nature or linkage of Text4PTSI and Text4Wellbeing with participants existing mental health care
Outcome of care	Patients' perceived health improvement	Patients' perceived mental health improvement

Table 2. Gantt chart for Text4PTSI and Text4Wellbeing text message project.

Milestone accomplishment	Timelines (months)						
	1-2	3-4	5-6	7-8	9-10	11-12	13-15
Ethics approvals: an amendment of existing ethics approval for the Text4Support and Text4Hope programs to cover the Text4PTSI and Text4Wellbeing programs	✓[a]						
Preimplementation stakeholder engagement: stakeholder participation in content development and program advertisement	✓						
Technology/content development: Text4PTSI and Text4Wellbeing technologies and content development	✓						
Launch of Text4PTSI and Text4Wellbeing programs: Text4PTSI and Text4Wellbeing in operational use for first respondents to self-subscribe	✓	✓	✓	✓	✓		
Program evaluation: conducting quantitative and qualitative evaluation		✓	✓	✓	✓	✓	
Preliminary report: availability of preliminary program evaluation report				✓			
Postimplementation knowledge transfer activities: stakeholder engagement on preliminary findings and dissemination of early results						✓	
Final report development: developing final report and disseminated						✓	✓

[a]The checkmark indicates that this milestone will be accomplished at this time point.

Inclusion Criteria

First responders who are 18 years or older who can provide informed consent will be eligible for the study. The Text4PTSI and Text4Wellbeing programs will be promoted to all first responders, including those who are healthy and may be seeking prophylactic psychological support to avert the onset of PTSI symptoms, those who might be experiencing PTSI symptoms but have not sought face-to-face psychological care, and those who are already accessing psychological care. First responders will also need to possess a mobile phone with an active line and have access to SMS text messages.

Exclusion Criteria

First responders will be ineligible if they do not meet the aforementioned inclusion criteria or reside outside of regular cell phone connection areas.

Recruitment

The first responders in Alberta (eg, firefighters, police officers, paramedics, corrections officers, and emergency health care

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workers) who regularly encounter difficult, risky, and traumatic events, and are willing to consent to the program will be targeted for recruitment. We will work with all first responder organizations to reach out to all first responders with information about the program. In addition, Text4PTSI and Text4Wellbeing would be the subject of a wide-exposure communications campaign (TV, radio, internet, and print media). First responders at risk of PTSI and those experiencing PTSI symptoms and on a waitlist to obtain care through the Alberta Health Services centralized Addiction and Mental Health intake service and the Operational Stress Injury Clinic with extra passageways such as private psychologists and counsellors will be included as the project evolves.

The Text4PTSI and Text4Wellbeing Interventions

First responders will participate in the Text4PTSI and Text4Wellbeing programs by simply texting "PTSI" and "Wellbeing," respectively, to a designated phone number. Text4PTSI and Text4Wellbeing will offer quick support to first responders encountering PTSI symptoms, including individuals who are on a waitlist for services or may experience issues getting to support because of geographic boundaries or other access considerations. Beginning on the first day of enrollment, first responders will receive daily unidirectional computer-programmed supportive SMS text messages, which will be specifically designed to alleviate PTSI symptoms. The messages will be written by cognitive behavior therapists and psychologists who have experience in treating PTSI in partnership with a cross section of first responders receiving treatment at the Operational Stress Injury and Addiction and Mental Health clinics in Edmonton and Calgary. The messages will be preprogrammed into a software program that will deliver the messages to subscribers automatically. The content of the SMS text message will focus on two dimensions. The first dimension includes general content that is indicated regardless of symptom presented, including messages of self-care, social support, hope, affirmation, and recovery. In the second dimension, specific content will be provided that focuses on the management of PTSI-related symptoms and conditions, including PTSD, generalized anxiety disorder, panic disorder, major depressive disorder, and suicidal ideation (eg, activity scheduling in depression). The ultimate goal will be to have SMS text message content customized based on end user characteristics. To this end, over time, we will appraise the individual needs of participants based on occupational category, age group, cultural identity, sex, gender identity and gender expression, sexual orientation, ethnicity, culture, religious perspective, income, and non-English language communication. This will be in accordance with the user identified needs and may enhance access for numerous groups, many of whom may be marginalized or underserved. For the program under study, the SMS text messages will target specific PTSI risk factors and symptoms with consideration for occupational and sociocultural context. An example [51] is:

Letting go of resentment is a gift you give yourself, and it will ease your journey immeasurably. Make peace with everyone, and happiness will be yours. Trauma can feel like a gloomy cloud over all areas of your life. The first step in treatment is to understand what trauma is, the symptoms, and how and why it is treated.

Sample Size Considerations

With Alberta's first responder population of about 33,000 [52], a 95% CI, and a 3% margin of error, the sample size needed for prevalence estimates for likely PTSI will be 1034. Based on baseline survey response rates of 20% achieved with both Text4Mood and Text4Hope programs [26,53,54], to achieve our sample size target, we plan to enroll 5170 first responders in the Text4PTSI and Text4Wellbeing programs.

Data Collection

At the beginning of the first message, respondents will be introduced to the program by completing an online mental health assessment, which will be repeated at 6 weeks, 3 months, and upon completion of the program at 6 months. A similar approach was successfully used to collect cross-sectional and longitudinal data from thousands of Text4Hope subscribers during the COVID-19 pandemic [53-65]. In-depth interviews on participant satisfaction with Text4PTSI and Text4Wellbeing will be conducted involving a cross-section of 10 to 15 participants selected randomly using an interview guide informed by the theoretical framework.

Outcome Measures

Key outcomes of interest in this study include change in scores measured by comparing pre- vs posttreatment responses to the following surveys: PTSD Checklist 5 [66], Generalized Anxiety Disorder-7 scale [67], Perceived Stress Scale [68], and the Patient Health Questionnaire-9 [69]. Secondary outcomes will include quality of life, as measured with the Well-being Index [70], and program satisfaction measured with the Text4PTSI and Text4Wellbeing exit questionnaire.

A patient satisfaction questionnaire will be programmed to measure the applicability of the technology as a valuable modality for delivering psychological therapies to large numbers of first responders experiencing PTSI symptoms. It is also designed to assess the benefits of the program to service users. A patient satisfaction questionnaire previously used to evaluate the Text4Mood program and Text4Hope program [26,55] will be adapted to evaluate the Text4PTSI and Text4Wellbeing Programs. As part of the sociodemographic variables, the satisfaction questionnaire will address multiple measures of satisfaction, including subscriber-reported effects of the program on symptoms and quality of life, and the usability of the technology. Table 3 illustrates an overview of the Text4PTSI and Text4Wellbeing outcome measures.

Table 3. Overview of the Text4PTSI and Text4Wellbeing outcome measures.

Outcome	Instrument	Time	Data source
Effectiveness			
Quality of life	5-Item World Health Organization Well-being Index	These measures will be assessed at baseline, 6 weeks, 3 months, 6 months, and 12 months	Clinical questionnaire
Depression symptom score	Patient Health Questionnaire-9	These measures will be assessed at baseline, 6 weeks, 3 months, 6 months, and 12 months	Clinical questionnaire
Anxiety symptom scores	Generalized Anxiety Disorder-7	These measures will be assessed at baseline, 6 weeks, 3 months, 6 months, and 12 months	Clinical questionnaire
Participants perceived stress	Perceived Stress scale	These measures will be assessed at baseline, 6 weeks, 3 months, 6 months, and 12 months	Clinical questionnaire
PTSD[a] symptom score	PTSD Checklist	Assessed at baseline, 6 weeks, 3 months, 6 months, and 12 months	Clinical questionnaire
Client satisfaction/experience surveys	Instrument developed and pilot tested, and published by the authors	Assessed at 6 weeks, 3 months, 6 months, and 12 months	Survey questionnaire
Implementation			
Reach	The proportion of first responders who receive the daily supportive text message	Assessed at baseline, 6 weeks, 3 months, 6 months, and 12 months	Survey questionnaire
Acceptability	Instrument developed and pilot tested, and published by the authors	Assessed at 6 weeks, 3 months, 6 months, and 12 months	Survey questionnaire
Fidelity	Part of first responders who read the supportive text messages at least once a day/percentage of scheduled follow up	Assessed at 6 weeks, 3 months, 6 months, and 12 months	Survey questionnaire
Cost	Administrative data	Assessed at baseline and 12 months	N/A[b]

[a]PTSD: posttraumatic stress disorder.

[b]N/A: not applicable.

Data Analysis

A quantitative evaluation will be used with a descriptive and inferential analytical approach. The analysis will demonstrate the distribution of likely PTSI with respect to sociodemographic characteristics of participants, as well as identify determinants of likely PTSI symptoms and outcomes across various predictor variables. Using subscriber data from the overall study, an additional benefit will be the application of machine learning to develop an artificial intelligence approach to predict characteristics and risk factors of first responders who commonly experience PTSI symptoms. This would allow us to generate predictive tools to differentially support first responders at risk of PTSI. This activity will be achieved through collaboration with the computational psychiatry group. This approach is well within the expertise of the computational psychiatry group members and in line with PTSI/PTSD trauma-related care [71,72].

Qualitative data will be analyzed to explore respondents' preferences, satisfaction, and other characteristics that will help improve outcome, program design, preventive strategies, and workplace and government policies as they relate to PTSI. Qualitative data analysis will involve inductive and deductive thematic analytic approaches using the study's theoretical framework. Qualitative descriptive methodology is an appropriate approach for qualitative research geared toward generating information to refine interventions in everyday terms [73]. In accordance with qualitative descriptive methods [73], qualitative content analysis will be conducted to summarize the content of the data [74].

What is also unique about this study is the demographic data collected from users. Collecting this information will also allow us to engage in comparative analysis, which may reveal new patterns or trends in the mental health of first responders based upon how they identify. This will allow the research team to

further customize text-based supportive messages based on characteristics including age, gender, race, sexual orientation, etc.

Ethical Considerations

The study received ethics approval from the Health Research Ethics Board (HREB) of the University of Alberta (Pro00108966). Informed consent will be obtained from all participants. Confidentiality and data security measures will be adhered to as approved by the HREB.

Results

We hypothesize that participants who will enroll in this program will have improved quality of life; reduced PTSI symptoms; and significantly improved associated moderate/high stress, depression, and anxiety symptoms, among others. Improvement will be in comparison to the baseline parameters.

Discussion

The nature of first responders' work impacts their health, daily activities, and psychological safety and well-being. The psychological impact on this cohort requires innovative, technologically driven psychological supports that have no waitlists, are geographic location independent, and can serve first responders at risk and those experiencing PTSI symptoms, while respecting confidentiality and reducing stigma. This approach will mitigate the potential adverse effects of first responders accessing psychological care. If Text4PTSI and Text4Wellbeing are effective for first responders in Alberta, we will explore opportunities for a national scale-up and global dissemination through engagements with first responder organizations as well as regional and national governments. This would be achieved through a Canadian federally registered not-for-profit organization, the Global Psychological eHealth Foundation [75] working in partnership with the research team. A similar program (Text4Mood) implemented in Alberta demonstrated an improved psychological treatment gap [26]: 77% of the participants felt capable of managing depression and anxiety, while 83% had improved overall mental well-being. Likewise, the Text4Hope program launched in Alberta during the COVID-19 pandemic reduced mental health distress by about 20% in subscribers [51]. It is expected that Text4PTSI and Text4Wellbeing supportive SMS text messages that seek to address access gaps to psychological care for first responders in Alberta and those experiencing or at risk of experiencing

PTSI symptoms will achieve results comparable to the Text4Mood and Text4Hope programs.

Text4PTSI and Text4Wellbeing supportive SMS text messages seek to address access gaps to psychological care for first responders in Alberta and those experiencing PTSI symptoms. The proposed mobile technology intervention is a potentially effective, economical, and accessible way of providing an intervention to first responders. Previous studies have proven positive outcomes with high satisfaction with the delivery of supportive messages [26]. Thus, Text4PTSI and Text4Wellbeing could alleviate onerous challenges of access to care for first responders, considering individual location, unique demographic considerations, financial constraints, stigma, and position on the waitlist for those already being managed for PTSI [76]. This project will provide support to the first responders irrespective of geographical location or identity.

This project will assess outcomes with standard validated questionnaires and provide essential statistics regarding the prevalence of PTSI among first responders in Alberta. Thus, information from this project will be beneficial for practitioners and important for policy- and decision-making regarding psychological interventions for PTSI in the target population.

The project will promote partnerships and networks among mental health stakeholders to improve knowledge and understanding of the social issues and challenges faced by first responders. The research and evaluation aspect of the project may scale up effective approaches to identify and respond to existing and emerging social issues that first responders and their families confront.

A potential limitation of the study design is that there may be selection bias since phone service coverage may be unstable in some rural remote locations in Alberta, which may skew the findings toward a more urban population. Another limitation is that the prevalence of anxiety, depression, and PTSI to be reported in this study is based on standardized self-rated scales rather than clinical interviews using the Diagnostic and Statistical Manual for Mental Disorders (Fifth Edition). These limitations notwithstanding, this study will provide valuable data about the prevalence of anxiety, depression, and PTSI symptoms in first responders and their correlates, as well as the impact of Text4PTSI and Text4Wellbeing on anxiety, depression, and PTSI symptoms in first responders. Similar to results achieved with earlier supportive SMS text messaging programs, we expect Text4PTSI and Text4Wellbeing programs to improve the mental well-being among first responders.

Authors' Contributions

VIOA conceived and designed the study. VIOA, GOD, and EE wrote the initial draft of the manuscript. VIOA, GOD, EE, JB, NP, SE, JH, YZ, FM, SC, RG, CJ, SBP, BC, KW, XML, CH, and AG made substantial contributions to the planning and design of the study, and contributed to the revision of the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

HREB: Health Research Ethics Board
PTSI: posttraumatic stress injury
PTSD: posttraumatic stress disorder

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Protocol

The Clinical Outcomes of Operative Treatment Versus Conservative Treatment for Dancer's Fractures: Protocol for a Retrospective Cohort Study

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Abstract

Background: Fifth metatarsal fractures are one of the most common foot fractures, and 11% to 25% of such fractures are Dancer's fractures (distal spiral fractures). Conservative therapy while wearing a cast and operative treatment have been used as preferred modes of treatment in the limited literature available. However, we often see healing problems, such as delayed union and nonunion, when Dancer's fractures are treated nonoperatively, resulting in a need for secondary intervention. In our institution, treatment has changed over the years from predominantly conservative treatment to mostly operative treatment. To investigate whether our hypothesis holds true that primary surgical treatment is beneficial, a retrospective study was designed.

Objective: The objective of the study is to compare differences between outcomes (delayed union and nonunion) of conservative and operative treatments for Dancer's fractures.

Methods: A retrospective comparative cohort study will be conducted in a level II trauma center (Zaandam Medical Center). Patients who experienced a Dancer's fracture in the period of 2012 to 2021 will be included and divided into 2 cohorts—the conservative (2012-2015) and operative (2016-2021) treatment cohorts. The primary outcome will be the differences in percentages of delayed union and nonunion between the two groups. The secondary outcomes will be the percentage of primary conservative treatment failure, the need for secondary operative treatment, complications (infection and hardware failure), and functional outcomes. If 118 patients are included in each group, sufficient power is expected to be reached, depending on the age distribution of patients. The percentages of delayed union and nonunion among the two groups will be calculated and statistically compared via chi-square statistics. A logistic regression analysis will be used to investigate possible associations between patient characteristics and failed conservative treatment. A Mann-Whitney *U* test will be used to compare functional outcomes between groups. An independent, 2-tailed *t* test will be used to compare mean 12-Item Short Form Survey scores if they are normally distributed, and a Wilcoxon rank sum test will be used if they are nonnormally distributed.

Results: In total, 2134 potentially relevant health insurance codes have been extracted from the hospital's register. We expect to find a total of 236 Dancer's fractures in this data set.

Conclusions: Our study has limitations due to it being a single-center study and data collection being performed retrospectively. However, it covers a large time period and may provide the possibility to show treatment outcome differences (delayed union and nonunion, complications, and functional outcomes) in 2 reasonably large cohorts (conservative and operative treatment cohorts), which has not been done before in literature on Dancer's fractures. If our hypothesis that surgery is beneficial for Dancer's fractures is proven true by our study, we plan to further corroborate it by conducting a prospective randomized controlled trial.

International Registered Report Identifier (IRRID): PRR1-10.2196/37171

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Introduction

Fifth metatarsal fractures are one of the most common foot fractures [1,2]. There is no unified classification system; however, the Lawrence and Botte classification is recommended [3]. The fifth metatarsal bone is divided into 3 anatomical zones where fractures can occur. Zone 1 is the tuberosity; zone 2 is the metaphyseal-diaphyseal junction, which extends into the fourth-fifth intermetatarsal facet and is also known as the *Jones fracture*; and zone 3 consists of the proximal diaphyseal fractures, which are located within 1.5 cm of the tuberosity [4]. Another type of fracture is the so-called *Dancer's fracture*—a long spiral fracture that extends into the distal metaphyseal area [4]. Dancer's fractures are diagnosed in 11% to 25% of fifth metatarsal fractures [1,5,6] and 5% of metatarsal fractures overall [7]. The optimal treatment for this fracture type is still under debate, and most of the available related literature only consists of small retrospective studies or case series.

Studies have shown different outcomes of treatments. Some have used conservative therapy with or without weight-bearing immobilization for 6 to 8 weeks and achieved excellent results [6-10]. Others have used surgical therapy with plates and screws, which resulted in excellent outcomes [11,12] that were comparable to those of the same therapy for shaft fractures of other metatarsal bones [13]. Patient characteristics such as age and osteoporosis [5,14], as well as fracture characteristics such as the angulation of the fracture and comminution of the fragments, are important factors in the choice of treatment [15]. Dancer's fractures are usually angulated and short [11]. It has been shown previously that dislocation is associated with functional impairment in patients with metatarsal fractures [2]. Therefore, malunion, delayed union, or nonunion is expected if Dancer's fractures are treated nonoperatively. Due to advancing insights, from 2016 onward, the preferred treatment in our hospital changed from predominantly conservative treatment to mostly operative treatment. Our hypothesis is that Dancer's fractures often result in healing problems, such as delayed union and nonunion, when treated nonoperatively.

The aim of our study is to compare outcomes of primary operative treatment for Dancer's fractures to those of conservative treatment. It is hypothesized that primary operative treatment can be beneficial when it comes to reducing delayed union and nonunion rates.

Methods

Study Objectives

The primary objective is to provide an overview of all Dancer's fractures, the applied initial treatments, and final outcomes—delayed union and nonunion rates and complications. The secondary objective is to determine how many fractures needed surgery after they were initially treated conservatively. The third objective is to identify associations between patient characteristics and failed initial conservative treatment. Finally, we will measure functional outcomes in both patient groups.

Study Design and Setting

Our study will be a retrospective cohort study. The researchers will be provided with records and diagnostic health insurance codes by the hospital's medical administration. These codes represent patients with foot injuries (codes 237 and 238 for metatarsal and tarsal fractures, respectively) over the past 10 years in a single, regional, level II trauma center—the Zaandam Medical Center, Zaandam. These cases will be retrospectively analyzed to select oblique diaphyseal fractures of the fifth metatarsal bone, which are known as *Dancer's fractures*. Since 2016, in our hospital, the preferred treatment changed from predominantly conservative treatment to mostly operative treatment. Therefore, the comparison of 2 historic cohorts will be made—the conservative treatment cohort (2012-2015) versus the operative treatment cohort (2016-2021).

Study Population

Patients aged ≥18 years who presented to the emergency department or outpatient clinic with a Dancer's fracture within 48 hours after trauma will be considered eligible for participation in our study.

Exclusion Criteria

Patients with multiple, simultaneous ipsilateral foot or ankle fractures; open fractures; known, pre-existing, significant impaired mobility; or any pretrauma, gross anatomical anomaly of the foot will be excluded from participation in our study.

Recruitment

A list of all foot fracture–related diagnostic health insurance codes in the Zaandam Medical Center dating from 2012 to 2021 will be provided by the hospital's medical administration. All corresponding radiographs of the foot will be reviewed by 2 trauma surgeons to identify Dancer's fractures. Patient characteristics such as age and sex, as well as fracture characteristics such as comminution, dislocation, the side of injury, and the occurrence of delayed union and nonunion, will be extracted from the electronic patient records manually by the researcher. Delayed union and nonunion are defined as absent or incomplete fracture healing after 3 and 6 months, respectively, and they will be assessed by reviewing the radiographs. The given treatments (cast vs surgery) and occurrence of complications (infection and hardware failure) will also be extracted from the electronic patient records manually by the researcher. The cohort will be divided into the following two groups: the conservative treatment cohort (2012-2015) and operative treatment cohort (2016-2021). Patients will receive a letter about providing informed consent. The letter will state that after they provide consent, a researcher will call them. Patients will be asked if they underwent secondary surgery in another hospital and be asked to provide data that are missing from the electronic patient files, such as the mechanism of injury and smoking status at the time of injury.

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Patients will also be asked to complete the 12-Item Short Form Survey (SF-12) questionnaire and to rate their functional outcomes by using 1 of the following 3 categories: (1) no more complaints or pain, (2) minor complaints or pain without an impact on daily living, and (3) significant complaints or pain with an impact on daily living [16].

If patients are lost to follow up, it will be assumed that they did not experience delayed union, nonunion, or other complications.

Outcomes

The primary outcome will be the delayed union and nonunion rates in the primary operative treatment group versus those in the conservative treatment group. The secondary outcomes will be the percentage of initial conservative treatment failure, which will be determined based on the percentage of patients who needed surgery after initially being treated conservatively; the number of patients who experience complications (infection and hardware failure); and associations between patient characteristics and failed initial conservative treatment. Functional outcomes—the complaints and impacts on daily living that are reported and experienced by patients—will also be secondary outcomes. These will be measured based on patients' responses to the SF-12 and 3 categories (no more complaints or pain, minor complaints or pain without an impact on daily living, and significant complaints or pain with an impact on daily living).

Sample Size

Based on the limited available literature, delayed union and nonunion have been found in 3% to 9% [7,8] of patients in the general population who were treated nonoperatively. For patients aged ≥40 years, the delayed union rate for nonsurgical treatment is 35% [5]. This rate ranges from 4% to 7% for patients who were treated operatively [11,12]. It is expected that 236 patients will be included in our study, with approximately 118 in each cohort. Based on a post hoc power analysis, a power of 34.3% can be achieved by recruiting patients from the general population, and a power of 100% can be achieved by recruiting patients aged ≥40 years. As the incidence rates of delayed union and nonunion are unreliable in the available (limited) literature, the post hoc power analysis showed large differences in power—a problem that is often encountered [17]. However, our cohort will be the largest cohort of patients with Dancer's fractures to date. Based on our clinical experience, we also believe that the incidence of delayed union and nonunion might be high in the nonoperative treatment cohort. The data collected in this study can be used to calculate the number of patients that need to be included in future prospective studies.

Statistical Analysis

Data will be processed and analyzed by using IBM SPSS Statistics version 25 (IBM Corporation). Descriptive data will be shown as numbers, percentages, or means with SDs when the data are normally distributed and as medians with IQRs when the data are nonnormally distributed. The percentages of delayed union and nonunion among the two groups will be calculated and statistically compared by using chi-square statistics. A multiple regression analysis will be used to investigate possible associations between patient characteristics

and failed conservative treatment. A Mann-Whitney U test will be used to compare functional outcomes between groups. An independent, 2-tailed t test will be used to compare mean SF-12 scores if they are normally distributed, and a Wilcoxon rank sum test will be used if they are nonnormally distributed.

Ethical Considerations

All collected data will be processed and filed anonymously on the hospital's secured servers. Data will be stored in separate files. One file will contain coded patient information, and a second file will contain all variables and diagnoses that are linked to these codes. The key to this code will be safeguarded by the head researcher. Patients will be asked via mail to provide informed consent prior to being contacted by telephone. The study is not subject to the Medical Research Involving Human Subjects Act (*Wet medisch-wetenschappelijk onderzoek met mensen* [WMO]). This Dutch act states that official medical ethics approval is not needed as long as patients are not subjected to invasive maneuvers, a specific code of conduct is used, and questionnaires do not contain sensitive questions (eg, those concerning mental health status) [18,19]. Confirmation of this status (*niet-WMO-verklaring*) will be obtained from the regional medical ethics committee.

Results

Approximately 2667 potentially relevant health insurance codes from a period of 10 years (2012-2021) will be extracted from the hospital's digital register. To date, 2134 codes have been extracted. We expect to find a total of 236 Dancer's fractures, of which approximately 50% (n=118) have been intentionally treated conservatively and 50% (n=118) have been primarily treated operatively. Based on our hypothesis and daily practice experience, it is expected that delayed union and nonunion rates will be higher in the conservative treatment group.

Discussion

Principal Results

We expect to find a total of 236 cases that are eligible for inclusion. Considering the type of injury and available literature, ours may be one of the largest cohorts for reviewing surgical treatment so far. It is hypothesized that the rates of delayed union and nonunion will be higher in the nonoperative treatment group. We may find that impacts on daily living are associated with more complaints and lower SF-12 scores and that a significant percentage of patients needed to undergo secondary surgery after conservative treatment. In concordance with previous literature, low postoperative infection rates and low rates of hardware failure are expected.

Comparison With Prior Work

Previous studies have looked at either nonoperative treatment [6-10] or operative treatment [11,12]. To our knowledge, no studies have compared operative treatment to nonoperative treatment before. We expect to find higher rates of delayed union and nonunion in older, female patients [5] and those who smoke, similar to previous findings in related literature. Patients

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with displaced fractures might benefit the most from surgical intervention, as suggested by Thompson et al [11].

Considering the knowledge gap in literature with regard to the optimal treatment of Dancer's fractures, it is important to first gain insight into our hypothesis before applying for grants for a costly randomized controlled trial.

Strengths and Limitations

Several limitations apply to our study. Since ours is a single-center study, included patients might not fully represent the general population when it comes to age, trauma mechanism, smoking status, and comorbidities. Although as much data as possible concerning baseline characteristics were retrieved, recollection bias could be an issue. Retrospective analyses do not allow for standardized follow-ups and the monitoring of outcome measures, such as fixed-term radiographs and final clinical recovery. However, we will be able to provide an overview of a large period of time to show possible differences in the outcomes of the two historic cohorts. Furthermore, as Dancer's fractures are relatively rare, it would take several years to include a sufficient number of cases prospectively. With the use of a retrospective design, it is possible to gain a first insight into the outcomes of patients with Dancer's fractures within a reasonable time frame.

Future Directions

If this retrospective study shows promising results, a multicenter randomized controlled trial will be designed. Due to the relatively low incidence of Dancer's fractures, a multicenter design is preferred. The information gathered in our investigation can be used for grant applications, future ethical approval, and patient selection.

Conclusions

If the study described in this protocol is performed, it will be the largest study on this topic so far and the first to compare nonoperative and operative treatments for Dancer's fractures. Our analysis will show if there are any associations among chosen treatments, delayed or absent fracture healing, and indications for secondary surgical intervention, as well as complications and functional outcomes. Our findings might be used as a basis for formulating a subsequent study protocol that intends to prove the superiority of either treatment modality prospectively and help guide decision-making for individual patients based on their characteristics.

Conflicts of Interest

None declared.

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Abbreviations

SF-12: 12-Item Short Form Survey
WMO: Wet medisch-wetenschappelijk onderzoek met mensen

<u>Protocol</u>

Children With Medical Complexity in the Canadian Maritimes: Protocol for a Mixed Methods Study

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Abstract

Background: Ongoing developments in the medical field have improved survival rates and long-term management of children with complex chronic health conditions. While the number of children with medical complexity is small, they use a significant amount of health resources across various health settings and sectors. Research to date exploring this pediatric population has relied primarily on quantitative or qualitative data alone, leaving significant gaps in our understanding of this population.

Objective: The objective of this research is to use health administrative and family-reported data to gain an in-depth understanding of patterns of health resource use and health care needs of children with medical complexity and their families in the Canadian Maritimes.

Methods: An explanatory sequential mixed methods design will be used to achieve our research objective. Phase 1 of this research will leverage the use of health administrative data to examine the prevalence and health service use of children with medical complexity. Phase 2 will use case study methods to collect multiple sources of family-reported data to generate a greater understanding of their experiences, health resource use, and health care needs. Two cases will be developed in each of the 3 provinces. Cases will be developed through semistructured interviews with families and their health care providers and health resource journaling. Findings will be triangulated from phase 1 and 2 using a joint display table to visually depict the convergence and divergence between the quantitative and qualitative findings. This triangulation will result in a comprehensive and in-depth understanding into the population of children with medical complexity.

Results: This study will be completed in May 2022. Findings from each phase of the research and integration of the two will be reported in full in 2022.

Conclusions: There is a current disconnect between the Canadian health care system and the needs of children with medical complexity and their families. By combining health administrative and family-reported data, this study will unveil critical information about children with medical complexity and their families to more efficiently and effectively meet their health care needs. Results from this research will be the first step in designing patient-oriented health policies and programs to improve the health care experiences, health system use, and health outcomes of children with medical complexity and their families.

International Registered Report Identifier (IRRID): DERR1-10.2196/33426

Introduction

Ongoing developments in the medical field have improved survival rates and management of children with complex chronic health conditions [1,2]. Frequently described as children with medical complexity, these children are often diagnosed with a wide array of pediatric conditions [3,4]. Recognizing the need for conceptual agreeance across clinical and research initiatives to distinguish this unique pediatric population, Cohen et al [3] presented a definitional framework for children with medical complexity. Rather than proposing a diagnosis-specific definition, this framework describes a noncategorical and inclusive approach to conceptualizing medical complexity in children. Cohen et al [3] identified 4 intersecting domains specific to children with medical complexity: (1) the presence of a diagnosed or suspected complex chronic condition, (2) significant family-identified needs, (3) functional limitations that are often severe and may require the use of technological assistance, and (4) high health resource use [3]. This definitional framework is now being used widely to describe this vulnerable and important pediatric group across policy, clinical, and research sectors [4,5].

Literature exploring pediatric complex care has been steadily increasing over the past two decades [1]. Evidence emerging over this time suggests that while children with medical complexity represent a small proportion of the overall pediatric population, they consume a disproportionate amount of health care resources [6,7]. Despite approximately 89% of these children being discharged home from inpatient settings [8], their resource-intensive needs are infrequently met by the current health care system, leaving a substantial burden on families to provide expert medical and supportive care and facilitate care coordination activities for their child. Furthermore, these families often report inadequate support, difficulty accessing services, and other unmet health care needs [9-14]. These findings highlight a clear disconnect between current health care services and the care needs of children with medical complexity and their families.

It is critical that we begin to develop and evaluate family-centered strategies tailored to the needs of this population. However, to achieve this, we must address major knowledge gaps within the literature. First, much of the empirical research has been conducted within the United States health care system [8,13-15], with only 2 main reports published in the last 10 years examining the prevalence and health service use of these children within the Canadian health care system [6,7]. While studies from the United States are informative, it is critical to gain greater regional and jurisdictional understanding of the prevalence, clinical characteristics, health resource use, and health care needs of this population within Canada. Second, the literature exploring this pediatric population primarily relies on routinely collected health administrative data [7,8,15,16]. While this data source has several strengths, such as having access to large population samples across various time frames, there are important limitations to the use of health data to consider. Families use a range of health resources not captured by health administrative data alone (ie, private respite care services, local community-run health programs, private physiotherapy, acupuncture, massage therapy, naturopathic doctors). This leads to a significant gap in our understanding of the true health resource use and care needs of children with medical complexity and their families. Qualitative research methods are designed to explore this gap whereby researchers speak directly to children and families about their lived experience. As such, combining health administrative data with richly descriptive qualitative reports from families is one strategy to fully explore their health resource use and care needs. Using a mixed methods approach could provide researchers, clinicians, families, and decision makers with a detailed and comprehensive understanding of prevalence, clinical characteristics, health resource use, and health care needs of children with medical complexity and their families. Without this information, decision makers may not have all the necessary information to create family-oriented recommendations to support the health of these children and their families.

There remains a significant gap in our understanding of the true extent of health resources used by children with medical complexity and their families living in their home communities. Greater efforts are needed to map health resource use across the public, private, and community sectors to provide the foundational knowledge needed to develop evidence-informed recommendations and strategic directions to support the health and needs of children with medical complexity and their families. As such, the objective of this research is to use health administrative and family-reported data to gain an in-depth understanding into patterns of health resource use and health care needs of children with medical complexity and their families in the Canadian Maritimes (Prince Edward Island [PEI], Nova Scotia [NS], and New Brunswick [NB]). To achieve this objective, the following research questions will be addressed: (1) What are the prevalence and clinical characteristics of children with medical complexity in the Canadian Maritimes? (2) What are the patterns of health care use as described by health administrative data for children with medical complexity? (3) What are the family-reported experiences, health resource use, and health care needs of children with medical complexity and their families? (4) In what ways do the family-reported experiences, care needs, and health resource use converge and diverge with the characteristics and health service use as reported by health administrative data among children with medical complexity and their families in the Canadian Maritime Provinces?

Methods

To achieve our research aim, an explanatory sequential mixed methods design (quantitative and qualitative) will be used [17].

Ethics Approval

Ethics approval has been obtained from the Izaac Walton Killam Health Centre research ethics board (#1026835 and #1024934).

Phase One

Design

To understand the prevalence and health service use of children with medical complexity, we will conduct a secondary analysis of routinely collected health administrative data. Access to these data will be obtained through the Health Data Nova Scotia Secure Data Repository Platform and the pediatric tertiary care facility's decision support services. To achieve this study objective, a 2-phase process will occur. First, discharge data from the Maritimes' only pediatric tertiary care facility will be used to identify and characterize children with medical complexity in the Maritimes. Next, the health card number of all NS residents identified within the cohort will be linked to the provincial's health administrative data sets to examine their health resource use.

Study Setting

The primary site of this research is the only pediatric tertiary care facility located in the Canadian Maritimes, providing a unique opportunity for multijurisdictional research given their mandate to care for children, youth, and families in all 3 provinces. This site was chosen for this research as children's hospitals have been identified as the main care site for children with complex chronic health conditions and can provide a representative sample of this population in the 3 provinces [8,18]. Based on the limitations in cross-provincial data linkages, health care resource use will only be explored in NS. NS data is the sole source of health resource use by children with medical complexity and will be relied upon to extrapolate use in the other Maritime Provinces (PEI and NB).

Data Sources

Five health care databases will be accessed in this study: the pediatric tertiary care facility's discharge data, MSI Physician Billings (MED), National Ambulatory Care Reporting System (NACRS), Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), Vital Statistics–Death (VITAL).

Study Population and Identification

All children and youth aged 0 to 18 years discharged from the pediatric tertiary care facility between April 1, 2004, and March 31, 2014, who meet the definitional framework of Cohen et al [3] for children with medical complexity will be included in the analysis. We know from previous published literature that children with medical complexity are small in number. As such, to ensure a cohort suitable to power a regression analysis, we will examine prevalence over a 10-year time period. This time frame also provides health resource data for up to 5 years (March 2019). The definitional framework of Cohen et al [3] will be operationalized through the application of the Pediatric Medical Complexity Algorithm (PMCA) 3.0 [19]. The PMCA is a validated algorithm to identify and classify the pediatric population based on level of medical complexity within health administrative data [19]. An individual child will only be

included once in the cohort. If a child was discharged more than once during the study period, the earliest discharge date with a complex chronic condition will be used as the index date to begin tracking health resource use. Our final cohort will be all children who are classified by the algorithm as children with complex chronic conditions. Health card numbers for the identified sample will be retrieved from the pediatric tertiary care facility's discharge database by a data analyst and sent to a health system partner organization for encryption to preserve confidentiality. These encrypted health card numbers are then sent directly to the provincial health data repository for linking with MED, NACRS, CIHI-DAD, and VITAL for all NS residents. At no point during this process will the research team have access to the unencrypted or encrypted health card numbers. A 3:1 matched control cohort will be identified by using age, sex, and postal code as matching variables. Matched cases will be used to provide a comparator population and control for potential confounders that may influence health resource use [20,21]. Once the cohort is identified, their health resource use will be followed up to a 5-year period or up to age 18 years.

Measures

Variables related to patient demographics will include age, sex, urban/rural residence, organ system involvement, and care team characteristics. Race and ethnicity data were not accessible, as they are not included as routinely collected variables in the health administrative data sets. Variables related to health care use will include inpatient hospital visits, outpatient hospital visits, home care services, emergency department visits, and transfers between care locations. This health data will encompass both tertiary and community care hospitals.

Data Analysis

To address our first research objective, the prevalence of children with medical complexity from 2004 to 2014 will be estimated using prevalence rate calculations. The estimated prevalence rate will be obtained by dividing the number of cases of children with medical complexity identified by the PMCA with the total number of children estimated in the Statistics Canada Census Data for Nova Scotia (2016). Prevalence will be further stratified based on age, sex (as assigned at birth), clinical diagnosis category (categorized by the PMCA [19]), and geographical location (urban/rural). Urban and rural residence will be determined by the first 3 digits of their postal code. Age will be analyzed categorically (0-11 months, 1-4 years, 5-9 years, 10-13 years, and 14-18 years). Descriptive statistics will be used to describe the characteristics of children with medical complexity (age, sex, clinical diagnosis category, and urban/rural location).

To address the second research objective, health resource use for both case and control cohorts will be explored using descriptive and inferential statistics. Descriptive statistics including mean (standard deviation), median (interquartile range), and count (percentage) will be used to describe the number of services received, types of medical specialties, and health resource use for children with medical complexity over a 5-year follow-up period. Health resources will be grouped by inpatient admissions, emergency department visits, length of

stay, location of care, outpatient services, home care use, and ambulance transfers. Rates of health resource use and length of stay will be further stratified by clinical diagnosis category, age, sex, urban/rural location, and level of health care facility (tertiary/community hospital).

To explore any associations between child characteristics and health system use, a negative binomial regression analysis will be run. The primary outcomes of interest will be counts of hospital readmission as defined by any type of inpatient admissions (ie, intensive care admissions), emergency department visits, and outpatient community services defined as primary care visits, home care services, and clinic services. Predictors of interest are age, geographical location, and sex. Last, to explore the hazard ratios for time to and between health resource use, a Prentice, Williams, and Peterson gap-time model will be used. This will illuminate patterns of health resource use within the identified cohort. All data analysis will be performed using the statistical software program Stata (version 9.3, StataCorp LLC).

Anticipated Outputs

There are 3 main outputs from this first phase. First, we will have a detailed description of the prevalence of children with medical complexity in 3 Canadian provinces. Second, we will have an understanding of the formal health service use of this vulnerable population. Third, results from this phase will inform participant recruitment and the development of a theoretically based [22] interview guide for use in phase 2 to capture family-identified health resource use and needs.

Phase Two

Design

A case study design will be used to examine the health resource use and health care needs of children with medical complexity and their families in each of the Maritime Provinces. While the definitional framework for children with medical complexity advances our characterization of this pediatric cohort, there remains little understanding regarding the key health outcomes and their measurability for this population [22]. Case study research is an approach to developing and generating a rich description of complex phenomena in the real-world context and can elicit the answer to how, what, and why questions [23]. For example, how children with medical complexity and their families use the health care system, what types of services are accessed, what gaps and areas for improvement exist, and why these patterns may be occurring. Each case will be informed by 3 sources of data: (1) interviews with families, (2) interviews with individual members of the care team in their home community, and (3) self-reported health resource use.

Study Population and Sampling

A purposive sampling strategy [24] will be used to recruit children aged 0 to 18 years matching the Cohen et al [3] definitional framework for medical complexity. We will purposively recruit children and families fitting specific characteristics (eg, demographics, clinical characteristics, level of complexity, health resource use) based on significant findings from phase 1. For example, this may include certain clinical

presentations or urban/rural residency that may prompt further examination. Families must be primary residents in one of the provinces of interest (NS, NB, or PEI); 2 cases from PEI, NB, and NS will be developed to capture the potentially varying experiences of children and families living inside and outside of the provincial boundaries of the pediatric tertiary care facility. Families within 1 to 3 months and one family within 2 to 3 years of their initial discharge from hospital will be recruited to explore the experiences of these children and their families at differing points in their care. Children and families must be able to speak the English or French language to be eligible to participate. We will not attempt to specifically recruit participants identified within the phase 1 data set. However, it is anticipated that potential participants in the qualitative phase will have been captured in the health administrative cohort.

The number of participants is not the focus in case study design; rather, it is about gathering multiple forms of data from various perspectives to develop a deeper understanding of a specific case. Two case studies will be developed for each Maritime Province (PEI, NS, and NB), resulting in a total of 6. This will allow for the examination of differing familial and contextual factors. One primary caregiver will self-identify as the primary contact for the study. If more than one caregiver would like to be interviewed, all caregivers will be interviewed at the same time. The primary caregiver will also be asked to identify a maximum of 2 key members of the care team who can be approached for an interview.

Multiple recruitment strategies will be used to reach our target population. Recruitment flyers will be posted to relevant units at the pediatric tertiary care facility, community pediatric care sites, and social media platforms. We will also circulate the recruitment poster and study summary via email to key stakeholders involved in care delivery for children with medical complexity and families to share with their networks. An email and phone number contact for the principal investigator will be on all recruitment materials. The principal investigator will respond to all inquiries related to study participation and will provide potential participants with additional study information and an eligibility screening checklist. Once eligibility is confirmed, the principal investigator will forward the consent form for their review. This consent form will be reviewed with participants prior to the interview and signed.

Measure

A semistructured interview guide for families will be developed based on significant findings from phase 1 and the 10 domains of health for children with medical complexity [22]. Barnert et al [22] provided the most comprehensive understanding of the conceptualization of population health for children with medical complexity and their families by creating a conceptual framework outlining 10 domains of health for children with medical complexity. These domains include (1) basic needs, (2) inclusive education, (3) child social integration, (4) child health-related quality of life, (5) long-term child self-sufficiency, (6) family social integration, (7) community system supports, (8) health care system supports, (9) high-quality patient-centered medical home, and (10) family-centered care [22]. This interview guide will also include prompts that are informed by

significant findings from phase 1. As case study research is designed to address how, what, and why questions, findings from phase 1 will be used to develop prompts and potential questions to create a more comprehensive understanding of observed and unobserved patterns of service use.

Before family interviews occur, the interview guide will be pilot tested through a think-out-loud session with a parent researcher who works at the tertiary care facility. Changes will be made as required following this pilot testing.

Procedure

All interviews will take place over the phone or using the Zoom video conferencing system. Family interviews are anticipated to last 45 to 60 minutes. Demographic and socioeconomic information will be collected on families at the beginning of the interview process. This will include number of individuals in the family unit, child's health conditions, type of medical device/technology, urban/suburban/rural community, child's gender (as identified by the child), participant's gender, child's age, participant's age, participant's race/ethnicity, employment status of the caregivers, and access to transportation services. Families will be asked to identify all of the individuals or specialty clinics involved in the care of their child. An additional data source for the development of the case studies will include asking families to track their health resource use over a 3-week period. This time frame was chosen through consultations with clinicians and researchers, and while we recognize that health resource use can vary greatly among individuals with complex chronic conditions, we did not want study procedures to place unnecessary burdens on families. Families will be provided a health resource journal with a draft template to follow. Within this diary, families will be encouraged to track encounters with services and supports needed to provide care for and support the health of their child. This includes but is not limited to ambulatory care clinic visits, inpatient stays, acupuncture, physiotherapy visits, home care visits, emergency department visits, respite care, and dental visits. Families will also be prompted to track the care coordination activities they undertake (ie, calling different clinics to arrange appointments on the same day). Additionally, we will ask study participants if they believe their 3-week time frame was representative of their average health resource use. A CAD $50 (US $40) gift certificate to either Superstore, Amazon, or Irving Gas will be provided to families in appreciation for their time.

Health care provider semistructured interviews will be composed of 3 to 4 questions developed based upon the respective family interview to reflect specifically on local context and the participating families. Interviews are anticipated to last 10 to 15 minutes over the phone or Zoom video conferencing system. This data will be used to supplement the family-reported experience, providing more context to the identified case. A CAD $10 (US $8) Tim Hortons gift card will be provided to participating care team members.

Data Analysis

All interviews will be transcribed verbatim and uploaded to NVivo (version 11, QSR International) qualitative data analysis software. Given the recognized need for theory-informed approaches to case study design [25], all interviews will be coded using a deductive content analysis approach based on the capability, opportunity, motivation–behavior (COM-B) theoretical mode [26]. The COM-B is a comprehensive framework created to explore the interactional factors that influence health behavior [26]. This will allow us to explore the use of health resources, why they might be the way they are, and what resources are required to meet the health care needs of families. Further, this analysis approach could be used in future studies aiming to map study findings to the behavior change wheel to design a knowledge translation intervention [26]. The COM-B will provide an initial theory-based coding scheme to deductively code qualitative findings. Two independent coders will code the 3 domains of capability, opportunity, and motivation. Following this, an inductive coding analysis approach will occur within each domain to group similar statements. This will reveal the presence of contradictory and common themes throughout the data while providing a theoretical foundation that can help better understand the phenomenon under investigation. Self-reported health resource data from the family health resource journaling will be examined using descriptive and frequency statistics (mean, median, range, count).

Interview and self-reported data for each case will undergo data triangulation to create a greater understanding of child and family experiences. All quantitative and qualitative data will be organized into a matrix table based on themes resulting from the interview and self-reported heath resource data to examine patterns of convergence and divergence within each case study [23,25]. Descriptive statistics will be used to describe the variables captured in the self-reported diaries. Each case will be analyzed separately to create an in-depth representation of their individual experiences. Member-checking will occur with the findings from each case by presenting the results back to the family to check that we captured their experiences accurately [24]. After data analysis is completed for each case study, a cross-case analysis will occur to examine common themes and patterns and areas of divergence among cases [23]. A matrix table will be created to display data from each individual case based on common and emergent themes [23]. This matrix will reveal patterns or uniqueness among cases [23].

Anticipated Outputs

There are 2 main outputs from this phase of the research. First, we will have a rich description of the first-hand experiences of children with medical complexity and their families, as well as their formal and informal health resource use. Second, we will use this family-reported data to compare it with findings from phase 1 to develop a greater and more comprehensive understanding of the health resource use and health care needs of children with medical complexity and their families.

Data Triangulation

The intent of data integration in an explanatory sequential design is to examine the extent to which the follow-up rich qualitative results connect or explain the initial quantitative data [17]. To do this, we will triangulate phase 1 and phase 2 data using a joint display table to visually depict the quantitative and qualitative phases. This joint display will be organized based

on a statistic-by-theme framework, linking relevant and related health administrative data with the follow-up case study findings [17]. Using this data triangulation approach, we will be able to create a greater understanding of the population, health resource use, and health care needs of children with medical complexity in the Canadian Maritime provinces.

Results

Phase 1 and phase 2 are in progress. Findings from each phase of research and the integration of the two will be reported in full in 2022.

Discussion

Principal Considerations

There is a current disconnect between the Canadian health care system services and the needs of children with medical complexity and their families [1]. By combining both health administrative and family-reported data, this study can unveil critical information about children with medical complexity and their families to health researchers, clinicians, policy makers, administrators, and families themselves. Mixed methods research has been underused in the current literature surrounding pediatric complex care, leaving gaps in our understanding of the responsiveness of our health care services caring for this vulnerable population. Current literature generally focuses on hospital-based health service use, such as emergency department encounters and inpatient admissions, with limited exploration into home and community-based resources [5,7,8]. This is of particular importance given the growing shift in care provision from hospital to community-based care for individuals living with medical complexity [1,8]. As such, this research study is designed to take a novel approach to the study of children with medical complexity and their health service use, contributing to the advancement of this body of research. We anticipate that this work will increase our understanding of the extent of health resources used and needed by children with medical complexity and their families to support their health and well-being while living in their home communities. While the development of an intervention is beyond the scope of this proposed research, the strong theoretical underpinning, methodology, and methods used will ensure its findings can be used in future work to advocate for and inform the design of health policy and programs in the Canadian Maritimes for this population of children and families. As such, this research has the potential to improve the health care delivery, experiences, and outcomes for children with medical complexity and their families.

Limitations

The findings from this research should be considered with the following limitations in mind. A limitation to secondary data analysis is that the researcher can only work with the data originally collected and stored. Hospital data are collected primarily for administrative purposes and are not specifically designed for research [20]. This can lead to incomplete or missing records and variability in diagnostic codes [20]. Further, although the inclusion criteria to identify the cohort of children with medical complexity has been used in previous studies [27-30], there are limitations to relying solely on diagnostic codes. The use of diagnostic codes may result in patients with medical complexity not being captured or capturing those who would not fit the definitional framework. Furthermore, we make the assumption that children with medical complexity will have received care at the pediatric tertiary care facility at least once during their initial or follow-up medical care. As such, our prevalence estimates may be slightly underrepresented given the possibility that some of these children may be seen and managed fully by their local/regional hospitals. We are also limited by the lack of sociodemographic variables, such as race and ethnicity, available in our health administrative data sets. We strongly believe, however, that these are critical intersectional factors in the lives of these families and require exploration in future work. Furthermore, not all community hospitals report to NACRS at the highest level, resulting in potentially incomplete reporting related to emergency department transfers. It is also important to note that due to constraints across provincial data linkage, we chose to use NS and their provincial health administrative databases as the exemplary province to explore health resource use for children with medical complexity. We recognize that health resource use as indicated by health administrative data may differ in PEI and NB.

Although purposive sampling will be used for phase 2 to explore results found during phase 1, participants' opinions or experiences may not be shared by other families or health care professionals. This study will also be limited to the experiences of children from one pediatric tertiary care center serving children and families in 3 small provinces in Eastern Canada that operates within a publicly funded health care system. Other health centers may differ in the structure, programs, and care provision for children with medical complexity; thus, results may not be reflective of other families and sites.

Conclusion

Improvements in medical treatments and technologies will likely result in an increased population of children with complex conditions. It is critical that we begin to develop a greater understanding of the health resource use of this vulnerable population to more efficiently and effectively meet their health care needs. Results from this research will be an important step forward in designing patient-oriented health policies and programs to improve the health care experiences, health system use, and health outcomes of children with medical complexity and their families.

Authors' Contributions

SB conceptualized and designed this study and wrote the initial draft of this protocol. This is SB's proposed doctoral dissertation and is being completed as a partial requirement for obtaining a doctorate degree in nursing at Dalhousie University. JAC is the primary supervisor of this work, helped conceptualize and design this study, and reviewed and revised this protocol for intellectual content. MM, WM, SAS, RMM, and JV are all members of SB's doctoral committee and have contributed to the conceptualization and design of this study and reviewed and revised this protocol for intellectual content.

Conflicts of Interest

None declared.

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Abbreviations

CIHI-DAD: Canadian Institute for Health Information Discharge Abstract Database
COM-B: capability, opportunity, motivation–behavior
MED: MSI Physician Billings
NACRS: National Ambulatory Care Reporting System
NB: New Brunswick
NS: Nova Scotia
PEI: Prince Edward Island
PMCA: Pediatric Medical Complexity Algorithm
VITAL: Vital Statistics–Death

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Protocol

Efficacy of a Digital Acceptance and Commitment Therapy Intervention for the Improvement of Self-management Behaviors and Psychological Flexibility in Adults With Cardiac Disease: Protocol for a Single Case Experimental Design

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Abstract

Background: Research indicates that the management of distress levels in those with cardiac disease is not only important for improving quality of life and functioning but also critical for condition management; adherence to treatment; and, ultimately, disease prognosis and progression. Acceptance and commitment therapy (ACT) has consistently demonstrated positive long-term outcomes across a wide array of conditions, including chronic illness. However, most empirical investigations conducted to date have also involved in-person therapy, which can be difficult to access, particularly for those dealing with the demands of chronic disease.

Objective: The objective of our research is to evaluate a digital ACT intervention for improving self-management behaviors and distress levels in those with cardiac conditions.

Methods: The digital ACT intervention will be delivered via a digital health self-management platform over 6 sessions. This will involve a randomized, multiple baseline, single case experimental design with approximately 3 to 15 adults with cardiac disease. The independent variable for each participant will be the pre-post intervention phase. The dependent variables will be a daily self-report measure of psychological flexibility as well as objective measures of condition self-management (eg, blood pressure readings) and engagement with the app (eg, completing guided mindfulness). One-to-one qualitative interviews will also be conducted to further examine participants' experiences with using the intervention and what factors contribute to or impede successful outcomes.

Results: Participant recruitment and data collection began in October 2021, and it is projected that the study findings will be available for dissemination by spring 2022.

Conclusions: The findings will be discussed in terms of how a digital ACT intervention can best meet the needs of cardiac patients.

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Introduction

Chronic illnesses typically result in a complex set of symptoms and demanding lifestyle adjustments, with upwards of 30% of individuals with 1 or more chronic health conditions also experiencing a clinically significant mental health concern [1]. Cardiac disease in particular is linked to high levels of depression and anxiety [2-4]. Even more concerning is that depression and anxiety are associated with poor treatment adherence, poor functionality, increased hospitalization rates, and increased mortality risk across studies [5-7].

To date, cognitive behavioral therapy (CBT) is the most widely tested psychotherapeutic approach for patients with chronic conditions in the psychology literature. Although CBT has been associated with improved mood and quality of life as well as decreased symptoms of depression and anxiety [8-10], positive psychological and mood outcomes have not been consistently observed in people with chronic health conditions [11]. Many therapeutic approaches, including CBT, strive to achieve emotional and behavioral change by attempting to change or suppress "faulty" thoughts. For those with chronic conditions, this is unlikely to be feasible, particularly because condition management requires participants to engage with and report on their symptoms in an honest manner, and attempts to suppress and avoid difficult thoughts and feelings regarding symptoms can be invalidating and disempowering and may lead to or increase the avoidance of self-management behaviors [12].

In order to meet the complex needs of those with cardiac disease and to develop more effective psychotherapeutic interventions for the improvement of mental well-being, adherence, and self-management behaviors in these populations, a transdiagnostic approach (ie, universally applicable treatment regardless of a condition or diagnosis) that reduces avoidance and results in lasting outcomes is needed. One such approach may be found under the remit of contextual behavioral science (CBS).

CBS is a psychological science that provides in-depth and theoretically coherent explanations of complex human behaviors [13,14]. The clinical application of CBS is known as *acceptance and commitment therapy* (ACT) [15], and its therapeutic aim is to foster a process known as *psychological flexibility*. Hayes et al [16] reported the following definition of psychological flexibility: "the ability to contact the present moment more fully as a conscious human being, and to change or persist in behavior when doing so serves valued ends." Distress reduction is not a goal in ACT; rather, it enables an individual to engage in a fully meaningful life despite the presence of distress by reducing ineffective behaviors and issues related to using thoughts and feelings as reasons for exhibiting or avoiding certain behaviors. ACT involves using a transdiagnostic approach, and over the last 30 years, empirical support has been observed for its use in managing a plethora of conditions, including but not limited to depression, anxiety disorder, stress, chronic illness, diabetes, addiction, chronic pain, and distress reduction in patients with cancer [16-18]. Further, even when presented in a very brief form, ACT results in positive outcomes for chronic conditions [19,20].

Despite the large body of literature demonstrating the efficacy of ACT for mental health concerns, chronic pain, and other conditions [17,18,21], there have only been a small number of investigations into ACT interventions for chronic disease conditions. However, desirable results from ACT have been observed for reported well-being, quality of life, adherence, and self-management behaviors across a range of populations, including those with diabetes, HIV, colorectal cancer, inflammatory bowel disease, obesity, and other health conditions [22-28]. To the best of our knowledge, there has only been 1 study published to date that explores the feasibility of ACT with a population of cardiac patients. Goodwin et al [29] conducted a feasibility study wherein 16 cardiac patients (12 following the drop out of 4 participants), who were mostly of lower socioeconomic status, completed 4 ACT workshops. Each workshop was conducted for 90 minutes. Large to medium improvements were observed for measures of patients' adherence to healthy lifestyle behaviors, including weight loss, increased physical activity, and improved diet. Similarly, significant or near significant improvements were observed for psychological self-report measures of acceptance, awareness, and cognitive defusion (ie, the undermining of unhelpful thought patterns). However, due to low power and the lack of a control condition, these findings must be considered tentatively, but these preliminary results are promising [29].

A systematic review by Graham et al [30] identified a number of investigations into ACT interventions for chronic health conditions that demonstrated promising findings, including improved psychological flexibility, medication adherence, and disease self-management. Poor study quality was a considerable issue, with many studies being underpowered and lacking a control condition and the authors calling for more rigorous investigations. Most empirical investigations conducted to date however have involved in-person therapy, which typically can be expensive, time-consuming, and difficult to access, especially for those dealing with the demands of chronic disease [31]. Interventions delivered in the form of a digital application may offer a solution for these problems. Although such interventions have not been extensively investigated among patients with chronic diseases, there are promising findings emerging [27,32,33].

In addition to being more cost- and time-effective [34], web-based and digital interventions have also been shown to increase health literacy and knowledge and improve coping [35]. ACT seems particularly effective when used in combination with health education and training [23], therefore making it particularly well suited for use in the management of chronic conditions.

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The aim of our study is to investigate the efficacy of a digital ACT intervention for the improvement of self-management behaviors, adherence, and psychological flexibility in a sample of participants with cardiac disease. The study will use a digital self-management platform that was developed and rigorously tested in large-scale trial with older adults with chronic health conditions, ensuring its suitability for use with such populations [36]. This technology supports participants in monitoring and reviewing symptom (eg, blood pressure, heart rate, and weight) and lifestyle parameters (eg, activity) that are relevant to their conditions and has been updated to include a newly designed app (ECME [Eastern Corridor for Medical Engineering Centre]-ACT; described further in the *Digital Platform* section). The platform also captures data on participants' engagement with devices as well as readings, therefore providing objective measures of target behaviors in real time. Participants will also complete a daily self-report measure of psychological flexibility.

Given the transdiagnostically applicable nature of ACT, our research will examine its suitability for all levels of disease severity and progression, with the goal of developing an intervention that will (1) increase engagement with relevant preventive behaviors among people with less severe cardiac disease (eg, hypertension) and (2) provide sufficiently high treatment dosages to those with more profound levels of disease (eg, advanced heart failure), who may require a lot of distress management. Therefore, individuals who have been diagnosed with any type or stage of cardiac disease will be invited to participate in the research.

Due to both the specific nature of the population under investigation and the fact that measures must be completed on a daily basis, our study will use a randomized, multiple baseline, single case experimental design (SCED). SCEDs offer practical and effective solutions by providing high-quality evidence for the efficacy of an intervention and using a considerably smaller sample than that of a randomized controlled trial. Such a design is particularly well suited to examining health and lifestyle behaviors in real time in the context of participants' daily lives to provide more accurate insights into how and when behavior change occurs. This can help to identify which intervention components are active (and which are not active) in producing meaningful changes.

Given the complexity of symptoms and varying levels of disease severity and prognoses among individuals with cardiac conditions, as well as the wide range of contextual factors that impact outcomes, it is important to understand these individuals' varying needs and how they may best be met. On this basis, participants will be invited to participate in one-to-one interviews upon their completion of the program to explore in further detail the factors that contributed to or impeded successful engagement with the overall intervention and any potential issues that arose. It is predicted that self-management behaviors will improve and that psychological flexibility will increase following the completion of the digital ACT intervention.

Methods

Ethics Approval

Ethical approval for the study was granted by the Research Ethics Committee of our host institution. Due to the sensitive nature of the study, participants will be provided with contact details for support services and reminded of their right to withdraw at any time. They will also be reminded that they may inform the research team about any concerns or any issues.

Design

Our research will involve a mixed methods design, which will include a nonconcurrent, randomized, multiple baseline SCED and one-to-one qualitative interviews. SCEDs treat each participant as a separate experiment in which data are collected at multiple time points for each participant and subsequently meta-analyzed across participants. This type of design is well suited to research involving niche or difficult-to-reach populations and provides advantages over group designs by examining the variability within and the experimental control of an individual's behavior as opposed to using group means [37,38]. The independent variable for each participant will be the pre-post intervention phase, and the dependent variables will be self-report measures of psychological flexibility, objective measures of self-management, and engagement with symptom and lifestyle parameter monitoring. The intervention will be randomly staggered across participants. Prior to the intervention being administered, baseline data will be collected from each participant for 2 weeks or until a stable baseline score is established for dependent variables, at which point the intervention will be introduced. At 1 week after the introduction of the intervention (or sooner), should an effect be observed, the next participant will begin to complete the baseline data collection process, and this will continue until the intervention is introduced to all participants. Randomization periods of 5 to 7 days are recommended [39].

Consistent with the aim of CBS, that is, to examine outcomes of interest at multiple levels of evidence analysis by using various methods [40], quantitative findings will be triangulated by using qualitative interviews wherein more detailed insights into each participant's experience with the trial will be examined.

Following the completion of the intervention, each participant will be invited to take part in a semistructured one-to-one interview, during which the following issues will be explored: the factors that facilitate and impede successful outcomes, the contextual factors that may affect one's ability to engage with and adhere to the intervention (eg, literacy levels and time commitments), the impact of disease severity on the ability to engage with the trial (eg, pain and fatigue), and whether the intervention was delivered as intended. Negative case sampling will also be performed if any participants choose to discontinue the intervention. They will also be invited to take part in one-to-one interviews to discuss the factors that led them to discontinue the intervention.

Recruitment

Potentially eligible participants will be invited to take part in the research via a living lab panel. The lead researcher will also contact relevant local services, including general practitioner and support services for those with cardiovascular conditions (eg, Irish Heart Foundation), and ask them to provide study details to potentially interested participants. General practitioner offices and support services will identify possible participants who meet the inclusion criteria and will provide them with the participant information leaflet, which contains details for contacting the lead researcher about participation.

If an individual wishes to participate, the lead researcher will phone them to discuss the study and arrange to obtain written informed consent. The inclusion criteria will include being over 40 years of age and having a diagnosis of cardiac disease, and the exclusion criteria will include symptoms of psychosis or suicidality, severe cognitive impairment or learning difficulties, or a below conversational level of English. For a multiple baseline SCED, samples of 3 or more participants are recommended [41]; therefore, in order to account for missingness and participant attrition, a slightly larger sample of approximately 10 to 15 participants who meet the criteria will be recruited.

Procedure

Upon agreeing to participate in the study and once informed consent is obtained, participants will receive an Apple iPad (8th Gen, 10.2-inch, Wi-Fi, 32GB; Apple Inc) with the ECME-ACT app installed as well as digital devices for monitoring symptoms and lifestyle parameters of relevance to their cardiovascular condition. Participants will either meet the researcher in their homes or in the research center (depending on their preferences and availability) wherein they will receive the devices and be verbally instructed on how to use them in addition to being provided with the relevant user manuals. Upon receiving the app (but prior to the ACT intervention being administered), baseline data for digital self-management behaviors and the self-report measure of psychological flexibility (see *Measures* section) will be collected for each participant over a 2 week period or until a stable baseline score is established. A multiple baseline SCED will be used, wherein the intervention will be staggered across participants (Figure 1).

Figure 1. Graphical display of hypothetical A-B single case experimental design data [41].
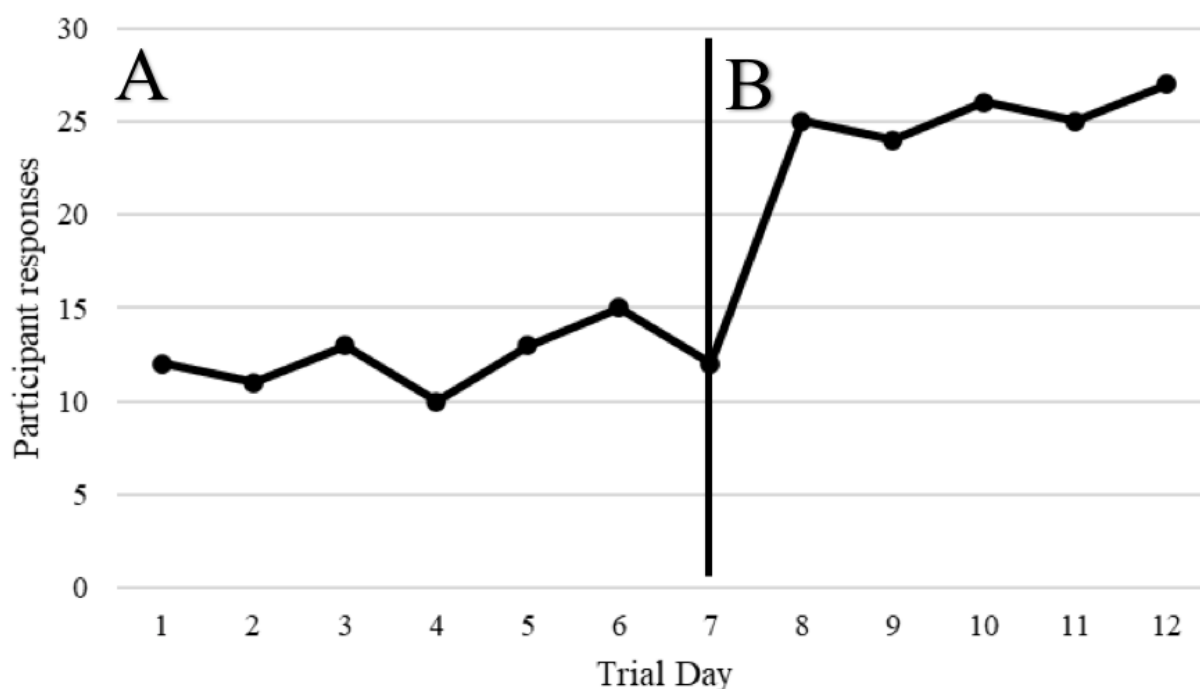
Participants will complete daily measures and homework by using the digital app, and the ACT intervention will be delivered by 2 ACT therapists via Zoom (Zoom Video Communications Inc) in once-weekly sessions over the course of 6 sessions at a particular time or on a day that suits each participant.

Measures

The Brief Acceptance Measure [42] is a 3-item self-report measure of psychological flexibility that was designed specifically for use in SCEDs. Participants will complete this daily within the app and will be sent a reminder to do so via a text message (sent by the primary researcher).

Symptom and lifestyle data and engagement with monitoring will be logged via the digital app for relevant self-management behaviors (eg, monitoring blood pressure and inputting weight). Participants will also receive a daily text message reminder to take readings. Engagement with the digital app will also be logged to ascertain the number of times that the participants use the app and its various features.

One-to-one interviews will examine participants' experiences with the intervention and explore the following:

- How are quality of life and day-to-day functioning following the completion of the intervention?

- What factors facilitated or impeded the ability to engage with the intervention?
- What changes to the intervention, if any, would participants make?
- If applicable, what factors lead the participant to discontinue their use of the digital intervention?

ACT Intervention

The intervention used in the study will be based on the *Acceptance and Commitment Therapy (ACT) Training Manual for Stress Reduction in Patients with Inflammatory Bowel Disease (IBD)* protocol [43], which will be adapted for use with cardiac conditions as opposed to inflammatory bowel disease. This protocol outlines a 6-session ACT intervention for populations with chronic illness with once-weekly sessions (approximately 1 hour). The intervention in this study will be delivered via Zoom by a peer-reviewed ACT trainer and expert and the lead researcher. Participants will also be provided with psychoeducation and mindfulness exercises (homework) via the digital app to help them implement and practice the strategies that they have learned throughout their day-to-day lives.

Treatment Fidelity

Sessions will be recorded and assessed by the lead researcher to ensure treatment fidelity and consistency.

Digital Platform

The ECME-ACT platform consists of the following components.

ECME-ACT App

The ECME-ACT app is the responsive web-based app on which participants will engage with data from digital health devices, including blood pressure, heart rate, weight, activity, and sleep (Figure 2), and features related to the digital ACT intervention (specifically, guided mindfulness audio recordings, psychoeducation and tips [Figure 3], and daily self-report measures [Figure 4]). The design of the digital app is based on findings from previous research, including interviews and co-design sessions, involving older adults with cardiac conditions [36,44]. Participants will be provisioned with an iPad for the duration of their participation in the study, through which they will engage with the ECME-ACT app and participate in the one-to-one therapeutic sessions conducted via Zoom.

Figure 2. ECME-ACT app dashboard. ACT: acceptance and commitment therapy; ECME: Eastern Corridor for Medical Engineering Centre.
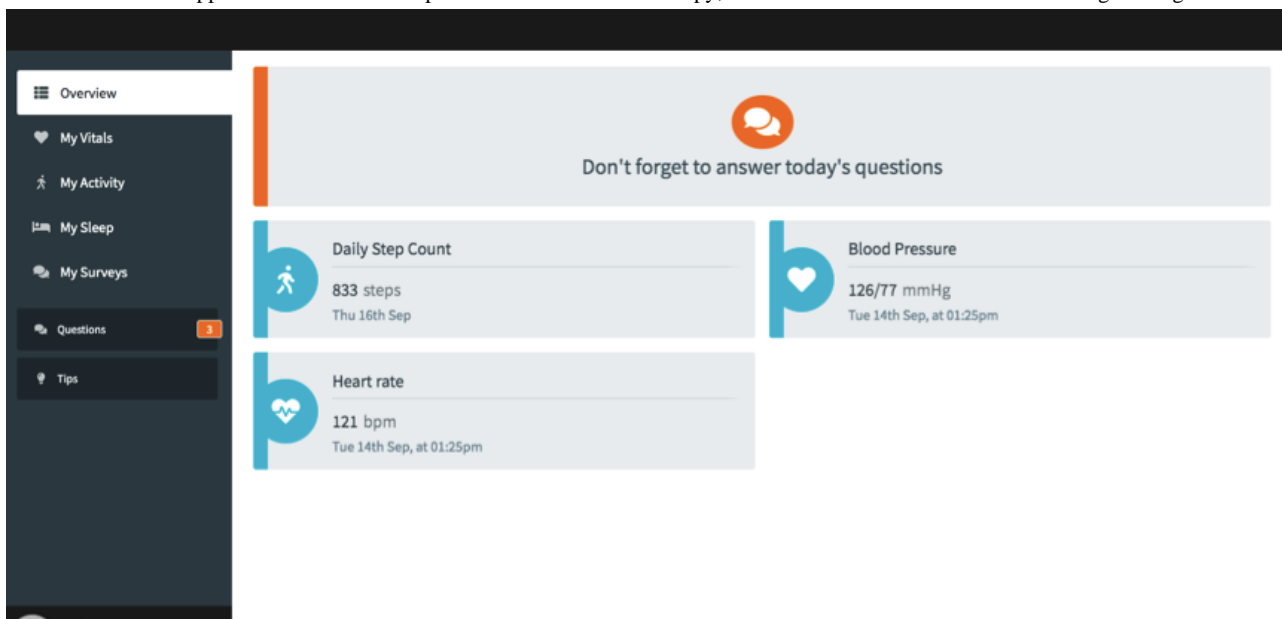
Figure 3. ECME-ACT app: tips and psychoeducation. ACT: acceptance and commitment therapy; ECME: Eastern Corridor for Medical Engineering Centre.
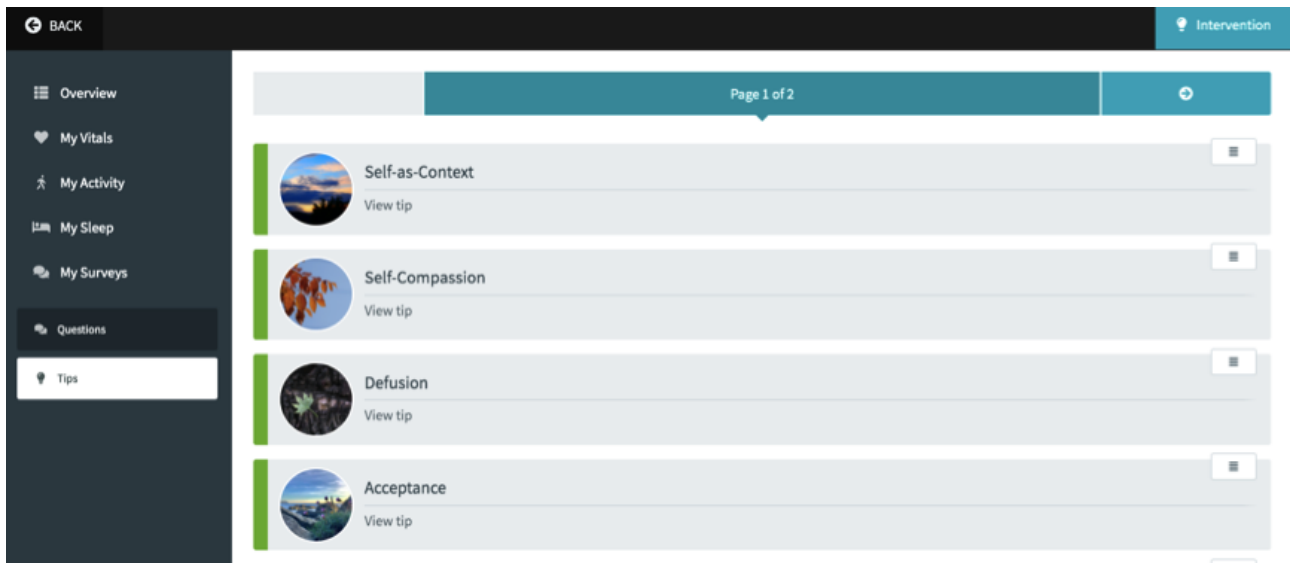
Figure 4. ECME-ACT app: daily self-report questions (Brief Acceptance Measure [43]). ACT: acceptance and commitment therapy; ECME: Eastern Corridor for Medical Engineering Centre.
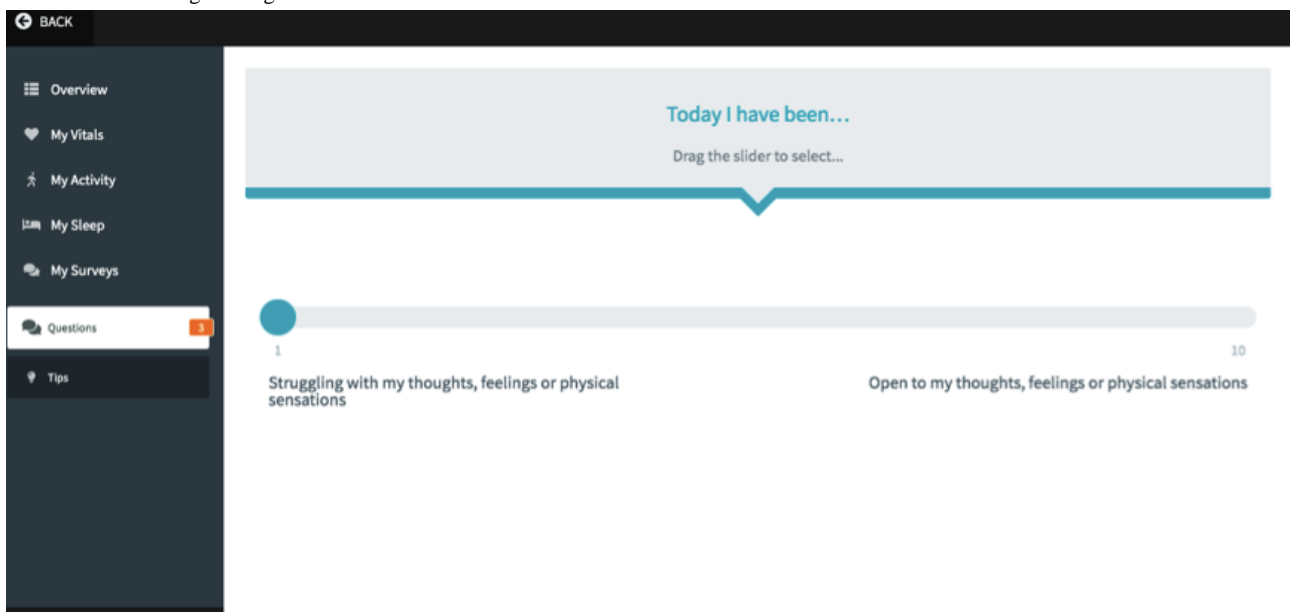
Context-Aware Broker and Inference Engine (Plus)

CABIE+ (Context-Aware Broker and Inference Engine [Plus]) is the data collection and aggregation system that will be used to organize and store the data acquired from the ECME-ACT app and integrated digital devices.

Subject Information Management System

SIMS (Subject Information Management System) is the information management system that will be used to allow the research team to view, analyze, and interpret the data collected from the app and the devices in close to real time for individual participants, including engagement data (Figure 5; further details are provided by Doyle et al [36]).

Figure 5. SIMS interface showing the inspection of daily self-report question data. SIMS: Subject Information Management System.
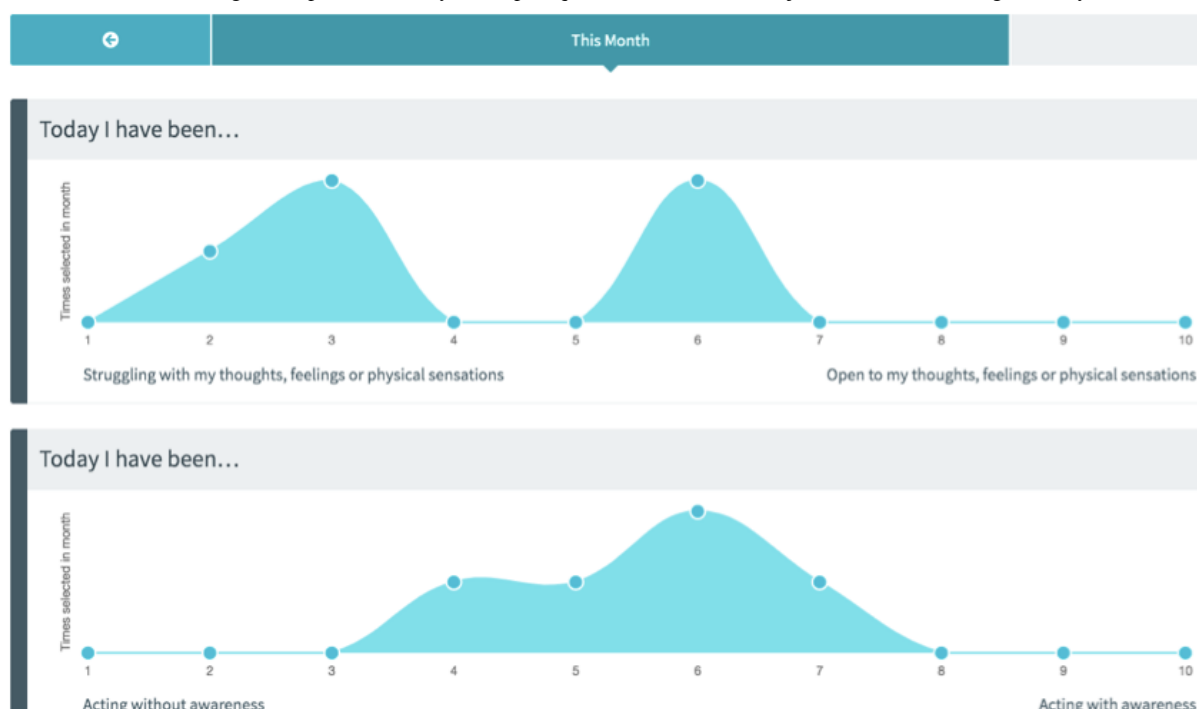
Digital Devices

Two off-the-shelf consumer devices—the Withings Smart Watch Activity Tracker (Withings) and the Withings BPM Connect (Withings)—are integrated with the digital platform. They will be used to collect health and well-being data over the course of the study. The Withings Smart Watch is a high-end smart device designed to monitor activity and sleep. The Withings BPM Connect has been clinically validated in terms of its ability to measure blood pressure and heart rate.

Analytic Strategy

Quantitative Analysis

Although SCED investigations typically involve visual data analyses [45], visual data inspection has been found to have low rates of interrater reliability [46-48]. Therefore, data will be analyzed quantitatively as well as visually in the study. Data will be analyzed quantitatively by using the SCED R package [49]. This R package was designed specifically for use in A-B SCEDs, and it allows for robust analyses, the plotting and meta-analysis of A-B SCED data, the use of exact tests, and the calculation and meta-analysis of robust effect sizes.

Raw data will also be visually plotted, allowing for the visual assessment of baseline trends, between-phase differences, and variability across each phase. Modified Brinley plots will be used to visually display data. Modified Brinley plots offer a means of conveniently identifying and interpreting changes at an idiographic level [50,51]. Modified Brinley plots also allow for the inclusion of cutoff points based on a measure's reliable change index, meaning that clinically meaningful idiographic patterns can be quickly observed and interpreted [51].

Qualitative Analysis

A thematic analysis [52] will be performed to analyze one-to-one interviews. The analysis will be primarily deductive in nature;

the researchers will use a top-down approach guided by the research questions to generate themes and patterns within the data. Following the completion of the initial coding by the primary researcher, all study authors will be consulted to discuss, recode, and categorize codes into themes until agreement is reached on all themes and subthemes. All interviews will be coded in full by 2 separate coders and then matched to assess interrater agreement by using the Cohen κ.

Results

Participant recruitment and data collection began in October 2021. The dissemination of study results in peer-reviewed journals is expected in spring 2022.

Discussion

Our study will examine the efficacy of a 6-session digital ACT intervention for improving the outcomes—self-management behaviors, treatment adherence, and psychological flexibility—of a sample of cardiac patients. By using previously validated self-management technology [36], participants' engagement with devices, as well as readings, will be captured in real time, therefore providing objective measures of target behaviors. It is predicted that improvements in self-management and treatment adherence, as well as increased psychological flexibility, will be observed following the digital ACT intervention. Should this digital intervention be found to be effective, it may address the need for transdiagnostically applicable, accessible, and wide-reaching treatment for improving the management of cardiac disease. Our findings will be of interest to health care professionals, psychologists, researchers, and policy makers.

Conflicts of Interest

None declared.

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Abbreviations

ACT: acceptance and commitment therapy
CABIE+: Context-Aware Broker and Inference Engine (Plus)
CBS: contextual behavioral science
CBT: cognitive behavioral therapy
ECME: Eastern Corridor for Medical Engineering Centre
SCED: single case experimental design
SIMS: Subject Information Management System

Protocol

Measuring Patient Compliance With Remote Monitoring Following Discharge From Hospital After Major Surgery (DREAMPath): Protocol for a Prospective Observational Study

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Abstract

Background: The incidence of major surgery is on the rise globally, and more than 20% of patients are readmitted to hospital following discharge from hospital. During their hospital stay, patients are monitored for early detection of clinical deterioration, which includes regularly measuring physiological parameters such as blood pressure, heart rate, respiratory rate, temperature, and pulse oximetry. This monitoring ceases upon hospital discharge, as patients are deemed clinically stable. Monitoring after discharge is relevant to detect adverse events occurring in the home setting and can be made possible through the development of digital technologies and mobile networks. Smartwatches and other technological devices allow patients to self-measure physiological parameters in the home setting, and Bluetooth connectivity can facilitate the automatic collection and transfer of this data to a secure server with minimal input from the patient.

Objective: This paper presents the protocol for the DREAMPath (Domiciliary Recovery After Medicalization Pathway) study, which aims to measure compliance with a multidevice remote monitoring kit after discharge from hospital following major surgery.

Methods: DREAMPath is a single-center, prospective, observational, cohort study, comprising 30 patients undergoing major intracavity surgery. The primary outcome is to assess patient compliance with wearable and interactive smart technology in the first 30 days following discharge from hospital after major surgery. Secondary outcomes will explore the relation between unplanned health care events and physiological data collected in the study, as well as to explore a similar relationship with daily patient-reported outcome measures (Quality of Recovery–15 score). Secondary outcomes will be analyzed using appropriate regression methods. Cardiopulmonary exercise testing data will also be collected to assess correlations with wearable device data.

Results: Recruitment was halted due to COVID-19 restrictions and will progress once research staff are back from redeployment. We expect that the study will be completed in the first quarter of 2022.

Conclusions: Digital health solutions have been recently made possible due to technological advances, but urgency in rollout has been expedited due to COVID-19. The DREAMPath study will inform readers about the feasibility of remote monitoring for a patient group that is at an increased risk of acute deterioration.

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KEYWORDS

digital health; telemonitoring; remote monitoring; telehealth; surgery; hospital; compliance; patient monitoring; wearable technology; smart devices

Introduction

Patients undergoing major abdominal and pelvic surgery have readmission rates of over 20% in the first 90 days after surgery [1-3]. Furthermore, 23% of postoperative deaths occur after hospital discharge, of which over 95% occur during the first 3 weeks following discharge [4]. Previously described risk factors for readmission to hospital include reduced functional capacity, chronic inflammatory lung disease, and previous anticoagulation therapy [5-7]. However, consensus is lacking, and patients are therefore not routinely monitored after discharge as patients are deemed to be medically fit. The availability of noninvasive home monitoring devices offers the opportunity to collect and report individualized physiological data, which can serve as surrogates for performance status in the home setting. Home monitoring can also include a means to collect patient-reported outcome measures (PROMs) using easy-to-use media. Such a framework would supplement the standard care discharge pathway, which consists of providing patient information on red-flag symptoms and interval outpatient appointments.

Home monitoring of patients with chronic conditions has previously been shown to be effective, for example, in the management of hypertension and congestive heart failure. A study of patients with hypertension found that during a 48-week period, 91.0% of participants measured their blood pressure regularly [8]. A randomized controlled trial comparing the titration of medication based on self-monitoring of blood pressure versus in-clinic blood pressure measurement in patients with hypertension reported that self-monitoring leads to significantly lower blood pressure [9]. Patient compliance with intermittent self-monitoring of weight and vital signs is similarly high, and benefits have been reported for interactions following changes in physiological status such as a reduction in hospital readmissions; this was found to reduce hospital length of stay from 9.5 days to 0.8 days per patient per year [10]. These reports support that patients can engage with home monitoring and that it is feasible. Furthermore, these studies suggest that engaging patients in the home setting with their own health can help inform their medical team of their health status, encourage patient empowerment, and lead to better health outcomes.

In addition to physiological measurements, PROMs, such as the Quality of Recovery (QoR) questionnaire, have been validated for measuring health status in the postoperative period [11]. The QoR tool and others are not used in routine clinical practice but have been successfully used in clinical trials as a measure of recovery and to discriminate between intervention and control arms [12]. This questionnaire can be applied across a wide range of operative procedures, and its 3 versions (QoR-40, QoR-15, and QoR-9) have been validated with domains for physical and mental well-being [13]. The QoR-40 has been used to track patients for up to 1 month following surgery. To date, the tool has not been used in the context of identifying postdischarge decline, although it has been reported that a low QoR score is independently associated with the development of postoperative complications [14]. As smart technology can be used to collect the QoR, the potential exists to utilize the tool in the postdischarge setting to monitor patients.

Smart devices are similar to their traditional electronic counterparts, but with the added feature of connecting to other devices or networks via different wireless protocols such as Bluetooth, near-field communication, Wi-Fi, 3G, etc. Smart technology has been applied to various medical devices suitable for home use. For example, pacemaker checks can now be safely performed remotely, reducing additional hospital visits [15]. Additionally, consumer-grade, wrist-worn pedometers and heart-rate monitors are commonplace, and many commercially available sphygmomanometers, pulse oximeters and other smart devices are able to wirelessly sync newly collected readings to smartphones. Smartphones can in turn upload data, which can facilitate remote monitoring. In theory, a smart health device can transmit data in real time, allowing for immediate identification and early intervention if deemed clinically necessary. Potential benefits of remote monitoring would enable quicker triage of deteriorating patients, to select patients for clinical review, and to further stratify patients requiring readmission to the index hospital of surgery.

In this study, we will explore the use of smart technology using devices to collect postdischarge data similar to the National Early Warning Score and PROMs in patients who were discharged from hospital after major intracavity surgery. The overarching aim of the study is to test the feasibility of using smart technology to collect physiological data and PROMs from this group of patients.

Methods

Study Design

This is a prospective, single-center, observational study to assess patient compliance with smart technology devices using the Home and Locally Observed (HALO) kit. The study will recruit patients undergoing any major intracavity surgery, which is associated with a readmission rate of >15% within 30 days of surgery or >20% in the first 90 days of surgery.

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Objectives

Primary Objective

The primary objective of the study is to assess patient compliance with wearable and interactive smart technology in the 30 days following discharge from hospital after major intracavity surgery.

Secondary Objectives

The secondary objectives are (1) to explore the relation between unplanned health care events and physiological measurements and PROMs in the postdischarge setting for patients undergoing major surgery, and (2) to explore the correlation between PROMs (QoR-15) and physiological measures in patients in the postdischarge setting.

Recruitment and Participation Criteria

DREAMPath will recruit patients attending anesthesia and surgical preassessment clinics. It is important to keep patient withdrawals from the study to a minimum; however, a patient may withdraw from the study at any time without prejudice to his or her subsequent treatment.

Inclusion Criteria

The inclusion criteria are as follows:

- Must be over 18 years of age;
- Scheduled to undergo or has recently undergone major intracavity surgery with a readmission rate of >15% within 30 days or >20% within 90 days;
- Able to provide informed written consent to participate.

Exclusion Criteria

The exclusion criteria are as follows:

- Deemed unfit for surgery;
- Unable or unwilling to comply with remote monitoring for any reason;
- Unable or unwilling to fill in a questionnaire in English.

Power Calculation

As this is a feasibility study, we aim to recruit 30 patients during this period. It is anticipated that compliance will be achieved for at least 27 of the 30 patients (90%). If 27 patients are observed to comply, then an exact 1-sided 90% CI suggests that the compliance rate will be at least as high as 82%. The timetable for each patient will be 1 calendar month, and patients will be interviewed at the end of the study to collect readmission event data, as well as feedback regarding ease of use.

Study Period

Patients will provide consent either prior to having surgery or in the immediate postoperative period while they are still in hospital. At the time of consent, patients will be familiarized with the smart devices and mobile app described. If the patients undergo cardiopulmonary exercise testing (CPET) as part of their routine assessment, the results for this will be recorded. This data will be used to compare the performance of CPET data and smart device data in predicting postoperative complications.

The 4-week monitoring period will commence upon discharge from hospital. Patients will be expected to wear the wearable device at all times, engage with other devices (see the *Remote Monitoring Equipment* section below for the list of devices) twice a day, and fill out 1 daily questionnaire. Compliance will be defined as completion of 70% of the daily PROM questionnaires or wearing the wrist-worn trackers for at least 10 hours per day over the study duration. A minimum of 1 reading in each hour of either step count or heart rate will constitute a successful hour of data collection. Patients will be given the opportunity to contact dedicated personnel in the study team for troubleshooting purposes only. Furthermore, the app provides clear feedback to patients to signal the successful collection of study data. We hope that this measure will help patients feel supported to engage with the study and reduce patient withdrawal. If patients are admitted to the hospital during the monitoring period, they will not be expected to bring the HALO kit to the hospital, and the admission period and subsequent use will not factor into their compliance rate.

The end of the study will be defined as completion of a 30-day follow-up after discharge from the hospital. Patients will be seen at the clinic or contacted by phone to conclude their participation. Postdischarge events will be collected at this time, which is defined as any unscheduled contact with a health care professional, which includes, but is not limited to, general practitioner (GP) visits, accident and emergency (A&E) visits, home visits by primary care team, etc.

All study assessments are summarized in Table 1, and the study flowchart is illustrated in Figure 1. As DREAMPath is an observational study, patients will be able to participate in other trials.

Table 1. Assessments for patients who consent to participate in the DREAMPath (Domiciliary Recovery After Medicalization Pathway) study.

Visit	Baseline	Postop	First 30 days after discharge	Appointment after 30 days
Identification and enrollment	✓			
Medical history	✓			
Consent and enrollment	✓			
CPET[a] (optional substudy)[b]	✓			
HALO[c] data collection (baseline)	✓			
POMS[d] score (day 5, postoperatively)[b]		✓		
Blood pressure, pulse oximetry, and temperature (twice daily)			✓	✓
Continuous wrist-worn tracker			✓	✓
QoR-15[e] questionnaire (once daily)	✓		✓	✓
CD[f] classification at 1-month postop				✓
Adverse events log and patient preferences				✓

[a]CPET: cardiopulmonary exercise testing.

[b]Optional components depending on clinical pathway.

[c]HALO: Home and Locally Observed.

[d]POMS: postoperative morbidity score.

[e]QoR-15: Quality of Recovery–15.

[f]CD: Clavien-Dindo.

Figure 1. Flow diagram illustrating visits and assessments for patients participating in the DREAMPath (Domiciliary Recovery After Medicalization Pathway) study. CPET: cardiopulmonary exercise testing; PIS: patient information sheet; POMS: postoperative morbidity score.
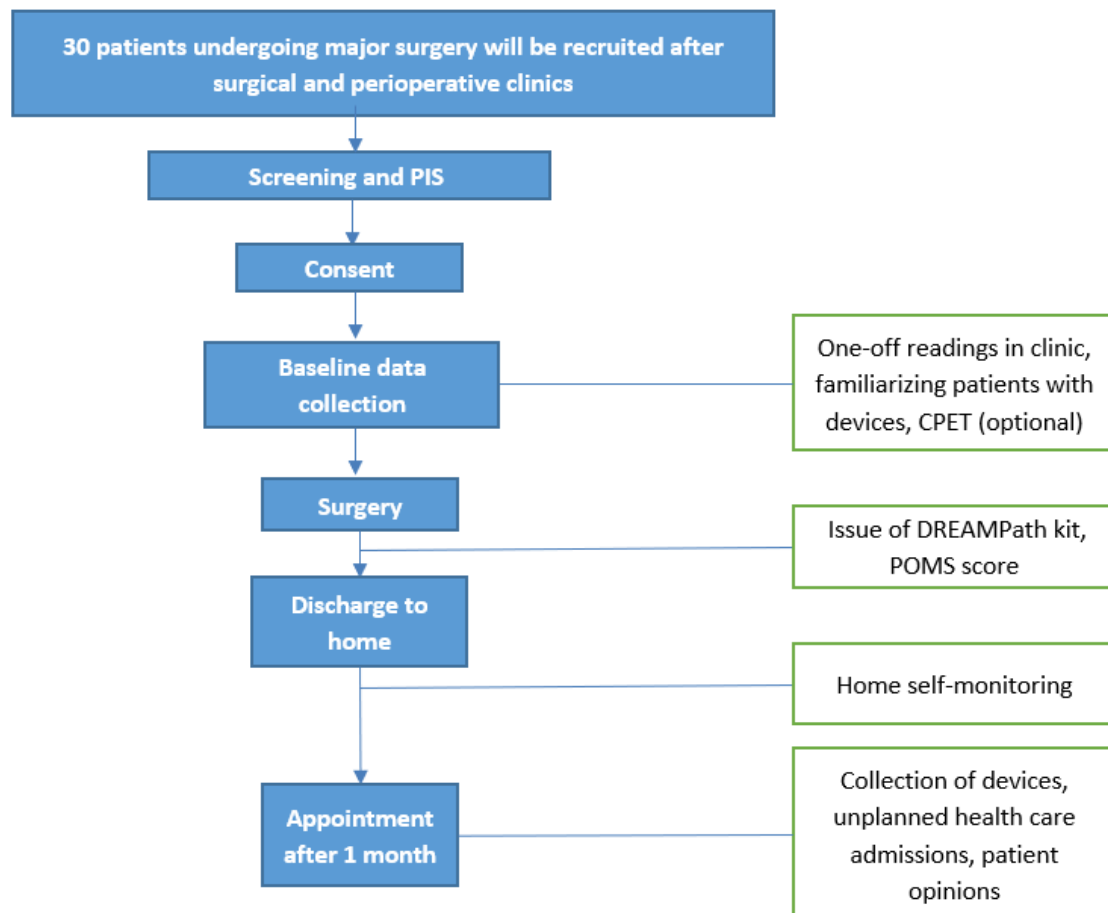
Remote Monitoring Equipment

The HALO kit is designed to be used with a cellular broadband device, such as a 4G-capable mobile phone, which can be used to complete questionnaires electronically. The broadband device remotely uploads data to an anonymized database. Patients will be issued a HALO kit before discharge from hospital and will be monitored remotely for 30 days. The HALO kit consists of 4 devices: a wrist-worn device with step count and heart rate measurement capability, an iHealth Air pulse oximeter, an iHealth Track blood pressure monitor, and a Koogeek Thermometer. These devices are shown in Figure 2. Patients without a smartphone will be provided with one for the duration of the study. Patients will be instructed to wear the tracker continuously and will be shown how to measure blood pressure, pulse oximetry, and temperature twice daily (morning and evening). All readings will be transmitted from the respective device to the iPhone wirelessly, with the option for patients to self-enter data if they prefer to. Additionally, they will be asked to complete a QoR-15 questionnaire once daily.

Figure 2. Smart devices issued to patients for twice-daily use: bluetooth enabled thermometer, puse oximeter, sphygmomanometer, Apple Watch and iPhone 7 (from left to right).

Patients will be registered and provided with a trial identifier to ensure all transmitted data are anonymized. They will be contacted via telephone to confirm activation of the system. At the time of consent, patients will be informed that the data collected will not be reviewed for clinical decision-making and that the data are anonymized. Unplanned health care engagement such as GP visits, A&E visits, and readmissions will be collected as "events." Postoperative complications will be recorded per the Clavien-Dindo classification and the postoperative morbidity score. An exploratory study to understand whether there is a relation between the measured physical parameters and health care events will be conducted. If a derangement of physiological parameters can reliably predict an unplanned health care engagement event, a similar remote monitoring solution could be used to triage patients at home instead of the current standard of care in which patients self-present to primary or emergency care facilities. Upon completion of the study, patients will be asked to return the devices, and information about unplanned health care events and adverse events will be collected. Patients will not be held responsible for any lost or damaged devices. Study devices will not have any patient-identifiable data; and in the event of a lost device, they will be remotely wiped using Apple's remote wipe feature on iOS. Upon return, devices will be cleaned and sterilized in line with hospital ambulatory device policy.

Data Collection System

Data is sent over HTTPS (Hypertext Transfer Protocol Secure) from the patients' phones to our backend server hosted at our affiliated university. The backend consists of a web application framework with a REST application programming interface. Each request delivered from a patient's mobile phone app is processed in the backend by extracting request payloads and then transforming the data so that they can be stored in a normalized database. All data were pseudo-anonymized, thus ensuring patient privacy. Patients do not have direct access to their data through the app, although interaction with the clinical team means that they can request their own data. A web-based secure portal has also been created so that anonymized data could be analyzed and hypotheses formed for the future creation of analytics and modeling.

Patient and Public Involvement

This study was planned with patient and public involvement (PPI) at various stages. Prior to planning the study, PPI meetings were held to gather patient views on remote monitoring. In these sessions, patients were asked to share their views on remote monitoring in general, remote monitoring using wearable and smart devices, as well as familiarity with technology-based solutions. Additionally, the study protocol was submitted to The Urology Foundation (TUF) for peer review as part of the TUF Research Scholarship application. Shortlisting is performed on the basis of PPI and scientific feedback, followed by an interview with a panel consisting of PPI and scientific committee members.

Availability of Data

The study team will control the final anonymized data set. Requests for access will be reviewed by the trial management group, subject to existing contractual arrangements with the sponsor and funders.

Ethics and Dissemination

The study has ethical approval from the South West – Cornwall & Plymouth Research Ethics Committee (REC reference 18/SW/0206) and has been registered with the ISRCTN Registry (ISRCTN62293620).

The results of the study will be published in peer-reviewed publications and will be presented at relevant national and international conferences. We will work with our patient panel to develop lay reports to disseminate our research findings to patient groups and the clinical teams at participating sites.

Results

Status and Timeline

The DREAMPath study is currently underway at our center. Due to the COVID-19 pandemic, research staff were redeployed to provide clinical cover, but we expect to complete recruitment as planned by the end of the first quarter of 2022.

Discussion

Benefits of the Study

The main objective of this study is to measure patient compliance with remote monitoring devices using a multidevice kit for patients in the community setting. This is an important step in order to measure patient engagement prior to any large-scale testing of clinical validity of a remote early warning system in a cohort of patients recovering after major surgery. Similar studies have been reported from prior to the smartphone era [16] and have relied on telemetry to collect data with patients actively reporting data. In the study by Kleinpell et al [16], 725 alarms were generated during a 3-month monitoring period of 10 patients, but only 6 of these alarms led to a clinician consult after phone triage. For remote monitoring to be adopted into routine care, false-negatives need to be kept to a minimum but must still capture all major clinical events. During our data analysis of secondary endpoints, we will explore different early warning systems such as modified versions of the national early

warning system [17,18] as well as machine-learning–driven algorithms. Due to the large amount of data being produced, a processing pipeline will be required to ensure that clinical resources are not overburdened by the implementation of remote monitoring.

The current study is designed to be an observational study. Data collected in the study will not be accessible to clinicians until after the completion of the monitoring period, as the study ethics do not allow for clinicians to use this data for clinical decision-making. According to the Medicines and Healthcare Products Regulatory Agency (MHRA) guidelines, any remote monitoring medical apps used that influence clinical decision-making are subject to approval [19]. Similar policies exist in other places including the United States, Australia, and the European Union [20]. If our secondary objective analysis shows that it is feasible to use remote monitoring to pre-empt clinical events, an important next step will be to comply with MHRA and other guidance to ensure that this model is validated for use to facilitate clinical adoption. With a marketplace full of mobile apps that can improve health, regulation is extremely important to ensure that end users are not given false assurances about their health. However, the burden of responsibility must not be passed on to patients to interpret medical data without clinical expertise.

Strengths and Limitations

This is a proof-of-concept remote monitoring study that aims to measure patient compliance with remote monitoring that could potentially improve postoperative care and reduce hospital readmission. The primary outcome will inform us whether remote monitoring is feasible, and the secondary outcomes will inform us of the clinical usefulness of the data collected.

One limitation is that patients will have access to their own data, which may influence their decision to seek medical attention. Further, as this is a pilot study, the sample size is small. A larger study will be necessary to make conclusions about the overall usefulness of remote monitoring.

Conclusion

Health care services have undergone a digital revolution during the COVID-19 pandemic. Hospitals were routinely giving patients medical devices to self-monitor, and this initiative was supported by national organizations such as NHS England [21]. This is based on evidence that the prehospital measurements of pulse oximetry can be a red flag for patients who may be experiencing "silent hypoxia" due to COVID-19 infection. However, these devices did not have any way of interacting directly with hospital systems and patients were asked to maintain a diary of readings, which can be reviewed by clinicians via remote consultation or A&E attendances. Our study was conceived prior to the pandemic, but offers an important improvement to the current pathway as patients do not need to enter any data manually as the devices included sync data directly using Bluetooth and our bespoke app allows for an automatic upload. After the completion of this study, we hope to integrate our backend server to communicate directly with hospital electronic health record systems to allow seamless data access for clinicians while patients are at home.

Authors' Contributions

JK, PK, NW, and JC were responsible for study conception and design. All authors were involved in study implementation. PK, JK, PÓS, RS, and ID contributed to the writing of the manuscript.

Conflicts of Interest

JC has received reimbursement for consultancy from AstraZeneca, Ferring, Roche, and Janssen; speaker fees from Bristol-Myers Squibb (BMS), MSD, Janssen, Astellas, Nucleix, and Roche; honoraria for membership of advisory boards for Ferring, Roche, Gilead, Photocure, BMS, QED Therapeutics, and Janssen; and research funding from Roche.

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Abbreviations

A&E: accident and emergency
CPET: cardiopulmonary exercise testing
DREAMPath: Domiciliary Recovery After Medicalization Pathway
GP: general practitioner
HALO: Home and Locally Observed
HTTPS: Hypertext Transfer Protocol Secure
MHRA: Medicines and Healthcare Products Regulatory Agency
PPI: patient and public involvement
PROM: patient-reported outcome measure
QoR: Quality of Recovery
TUF: The Urology Foundation

Protocol

The Effect of the COVID-19 Pandemic on Glycemic Monitoring and Other Processes of Care for Type 2 Diabetes: Protocol for a Retrospective Cohort Study

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Abstract

Background: Social distancing and other nonpharmaceutical interventions to reduce the spread of COVID-19 infection in the United Kingdom have led to substantial changes in delivering ongoing care for patients with chronic conditions, including type 2 diabetes mellitus (T2DM). Clinical guidelines for the management and prevention of complications for people with T2DM delivered in primary care services advise routine annual reviews and were developed when face-to-face consultations were the norm. The shift in consultations from face-to-face to remote consultations caused a reduction in direct clinical contact and may impact the process of care for people with T2DM.

Objective: The aim of this study is to explore the impact of the COVID-19 pandemic's first year on the monitoring of people with T2DM using routine annual reviews from a national primary care perspective in England.

Methods: A retrospective cohort study of adults with T2DM will be performed using routinely collected primary care data from the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC). We will describe the change in the rate of monitoring of hemoglobin A_{1c} (HbA_{1c}) between the first year of the COVID-19 pandemic (2020) and the preceding year (2019). We will also report any change in the eight checks that make up the components of these reviews. The change in HbA_{1c} monitoring rates will be determined using a multilevel logistic regression model, adjusting for patient and practice characteristics, and similarly, the change in a composite measure of the completeness of all eight checks will be modeled using ordinal regression. The models will be adjusted for the following patient-level variables: age, gender, socioeconomic status, ethnicity, COVID-19 shielding status, duration of diabetes, and comorbidities. The model will also be adjusted for the following practice-level variables: urban versus rural, practice size, Quality and Outcomes Framework achievement, the National Health Service region, and the proportion of face-to-face consultations. Ethical approval was provided by the University of Oxford Medical Sciences Interdivisional Research Ethics Committee (September 2, 2021, reference R77306/RE001).

Results: The analysis of the data extract will include 3.96 million patients with T2DM across 700 practices, which is 6% of the available Oxford-RCGP RSC adult population. The preliminary results will be submitted to a conference under the domain of primary care. The resulting publication will be submitted to a peer-reviewed journal on diabetes and endocrinology.

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Conclusions: The COVID-19 pandemic has impacted the delivery of care, but little is known about the process of caring for people with T2DM. This study will report the impact of the COVID-19 pandemic on these processes of care.

International Registered Report Identifier (IRRID): DERR1-10.2196/35971

Introduction

Background

The COVID-19 pandemic and recommended social distancing and other nonpharmaceutical interventions have had a substantial impact on primary care services in the United Kingdom [1,2]. Face-to-face consultations were markedly reduced, and primary care appointments decreased by 64.6% and home visits decreased by 62.6% from the week commencing March 9, 2020, coinciding with national policy changes [3]. This was a consequence of lockdown restrictions and changes made by a series of scientific advisory groups to minimize the risk of exposure to COVID-19, which included encouraging telemedicine as the preferred alternative for face-to-face consultations [1,4]. During the initial stages of the pandemic, primary care services reserved face-to-face consultations for priority appointments, while the policy for delivering routine care via telemedicine was adopted [1]. The changes in methods of consultation and interrupted routine care may have adversely affected the management of people with type 2 diabetes mellitus (T2DM) [5].

Previous studies have identified that missed hemoglobin A_{1c} (HbA_{1c}) monitoring appointments is associated with higher HbA_{1c} [6,7]. A recent study showed a 40% reduction in HbA_{1c} testing during the first year of the COVID-19 pandemic compared to the preceding year [8]. It is well established that impaired glycemic control is associated with the increased risk of micro- and macrovascular complications [8,9], indicating the benefit to people with T2DM having regular HbA_{1c} monitoring.

In 2014, the National Institute for Health and Care Excellence (NICE) introduced clinical guidelines for its Quality and Outcomes Framework (QOF) indicator menu to encourage regular monitoring and management of diabetes [10,11]. These are known as *routine annual reviews*, which include eight health checks: HbA_{1c}, blood pressure, cholesterol, serum creatinine, urine albumin, foot surveillance, BMI, and smoking status [11]. The proposed indicators are based on the best evidence and are implemented to provide high standards of care and improved results for patients.

However, the extent to which interruptions in primary care services (eg, face-to-face appointments) affected the monitoring of people with T2DM in the United Kingdom during the COVID-19 pandemic has yet to be established. This protocol describes our planned methods to explore the impact of the pandemic on the monitoring of people with T2DM in a UK-based setting.

Aims and Objectives

Our primary objective is to assess the impact of the COVID-19 pandemic on HbA_{1c} monitoring in people with T2DM. As a secondary objective, we will explore changes in the rates of *routine annual reviews* between the pre–COVID-19 pandemic period and during the first year of the COVID-19 pandemic.

Methods

Study Design

We will conduct a retrospective cohort analysis using observational data of adults with T2DM from the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) sentinel network database. The study cohort will be observed at two time points: the year preceding the COVID-19 pandemic (January 1 to December 31, 2019) and the first year of the COVID-19 pandemic (January 1 to December 31, 2020).

Data Source

The Oxford-RCGP RSC is a sentinel network of volunteer primary care practices across England and Wales, currently comprising more than 15 million patients registered with over 1800 affiliated practices [12]. Pseudonymized coded clinical practice data is uploaded and available in near real time within a secure network, supporting the RSC's influenza surveillance, identification of epidemics, and other research activity. The network provides a broadly representative sample of the national population [13].

UK primary care data is registration based (ie, patients have unique identifiers—National Health Service [NHS] numbers). Patient electronic health care records are coded using the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) code system, a machine-readable clinical vocabulary offering a high degree of granularity and linkage to other classifications and international terminologies [14]. Most of the T2DM management occurs in primary care and pay-for-performance targets to incentivize chronic disease management including T2DM, resulting in well-maintained disease registries, thus ensuring high-quality data for this study [5,15,16].

Study Population

We will identify adults (aged ≥18 years) with T2DM using diagnosis codes. The cohort for this study will comprise individuals diagnosed with T2DM on or before December 31,

2018, and who are registered with an Oxford-RCGP RSC practice on this date.

Exposure

The exposure variable will be binary to indicate the first calendar year of the COVID-19 pandemic (January 1 to December 31, 2020) and the year before the pandemic (January 1 to December 31, 2019).

Outcomes

Our primary outcome measure will be the rate of HbA_{1c} monitoring in the year 2020; this will be compared to HbA_{1c} monitoring in the preceding year.

The secondary outcome will be a measure of the NICE eight health checks that make up the *routine annual review* in each study period. We will sum the number of types of checks conducted in the year per patient and code this to an ordinal variable (≤5 care processes, 6-7 care processes, 8 care processes).

Study Variables

The study variables of interest are divided into personal characteristics and practice characteristics.

Personal Characteristics

The following personal characteristics will be used: age (treated as a continuous variable), gender (male or female), socioeconomic status (quintiles of the Index of Multiple Deprivation [IMD]) according to the national distribution of IMD scores based on the postal code of the patient [17], ethnicity (categorized into major ethnic groups, defined by the Office of National Statistics, Asian, Black, Mixed, White, or other ethnic group) [18,19], COVID-19 shielding status, duration of diabetes, and presence of comorbidities (eg, hypertension and chronic kidney disease; determined by diagnosis codes).

Practice Characteristics

For the practice characteristics, urban versus rural primary care practices will be identified from the practice Lower Layer Super Output Area. The practice size, QOF linkage, NHS region (East of England, London, Midlands, North East and Yorkshire, North West, South East, South West), and the number/type of consultations will be taken into account [20].

Statistical Analysis

The summary statistics will be reported as counts and percentages for categorical data and means (with SDs) for continuous data.

If the missing data is <5% (as routine primary care data is incomplete, we anticipate a small degree of missing data in most, if not all, covariates), no attempt will be made to impute the missing values. Missing data >5% will be handled through multiple imputation by chained equations using the MICE package, version 3.14.0 [21].

To assess the impact of the COVID-19 pandemic on HbA_{1c} monitoring, we will estimate the odds ratio of HbA_{1c} monitoring during the pandemic period and the pre–COVID-19 pandemic period in a multilevel logistic regression model with the first

COVID-19 year as an indicator variable. The random intercept model will enable the variation of the impact of the pandemic at the patient, GP, and geographical level to be assessed and enable the estimation of robust effect sizes. We will use ancillary analyses to estimate the population-level effects of covariates measured at the patient and practice level to better describe the impact of interpractice variation.

The secondary outcome, measuring the degree to which patients received all eight *routine annual review* checks, will be modeled using a mixed effects ordinal regression, adding random effects at the practice level. Current research has shown variation in the attainment of the individual checks. We will describe the attainment of the individual checks and achievement of all eight checks. We will adopt the methods used by Holman et al [22] and define the secondary outcome measure as an aggregate score of the varying degrees of partial attainment with an explicit natural ordering. This secondary outcome measure will then be modeled using mixed effects ordinal regression adding random effects at the practice level, accounting for the ranking of the levels of attainment.

The data analysis will be carried out using the statistical software, R version 4.1.1 (The R Foundation for Statistical Computing) [23].

Ethical Considerations

Research ethics approval (Reference R77306/RE001) was obtained from the University of Oxford Medical Sciences Interdivisional Research Ethics Committee in September 2021. Data are pseudonymized at the point of data extraction and will be held on a secure network at the University of Oxford. This network is compliant with NHS Digital Data Security and Protection toolkit standards [24]. The data analysis will begin in November 2021.

Results

A power calculation has been made, based on a *Z* test, for the study. A study with an effect size of 0.05 (1% change in monitoring rates) and at a power of 75% will require a total sample size of 237,026 people with T2DM. The power calculation was carried out using G*Power 3.1.9.7 (Buchner A).

The analysis of the data extracted will include 3.96 million patients with T2DM across 700 practices, which is 6% of the available Oxford-RCGP RSC adult population. The preliminary results will be submitted for presentation at a primary care–themed conference. The resulting publication will be submitted for publication in a peer-reviewed journal.

Discussion

Overview

This protocol describes how we will explore the effect of the COVID-19 pandemic on the monitoring of people with T2DM by sociodemographics and other individual clinical characteristics. The Oxford-RCGP RSC database is appropriate to use, as the majority of the people with T2DM are managed in primary care.

It is valuable to study primary care practices with respect to diabetes monitoring during the pandemic using evidence-based research. People with T2DM require regular monitoring to minimize the risk of diabetes-associated complications. However, changes in the delivery of primary care services as a result of the COVID-19 pandemic has brought challenges in T2DM assessment and monitoring [2]. The existing literature has focused on an unprecedented reorganization of UK primary care during the pandemic [3]. Remote monitoring systems proved to be feasible and were supported by the current clinical guidelines [3]. However, the study results might represent a considerable burden of unmet need, validating the results of other studies [2,8].

Strengths and Limitations

The Oxford-RCGP RSC is a large network of primary care practices with wide coverage. Although the network covers England and Wales, previous literature has reported that it provides a representative sample of the UK population, and hence, the final results will be broadly generalizable to the United Kingdom as a whole [13]. Furthermore, the quality of computerized medical records is high due to pay-for-performance targets [15].

However, there are several limitations. Being routinely collected data, there may be issues of missingness and inaccurate recordings. This will be accounted for by using multiple imputation. Moreover, since this is an observational study, one limitation will be unmeasured confounding factors that may result in biased effect estimates, which we will mitigate by performing a sensitivity analysis. Additionally, the enrollment of practices depends on the types of ongoing projects and clinical trials; therefore, our identification of practices will vary. They are signed up to the Oxford-RCGP RSC network on a voluntary basis, which may cause a higher representation of the more affluent areas compared to the average national population [13]. Any additional strengths and limitations observed during the study will be reported in the final manuscript.

Conclusion

This study will provide insight into the impact of the pandemic in the monitoring of NICE *routine annual reviews* of people with T2DM managed in an English primary care setting. We expect the outcomes from this study to highlight the need for "catch up" in order for primary care to enhance best practices and prevent T2DM complications.

Authors' Contributions

MM, JvV, WH, and GD wrote the manuscript. BMT, WH, GD, and MF contributed to the design and reviewed/edited the manuscript. XF and HL helped with data extraction. MJ, FC, MF, and SdeL contributed to the conception of the study, developed the statistical analysis plan, and reviewed/edited the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest associated with this project. However, SdeL is the Director of the RCGP Research and Surveillance Centre, and holds or had recently held grants from EU Horizon 2020, European Association for Study of Diabetes Primary Care Diabetes Europe, Eli Lilly and Company, AstraZeneca, and Novo Nordisk Ltd through his University for lead investigator research in diabetes.

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Abbreviations

HbA$_{1c}$: hemoglobin A$_{1c}$

IMD: Index of Multiple Deprivation

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

QOF: Quality and Outcomes Framework

RCGP: Royal College of General Practitioners

RSC: Research and Surveillance Centre

SNOMED CT: Systematized Nomenclature of Medicine Clinical Terms

T2DM: type 2 diabetes mellitus

Protocol

Acceptability and Feasibility of a Return-to-Work Intervention for Posttreatment Breast Cancer Survivors: Protocol for a Co-design and Development Study

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Related Article:

Abstract

Background: The mortality rate from breast cancer has been declining for many years, and the population size of working-age survivors is steadily increasing. However, the recurrent side effects of cancer and its treatment can result in multiple disabilities and disruptions to day-to-day life, including work disruptions. Despite the existing knowledge of best practices regarding return to work (RTW) for breast cancer survivors, only a few interdisciplinary interventions have been developed to address the individualized needs and multiple challenges of breast cancer survivors, health care professionals, and employer and insurer representatives. Thus, it seems appropriate to develop RTW interventions collaboratively by using a co-design approach with these specific stakeholders.

Objective: This paper presents a protocol for developing and testing an innovative, interdisciplinary pilot intervention based on a co-design approach to better support RTW and job retention after breast cancer treatment.

Methods: First, a participatory research approach will be used to develop the intervention in a co-design workshop with 12 to 20 participants, including people affected by cancer, employer and insurer representatives, and health care professionals. Next, a pilot intervention will be tested in a primary care setting with 6 to 8 women affected by breast cancer. The acceptability and feasibility of the pilot intervention will be pretested through semistructured interviews with participants, health care professionals, and involved patient partners. The transcribed data will undergo an iterative content analysis.

Results: The first phase of the project—the co-design workshop—was completed in June 2021. The pilot test of the intervention will begin in spring 2022. The results from the test will be available in late 2022.

Conclusions: The project will offer novel data regarding the use of the co-design approach for the development of innovative, co-designed interventions. In addition, it will be possible to document the acceptability and feasibility of the pilot intervention with a primary care team. Depending on the results obtained, the intervention could be implemented on a larger scale.

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Introduction

It has been reported that 1 in 8 Canadian women will develop breast cancer in their lifetime [1,2]. Of these, 88% will survive for more than 5 years, and of these survivors, 50% are of working age. In the current context of labor shortages [3], the contribution of those with a cancer diagnosis who want to return to work (RTW) is valuable. Indeed, many survivors desire to RTW because it is a sign of a return to a "normal" life [2,4-7]. On the other hand, 1 in 5 women will leave their jobs due to an inability to perform their tasks resulting from recurrent side effects of cancer or its treatments [8]. There are a variety of reasons for the development of these limiting side effects. Breast cancer treatments, such as mastectomy or chemotherapy, can cause significant physical symptoms [9] (eg, pain, the loss of arm mobility, and lymphedema) that may limit the act of lifting or work involving repetitive motions [10]. These symptoms and physical limitations can severely complicate and even hinder daily work [7,10]. Fatigue, as well as memory loss and difficulty concentrating, can also impact RTW [11]. Furthermore, breast cancer survivors often live more precariously than the general population due to taking repeated sick leaves from work or having only part-time employment after cancer treatments [12-16]. Despite these challenges, both working and having good working conditions are related to better health [17], as is allowing for the maintenance of social interactions, self-esteem, psychological well-being, and financial security [2,18,19].

Interdisciplinary interventions that support RTW and are specifically tailored to the issues experienced by breast cancer survivors remain rare in Canada and do not exist in Quebec, and this scarcity of tailored interventions seems likely to continue [20-22]. Indeed, a Cochrane review about RTW interventions for patients who have completed cancer treatments revealed that interventions that targeted multiple modalities (physical, psychological, and vocational) and were delivered by an interdisciplinary team seemed more appropriate for addressing the needs of cancer survivors [23]. This multimodal type of intervention appears promising, although the effect size remained tenuous and suggested the need for further study [23]. Other studies suggest using more comprehensive approaches, such as discussing work-related issues during psycho-oncological care [24,25], involving employers [26], and performing early intervention [27]. It has even been suggested that work-related issues should be discussed as early as the active treatment period to maintain social roles, including those of workers [25,28]. According to a scoping review [27], RTW interventions that have been identified to support breast cancer survivors are offered in ad hoc interventions by different health

care professionals and are highly variable in terms of information booklets, physical activities, and deployment times (eg, at the end of treatment) [27]. More structured interdisciplinary interventions remain to be developed to meet the unique needs of this clientele regarding RTW.

It seems desirable and realistic that interdisciplinary interventions be offered by a primary care team [20]. By definition, primary care can include health promotion, disease prevention, the monitoring of chronic and episodic diseases, and rehabilitation [29]. It is also possible that such a team would be able to address the RTW-related concerns of women affected by breast cancer, which include symptom management, RTW-related decision-making, resource navigation, and the reintegration of daily activities [4,30]. Primary care teams promote interdisciplinary work and provide services as close to a given population as possible [31]. Furthermore, given the scope of primary care, it is strongly recommended that those affected by cancer be managed by such teams during the recovery period [32,33]. It is also suggested that intervention components should be deployed during key points in the experience of cancer survivorship at 1, 3, and 6 months after cancer treatment and encourage the self-management of side effects (eg, cognitive difficulties and fatigue), RTW-related decision-making, resource navigation, and the reintegration of daily activities [4,21]. As for the intensity of interventions that should be offered, it is mentioned that nearly 50% of affected individuals require more assiduous support due to the presence of persistent side effects [34], such as severe fatigue or physical limitations induced by lymphedema [35,36]. Moreover, studies have shown that women affected by breast cancer who have received chemotherapy treatments experience more difficulty during RTW due to persistent side effects [37-40]. This clientele therefore should receive personalized support for coping with the challenges of completing cancer treatments, including RTW.

RTW after cancer treatment is complex because it involves multiple stakeholders [41], including breast cancer survivors, health care professionals, employers, and insurer representatives, who come from multiple settings and have divergent concerns, constraints, and resources. The available interventions that support RTW after cancer treatment have proven to be insufficient in connecting workplace stakeholders and addressing RTW-related coordination challenges [20,27]. Our project aims to develop a supportive RTW intervention to address the current lack of coordinated, interdisciplinary interventions offered in primary care. Based on current evidence, it is imperative to develop new interventions to support the RTW of breast cancer survivors. These interventions should have several characteristics that align with the Medical Research Council

criteria [42]. As such, these interventions will be complex, especially given the variety of the intervention components needed, the interactions between these components, the number of people or organizational levels involved, the degree of flexibility required, and the need for the ability to adapt to specific contexts. The development of a complex intervention requires several phases that do not follow a linear sequence [42]. To address this complexity, it is advisable to combine theoretical, empirical, and experiential approaches when designing interventions [43]. However, these approaches are time-consuming, and it is difficult to address all of the issues related to implementing interventions [44]. To engage stakeholders and achieve contextually appropriate intervention components, our project will involve a coideation process for developing an RTW intervention and its components through a co-design approach. This novel methodological approach to developing RTW interventions brings together cross-sectoral stakeholders, including health care professionals, employer and insurer representatives, and breast cancer survivors. The components of interventions can be difficult for stakeholders to understand, and such components can be difficult to contextualize during the development process. The co-design approach is therefore appropriate, as it was developed so that stakeholders can actively participate in a process of coideation for the interventions that are dedicated to them. The proposed approach differs from others because it offers the possibility for all participants to cocreate and negotiate ideas simultaneously, starting from the beginning (conceptual phase) of the co-design process [45]. Another characteristic of the

approach is the presence of design professionals who facilitate the coideation process [46] by making graphic representations that are adapted to the participants to support the creative process. Finally, coideation has proven to be an innovative approach that has several potential benefits. First, coideation allows for the creation of an intervention without preconceived ideas. Second, the creation of an intervention can be faster, allowing for quicker testing in a pilot study context. This provides better direction for subsequent developments.

Given the need for support among breast cancer survivors, the inherent challenges of RTW, and the complexity of intervening to support RTW, there is a need to coconstruct a coordinated, interdisciplinary intervention with RTW stakeholders that is offered by a primary care team. To achieve this, we propose a co-design approach. The goal of the study is to develop and test a pilot intervention for supporting RTW after breast cancer treatment. The intervention will be offered by a primary care team. The objectives are to (1) develop an innovative intervention in collaboration with key stakeholders, (2) test the intervention with a primary care team, and (3) determine the acceptability and feasibility of the intervention in a primary care setting.

Methods

The project is divided into the following two phases: the development of the pilot intervention and the feasibility assessment (Figure 1).

Figure 1. Study design. RTW: return to work.
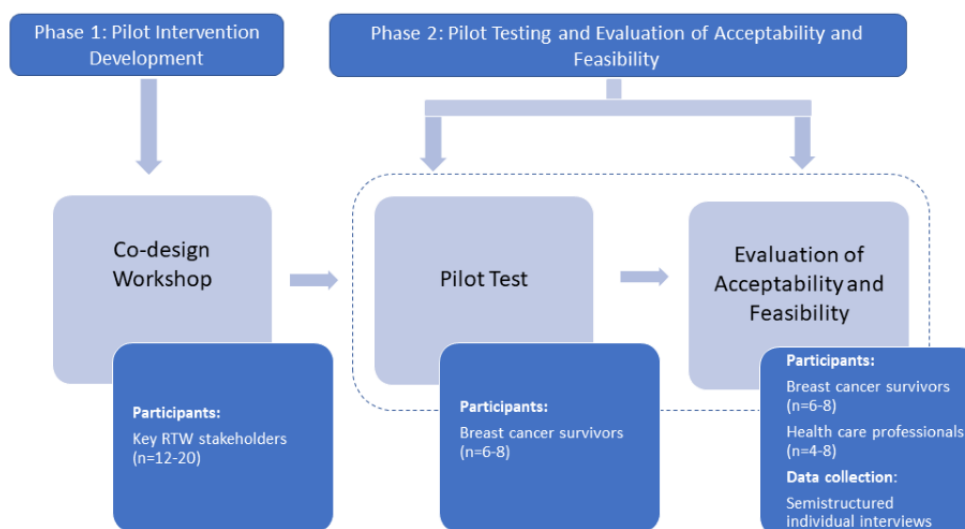
Phase 1: Pilot Intervention Development

Study Design

A participatory action research design [47] and a co-design approach [48] will be used. A participatory action design engages researchers and participants in a reflective process when they seek solutions [47,49]. In addition, it encourages the partnership between researchers and stakeholders throughout the research process. Participatory research makes it possible to produce useful and precise knowledge that is consistent with

the realities of key RTW stakeholders. The synergy created in partnerships allows for studies that are both culturally appropriate for target audiences and logistically realistic [50]. The development of the pilot intervention will be inspired by the reflexive cycle—a key part of the participatory approach that encourages describing and defining observations, analyzing and interpretating ideas, and finding solutions [49,51]. In our case, the solutions will be creative and innovative. This process will take place during a co-design workshop with key stakeholders. Co-design allows people to actively participate in a process of coideation for finding innovative solutions,

during which they can simultaneously participate in the cocreation process at the beginning of a project by following a democratic and multidisciplinary perspective [48].

Population and Recruitment

A variety of participants (n=12-20) representing key RTW stakeholders will participate in the codevelopment of the pilot intervention. For this phase, snowball sampling will be conducted [52]. All participants must speak French and be aged ≥18 years. To be selected for the codevelopment phase, breast cancer survivors must have experienced RTW after cancer treatments for at least 1 year, employer or insurer representatives must have at least coordinated or accompanied the RTW of a woman affected by breast cancer, and health care professionals must have previously provided support to a woman with breast cancer during either oncology or primary care. Participants will be approached through the research team's professional networks. This strategy is appropriate, given the nature of the interactive activity and the need for participants to be engaged and involved in the RTW journey. These are features of some participatory and co-design approaches [53].

Sequence of the Co-design Workshop

In preparation for the workshop, a 10-minute informational video will be sent to participants. This video will present the current knowledge regarding RTW for cancer survivors as well as recommendations from research. By using the Zoom platform (Zoom Video Communications Inc), a co-design workshop will be held over 4 hours. Participants will be informed that the purpose of the workshop is to co-design components of a pilot intervention that will be performed by a primary care team to address the issues faced by survivors who RTW after breast cancer treatment. Further, 3 case scenarios that represent the potential issues of RTW after breast cancer treatment will be presented to participants. Because the workshop will include key RTW stakeholders, the scenarios will serve as a "representative artifact," that is, a deliberation strategy involving interactions between public participants and health professionals that encourage exchanges via a common and appropriate language [54]. Participants will also be guided through the following two dimensions of intervention: the assessment of cancer and treatment side effects and RTW discussion and planning. Instead, participants will be invited to think of novel solutions.

During the workshop, participants will interact in plenary and breakout sessions. Further, 2 to 4 diverse subgroups will be created, depending on the number of participants and the representativeness of the RTW stakeholders, for activities in a breakout room. Each subgroup will be accompanied by a facilitator and a design professional who will help to frame the discussions. The facilitator will be a postdoctoral fellow or a graduate student from an undergraduate design program (eg, industrial design). The involvement of design professionals is recommended for health science initiatives [46]. As presented in Table 1, the workshop will be divided into the following five steps: (1) the reframing of the problem, (2) immature coideation, (3) mature coideation, (4) the presentation of subgroup solutions, and (5) the debriefing of the workshop experience. In step 1, participants will be invited to discuss the problem of RTW after cancer treatment. The facilitator can refer to the case scenarios and frame the discussions to raise priority issues. In step 2, participants will be asked to develop solutions. The facilitator will assist the participants in developing solutions that are relevant to issues that were identified earlier and representing them graphically (eg, diagrams and drawings). At this stage, the ideas are to be formulated but not yet fully developed. In step 3, participants will be invited to fully develop the solutions that they find the most important, in some cases by making more detailed graphic representations. At this stage, specific details will be offered by participants in each subgroup with regard to the implementation or components of the selected solutions. In step 4, a plenary discussion will be held to summarize the work of each subgroup. Finally, in step 5, the workshop will end with a debriefing on the participants' perceptions of the positive and negative aspects to be retained or considered for the repetition of the workshop. Of note, throughout the workshop, participants will make use of a graphical representational ecosystem (eg, drawings and digital sketches) [55], along with the verbal exchanges, to externalize their ideas and discuss proposals more clearly. In addition, subgroup discussions can be structured by using the following key principles of design conversation [48,56]: (1) naming the problem, (2) constraining the ideas, (3) proposing the ideas (the key element), (4) negotiating the ideas through questioning and explaining, (5) making decisions, and (6) making design advances with graphical representations. This approach keeps discussions focused on a common goal and ensures that stakeholders collaborate within a limited time frame during all of the workshop stages. The activity will take place on the internet due to the current pandemic context and will be conducted by using the Miro platform (Participatory Culture Foundation; Figures 2-4). A pretest of the workshop will be conducted with students before the activity.

The workshop will be recorded, and explicit notes will be written verbatim. The deliverable at this stage will be the general guidelines for an intervention that supports RTW after breast cancer treatment. The intervention will be designed so that it is fit for use in primary care settings.

Table 1. Sequence of the co-design workshop.

Activities and steps	Length (total: 235 minutes)
Welcome and introduction	• 10 minutes (plenary session)
Step 1: reframing the problem	• 30 minutes (subgroup session) • 15 minutes (plenary session)
Transition and breakout room integration	• 5 minutes
Step 2: immature coideation	• 30 minutes (subgroup session) • 15 minutes (plenary session)
Break	• 15 minutes
Step 3: mature coideation	• 30 minutes (subgroup session) • 15 minutes (plenary session)
Transition and breakout room integration	• 5 minutes
Step 4: presentation of subgroup solutions	• 30 minutes (plenary session)
Transition and breakout room integration	• 5 minutes
Step 5: debriefing the workshop experience	• 30 minutes (plenary session)

Figure 2. Miro interface for "Reframing the problem."

Figure 3. Miro interface for "Immature coideation."
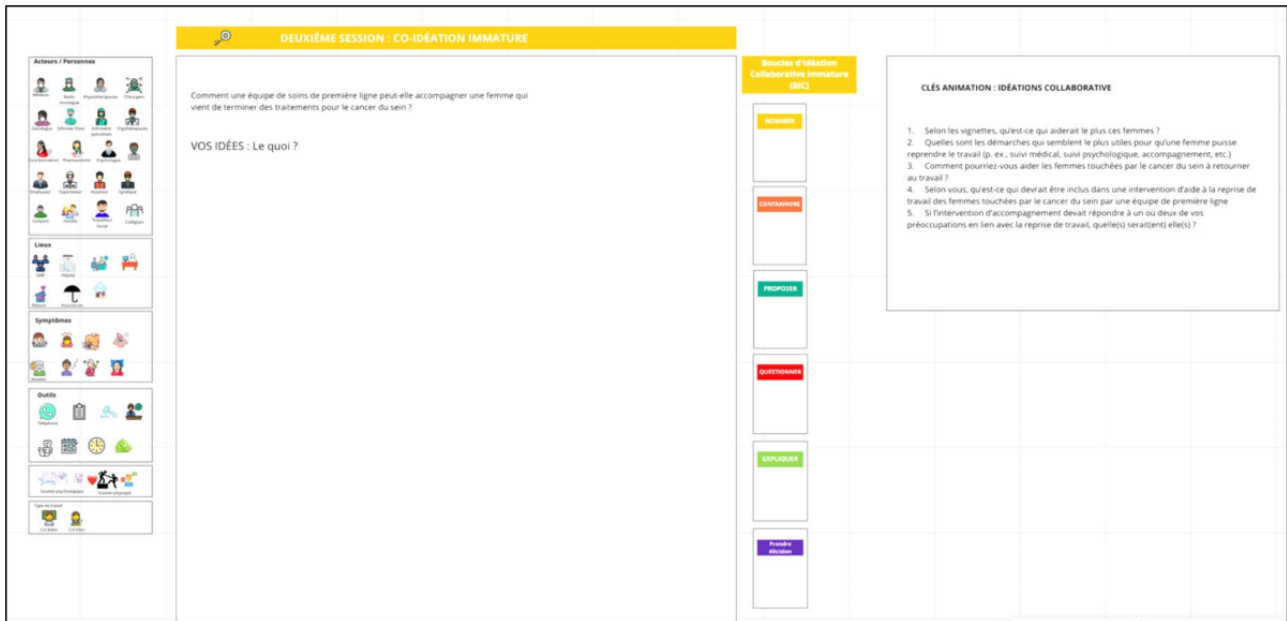
Figure 4. Miro interface for "Mature coideation."

Phase 2: Pilot Test and Evaluation of Acceptability and Feasibility

The pilot intervention will be delivered by a primary care team and patient partners who will be trained in the intervention. A resource person will be available to answer their questions or provide coaching during the project.

Population and Recruitment

By using purposive sampling [57], 6 to 8 breast cancer survivors will be recruited to test the pilot intervention. The selection criteria will include women aged 18 to 60 years; those who have completed breast cancer treatments, such as surgery, chemotherapy (doxorubicin, cyclophosphamide, and paclitaxel), and radiation therapy; and those who are planning to RTW within the next year. Surgeon oncologists will help with

targeting potential participants who are nearing the completion of their cancer treatments.

Evaluation of Acceptability and Feasibility

At the end of the project, the acceptability and feasibility of the pilot intervention will be measured by conducting semistructured individual interviews with participants (n=6-8) and health care professionals, as well as patient partners who participated in the intervention (n=4-8). The use of qualitative interviews is recommended during a feasibility study [58]. The interview guide and analysis will be based on the Theoretical Framework of Acceptability [58], which explains that acceptability is a multidimensional construct with 7 components. Specifically, the interview questions will address (1) affective attitudes toward the intervention, (2) the effort required to complete the intervention, (3) consistency with the individuals' values, (4) individuals' understanding of the intervention and how it works, (5) the perceived benefits provided by the intervention, (6) perceived efficacy, and (7) the perceived ability to complete the intervention. The interview guide will be pretested with 2 people who have the same characteristics as those of the participants.

Data Analysis

The transcribed interview will undergo an iterative content analysis, which will include the following activities: condensation, data presentation, and the development and verification of findings [59]. Further, 2 team members will conduct the coding process. The data from the breast cancer survivors will be contrasted to highlight similarities and differences in experiences with the pilot intervention. The same exercise will be conducted for the health care professionals. In addition, to validate the emerging findings, a discussion with the coresearchers will be conducted throughout the research process. This discussion will consider the data transcripts and field notes. NVivo software (QSR International) will be used for qualitative data management. To ensure the quality of the study, techniques such as data triangulation will be used to ensure internal credibility and validity. Further, we will validate some of the participants' data to ensure their reliability, assess the procedural documentation of the research process to determine accountability, and provide a detailed description of the context to ensure external transferability and validity [59].

Ethics Approval

Ethics approval was granted in May 2021 for the first component of the project (Centre intégré universitaire de santé et de services sociaux de l'Est-de-l'Île-de-Montréal; project number: #2022-2610).

Results

The project received funding in March 2021. The co-design workshop took place on June 16, 2021. A total of 11 people participated in the activity. The transcripts of the discussions were analyzed and helped to target the following intervention themes for intervention development: (1) mitigating the assessment and self-management of side effects, (2) assessing RTW needs and abilities, and (3) communicating with the employer. The clinical tools for the intervention (questionnaire

and decision support tree) and the intervention logic model remain to be finalized. The preliminary results suggest that the pilot intervention should take place in a primary care setting in the Montreal area (Quebec, Canada). It is anticipated that 3 meetings will occur at 1, 4, and 6 months after treatment is completed [21]. During these meetings, a health professional will analyze RTW challenges and may propose solutions that are tailored to women's needs. The intervention will include pairing participants with patient partners who will be able to answer the participants' questions and share their RTW experiences [60]. Depending on the pandemic context of COVID-19 in Canada, recruitment will begin in spring 2022.

Discussion

Principal Results

In brief, the project will allow us to document the relevance of an RTW intervention that is delivered by a primary care team. The shared views of patients and health care professionals will help us determine the feasibility and acceptability of the intervention. In addition, the project will offer methodological recommendations for the use of a co-design approach in intervention development. More specifically, the project will have clinical, methodological, and organizational benefits.

On the clinical level, the primary outcome of the project is the development of a program that supports RTW and is based on the perspectives of RTW stakeholders, including breast cancer survivors [41]. Only a few European studies have mobilized these actors for the development of RTW interventions for patients who have completed cancer treatments [61,62]. The participatory approach that will be used in the project properly contextualizes the intervention to a Canadian context. This should facilitate implementation in the second phase of the study. The results of the pilot project will also provide information for improving the intervention before large-scale implementation, which will make it possible to evaluate its effects. The project will also offer an initial solution for women affected by breast cancer who need support [63] but are not covered by current health services [21]. Indeed, it is more urgent than ever to address the issues of RTW after cancer treatment to limit the development of disabilities, particularly as work is a known determinant of health and social participation is beneficial to individuals [17,63]. Additionally, and perhaps more broadly, RTW-related disabilities result in considerable consequences that also affect society as a whole [64-66], especially when absences are prolonged over time [64]. Fostering RTW is therefore essential, especially in the context of an aging population and labor shortages [67].

In terms of methodology, the project will explore an innovative and participatory approach that is perfectly suited to the trend of including patients and those who are involved in creating interventions (eg, a patient-centered research strategy [68]). To engage patients and partners, the use of approaches that have been adapted from design-related approaches [46] (eg, experience-based design [69] and Hacking Health hackathons [70]) has become increasingly common in health care. These approaches are appreciated and are essential, given the complexity of the interventions that are to be developed in health

care [42]. That said, many deplore the time and investment required to complete such processes [71,72]. Our project addresses this concern via the use of a structured co-design ideation approach to develop innovative and robust solutions within a reasonable time frame. Through this approach, we will be able to decrease intervention development time, increase cross-sectoral stakeholder participation, and make the intervention creation process more efficient. The coideation process will promote the creation of robust solutions for effective implementation and result in a decrease in the time required for the intervention creation cycle (ie, from ideation to implementation). The new data provided by our project will facilitate the development of new interdisciplinary interventions that benefit clientele in various health care settings.

This protocol is the first to propose a pilot RTW intervention for patients who have completed cancer treatments that will be delivered by a primary care team. It is widely documented that the supply of care after cancer treatment is inadequate [21,73,74]. It remains difficult to provide services to people affected by cancer beyond specialized oncology services, despite numerous international recommendations [75]. It is hoped that our RTW-themed project will encourage health care professionals and employers to commit to its goals and principles by demonstrating that the intervention will be acceptable to participants and consistent with the mission of primary care teams (ie, promoting health and preventing disease). The project will thus offer new data on the feasibility of offering this follow-up intervention in a primary care setting.

Anticipated Challenges and Limitations

This protocol is proposed in a Canadian context (province of Quebec). In Canada, health care is free and primary care services are readily accessible to the general population. It should be noted that the majority of Canadians affected by cancer have paid sick leave included in their private insurance contracts [16]. Many people, including those without private insurance, only have access to 15 weeks of compensation from the Canadian government. Moreover, with regard to RTW after cancer treatment, no agreement has been reached with employers, and no legislation has been created, as is the case in France. This protocol must therefore be interpreted in this context. Furthermore, the evaluation of feasibility and acceptability will be based on a few qualitative interviews. The number of interviews should be sufficient, that is, from a scientific point of view [76], for documenting whether the intervention is feasible in this context. Finally, the pandemic context of COVID-19 may limit the testing of the project. Primary care teams are facing the off-loading of their professionals to other areas, including those that require vaccination efforts. To mitigate these effects, we will rely on the support of primary care physicians; oncology specialists; and members of the research team (DL and LLD), who are also clinicians. Despite the unfavorable context, health care professionals have reiterated their willingness to move forward, which demonstrates the relevance of the project and the interest of the health care organizations.

Conclusions

This protocol proposes to develop and test an intervention that supports RTW after breast cancer treatment and is delivered by a primary care team. The project will provide novel data on the use of a co-design method for the development of complex interventions. In addition, the results of the project will allow us to better document the acceptability and feasibility of the intervention, which will be delivered by a primary care team. Depending on the results obtained, the project could be tested on a larger scale.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review reports.
[PDF File (Adobe PDF File), 626 KB - resprot_v11i4e37009_app1.pdf]

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Abbreviations

RTW: return to work

Protocol

Investigating New Sensory Methods Related to Taste Sensitivity, Preferences, and Diet of Mother-Infant Pairs and Their Relationship With Body Composition and Biomarkers: Protocol for an Explorative Study

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Abstract

Background: Early experiences with different flavors play an important role in infant development, including food and taste acceptance. Flavors are already perceived in utero with the development of the taste and olfactory system and are passed on to the child through breast and bottle feeding. Therefore, the first 1000 days of life are considered a critical window for infant developmental programming.

Objective: The objective of our study is to investigate, both in the prenatal and postnatal period, taste sensitivity, preferences, and dietary diversity of mother-infant pairs. The explorative study design will also report on the impact of these variables on body composition (BC) and biomarkers. In contrast to conventional methods, this study involves long-term follow-up data collection from mother-infant pairs; moreover, the integration of audiovisual tools for recording infants' expressions pertaining to taste stimuli is a novelty of this study. Considering these new methodological approaches, the study aims to assess taste-related data in conjunction with BC parameters like fat-free mass or fat mass, biomarkers, and nutritional intake in infants and children.

Methods: Healthy pregnant women aged between 18 and 50 years (BMI≥18.5 kg/m^2 to ≤30 kg/m^2; <28 weeks of gestation) were recruited from January 2014 to October 2014. The explorative design implies 2 center visits during pregnancy (24-28 weeks of gestation and 32-34 weeks of gestation) and 2 center visits after delivery (6-8 weeks postpartum and 14-16 weeks postpartum) as well as follow-up visits at 1, 3-3.5, and 6 years after delivery. Data collection encompasses anthropometric and biochemical measurements as well as BC analyses with air displacement plethysmography, taste perception assessments, and multicomponent questionnaires on demographics, feeding practices, and nutritional and lifestyle behaviors. Audiovisual data from infants' reactions

to sensory stimuli are collected and coded by trained staff using Baby Facial Action Coding and the Body Action Posture System. Birth outcomes and weight development are obtained from medical records, and additional qualitative data are gathered from 24 semistructured interviews.

Results: Our cohort represents a homogenous group of healthy women with stringent exclusion criteria. A total of 54 women met the eligibility criteria, whereas 47 mother-child pairs completed data collection at 4 center visits during and after pregnancy. Follow-up phases, data analyses, and dissemination of the findings are scheduled for the end of 2023. The study was approved by the ethics committee of the Medical University of Graz (EC No 26–066 ex 13/14), and all participants provided informed consent.

Conclusions: The results of this study could be useful for elucidating the connections between maternal and infant statuses regarding diet, taste, biomarkers, and prenatal and postnatal weight development. This study may also be relevant to the establishment of further diagnostic and interventional strategies targeting childhood obesity and early body fat development.

International Registered Report Identifier (IRRID): DERR1-10.2196/37279

KEYWORDS

Introduction

Background

Many factors contribute to the development of overweight and obesity. Based on the work of Barker and Osmond in 1986 [1], recent research indicates that the risk of becoming overweight or even obese may be programmed during the prenatal and early postnatal phase. Besides genetic and hormonal factors, at the prenatal stage, the maternal environment further influences growth and can alter tissue function. To date, only limited data are available concerning prenatal and postnatal biomarkers predicting metabolic programming [2]. However, there is strong evidence that women's prepregnancy weight and weight gain in early pregnancy are influential factors for infants' birth weight and body composition (BC) [3,4]. Studies suggest that a healthy maternal diet and balanced nutritional status before and during pregnancy as well as physical activity have positive effects on preventing excess gestational weight gain (GWG) and a sustained impact on infants' and adults' health [5-7].

Therefore, the prenatal and early postnatal periods, particularly the first 1000 days from conception, are critical, wherein changes in maternal lifestyle may have far-reaching impacts [8]. The biological predispositions for sweet foods, aversion to bitter-tasting foods, and liking for salty foods in infants and children are well known [9-11]. However, taste preferences may be programmed in utero, could be modified early in life, and may play an important role in food choices later in life [11-15]. During the prenatal phase, taste buds recognizing and transmitting information to the central nervous system develop in the last trimester [16]. Maternal dietary diversity contributes to the intrauterine environment that is rich in flavors transmitted from the maternal diet to the amniotic fluid [17-19] and mother's milk composition [20]. To identify early hedonic responses to taste stimuli in infants, studies used modified facial behavior methods, such as the Baby Facial Actions Coding System (BabyFACS), to quantify taste-elicited facial expressions in infants and their relationship to their mothers' diet and feeding behavior [21,22].

Breastfeeding is associated with positive effects on later eating habits [23,24], adequate weight gain during infancy, and a moderately lower risk for childhood obesity [25,26]. Previous data showed that during the milk-feeding period, flavor stimulation may enhance later food acceptance. Compared to formula-fed infants, breastfed infants are more likely to accept new tastes in early childhood [27], reinforcing the effect of variety early in weaning [17,28,29]. For example, fetuses who were exposed to carrot juice for 3 consecutive weeks during the last trimester of pregnancy and during the first 2 months of lactation showed a less negative response to carrot-flavored cereals compared to plain cereals. No such preference was observed in nonexposed fetuses [17]. Thus, predispositions and preferences can be modified early through repeated exposure to flavors in amniotic fluid, mother's milk, formula, and solid foods [30]. However, the underlying mechanisms for possible protection against later obesity by breastfeeding and the influence of early feeding practices should be further explored [31], especially to enhance the understanding of how preferences can be modified to promote a healthy diet for children [32].

Owing to the multifactorial process involved in becoming overweight or obese, sensory taste characteristics like taste preferences and sensitivity may be contributing factors. Children are reportedly predisposed to prefer food high in energy, sugar, and salt, and this contributes to the interaction between taste and fat perception, thus influencing their food intake and weight status [33,34]. The association between fat and sweet taste preferences, and weight status was determined in European children, with the odds of 50% being overweight or obese, when fat-added crackers or sugar-sweetened juices are preferred to natural crackers or natural juices by children [35-37]. There are considerable efforts focused on examining maternal lifestyle and nutritional behavior in relation to children's and mothers' health outcomes regarding overweight and obesity [38,39]. However, further long-term research considering various impacts and using new methodological approaches is needed to obtain taste-related data on BC, weight, and nutritional intake in infants and children [34,40].

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Objectives

The overall aim of the study is to explore new methods on taste-related dietary preferences and its association to anthropometric and biochemical parameters as well as the long-term impact on programming in utero and during early infancy. Therefore, the specific objectives are as follows:

1. To assess the prenatal data of pregnant women, including taste sensitivity and preferences, dietary intake, weight development, physical activity, and biochemical parameters; and postnatal data of mothers and their children, including taste sensitivity and preferences, dietary intake, feeding practices, weight development, BC, biochemical parameters, and lifestyle factors like physical activity, smoking, alcohol consumption, sleep, and stress perception

2. To apply new sensory methods like BabyFACS and Body Action Posture System to quantify taste-elicited expressions in infants and their relationship to their mothers' diet and feeding behavior

3. To investigate the development of anthropometric outcomes and BC like fat-free mass (FFM) or fat mass (FM); the relationship between taste sensitivity, preferences, and dietary intake, habits, and preferences; and the association of several biochemical parameters of mothers and their children with the anthropometric outcomes, BC, taste sensitivity, and dietary preferences and habits

Methods

Study Design and Population

This study is an ongoing prospective longitudinal study involving 57 healthy pregnant women (≥18 years) and their offspring, with an embedded qualitative design, performed at the Health Perception Lab, a laboratory for health-relevant sensory research in Graz, Austria. The recruitment and enrollment process for low-risk pregnant women lasted from January 2014 to October 2014 in a prenatal clinic at the Styrian State Health Insurance Fund, where women underwent an oral glucose tolerance test (<28 weeks of gestation). During this visit, all pregnant women were informed in person about the study details and were given written information with contact details. To support the recruitment of participants, the study was additionally advertised on social media channels such as Facebook, on the website and in the emails of the FH JOANNEUM University of Applied Sciences and the Medical University of Graz, as well as in newspapers between January and October 2014. All documents for recruitment like posters, information folders, and advertisements were submitted for ethics approval by the review board of the Medical University of Graz.

The main inclusion criteria were pregnancy less than 28 weeks, unobtrusive oral glucose tolerance test, nonsmoking, BMI≥18.5 kg/m^2 to ≤30 kg/m^2, age between 18 and 50 years, and written informed consent. Detailed inclusion and exclusion criteria for the study are shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria of the study.

Inclusion criteria

- Pregnant women 18 to 50 years of age
- Pregnancy <28 weeks from gestation
- Written informed consent
- Prepregnancy BMI≥18.5 kg/m^2 to ≤30 kg/m^2
- Unobtrusive oral glucose tolerance test

Exclusion criteria

- Birth before the 37th week or after the 42nd week of gestation
- Multiple pregnancies
- Children with severe congenital malformations or diseases
- Congenital metabolism disorders
- Drug abuse
- Drug-administered mental illnesses
- Metabolic diseases of the mother (eg, thyroid disorders)
- Autoimmune diseases of the mother (eg, Crohn disease)
- Birth complications (postpartum hemorrhage>1000 mL or eclampsia)
- Preconceptional diabetes (type 1 or 2)
- Celiac disease and wheat protein allergy of the mother
- Breast surgery and hypomasty

Based on our strict inclusion and exclusion criteria, 3 of the 57 recruited women were excluded from the study. Therefore, a total of 54 women were eligible to participate in 2 center visits during their pregnancy, the first between 24 and 28 weeks of gestation (TP1) and the second in the third trimester of pregnancy, preferably between 32 and 34 weeks of gestation (TP2). Further, 2 visits were conducted with the same mother-infant pairs between 6 and 8 weeks (TP3) and between 14 and 16 weeks after delivery (TP4). The study participants are subsequently followed-up by (1) an internet-based questionnaire survey and a stool sample 1 year postpartum (FU1) and (2) a center visit to the laboratory with the mother-infant pairs at 3 to 3.5 years (FU2) and 6 years after

delivery, including an extended web-based questionnaire survey (FU3), scheduled until the end of 2022. For the qualitative approach, 1 year after delivery, a purposive sampling strategy was used to record a wide variety of experiences and perspectives to obtain greater insights into women's attitudes and beliefs regarding lifestyle changes. Within the first-year follow-up, qualitative semistructured interviews were conducted with a subsample of 24 women from the study population. Sociodemographic factors like income, educational and migration background, and age as well as further gravidity were considered and self-reported by the participants at the first center visit and updated regularly (Figure 1).

Figure 1. Study outline and time points of measurement.
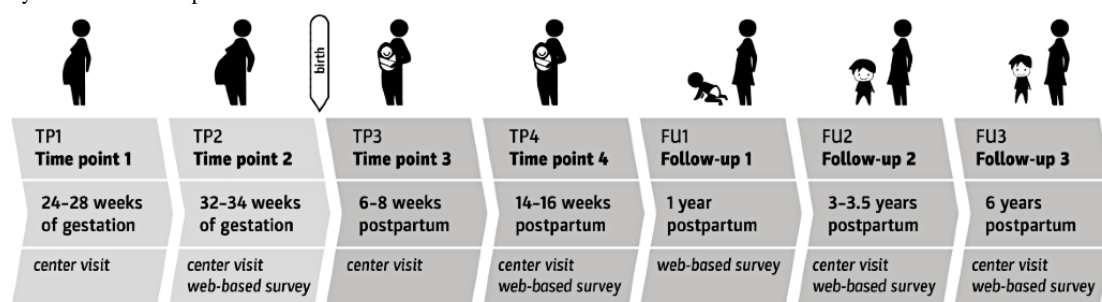
Ethics Approval

The study protocol was approved by and registered with the ethical review board of the Medical University of Graz (EC No 26-066 ex 13/14). All participants were informed in detail about the procedures and measurements by a medical doctor and they provided written consent. Access to the generated data is restricted to the immediate research team, and only coded data stored on a secure internal server of the FH JOANNEUM University of Applied Sciences are used for analysis.

Sample Size

We decided the number of participants for our study based on studies where sample sizes reached approximately 50-70 persons [21,40]. Additionally, feasibility reasons and recruitment experiences were considered for the laboratory setting and geographical region. Thus, we aimed to include up to 60 women.

Data Collection

This study is conducted by an interdisciplinary team of dieticians, midwives, health scientists, information managers, nutritionists, statisticians, and biomedical analysts. Data were collected by trained health professionals twice during pregnancy, during the second and fourth month postpartum, and within the follow-up phase at 1, 3 to 3.5, and 6 years after delivery. Data collected during each stage included anthropometry, questions about health, and smoking and drug status, as well as changes regarding sociodemographic information.

Methods of Measurement

Anthropometry and BC

Maternal prepregnancy BMI was calculated from the height measured with a stadiometer (seca 213, seca) without shoes, and the prepregnancy weight was obtained from the medical

records or was self-reported at the first study visit to the laboratory. All the data on weight during pregnancy were obtained from the medical records (national mother-child booklet), whereas weight measurements after delivery were collected with a calibrated scale (seca 877, seca), with the participants lightly dressed and not wearing shoes. GWG was determined by subtracting the women's prepregnancy weight and, if not available, the early first trimester weight from their last measured weight before delivery.

The infants' length, weight, head circumference, and BC were collected in the laboratory by trained midwives. The BC, FM, FFM, and weight at TP3 and TP4 were assessed using air displacement plethysmography (ADP)(PEA POD, COSMED). Length was measured with a mobile measuring board (seca 210, seca) and head circumference with a nonflexible head circumference tape measure for infants (seca 212, seca). The BMI, fat mass index (FMI), and fat-free mass index (FFMI) were calculated in kg/m² by the system using the following equations: BMI = body mass (kg) / (body height [m])², FMI = fat mass (kg) / (body height [m])², and FFMI = fat-free mass (kg) / (body height [m])².

Follow-up data collection of the BC is ongoing for the mother-child pairs, and it is measured by ADP (BOD POD, COSMED). Additionally, triceps skinfold thickness measurements of the children are performed by trained nutritional experts using a Harpenden Skinfold Caliper in triplicate on the left arm with the arm slightly bent. In addition, the upper arm circumference of the child is determined using a tape measure. Further data on the weight, length, and head circumference at birth and beyond are being obtained from medical records.

Taste Perception and Facial Expression

As a measure of taste sensitivity threshold, tests for sweet and salty tastes were performed with women at TP2 and after delivery at TP3 and TP4. To keep the time burden low for participants, simplified, modified versions of the original DIN ISO 3972 and the Busch-Stockfisch version (2012) were used. The aqueous solutions were prepared according to DIN ISO 3972 using sucrose and iodine-free sodium chloride. The number of samples for the determination of taste sensitivity was modified from 10 to 5 for each stimulus, whereby the concentrations were not changed. Each sample was prepared from the respective stock solution (50 g sucrose/500 mL; 25 g sodium chloride/250 mL). Sensory tests were performed under standardized conditions in sensory booths to keep external influences as low as possible.

Preferences for the sensations of fat, sweet and fat, and salt and fat were assessed in women by making them taste crackers. Pretests aimed to find a common and well-known food item that provided the potential for experimentally modifying the fat, sugar, and salt concentrations. Considering the storage and preparation possibilities, crackers were found suitable. The crackers contained wheat flour, water, refined plant oil, salt, and sugar in specified concentrations. The basic recipe was adapted from Knof et al [41]. The participants' preferences (sweet: sucrose-high 30% vs low 15 % and fat-15% each; salty: sodium chloride-high 2.5% vs low 1% and fat-15% each; fatty: fat-high 25% vs low 10 % and salt-0.7% each) were assessed by performing 3 pairwise comparisons of 2-alternative forced-choice tests with specified amounts of salt, sugar, and fat. Concentrations of sugar, salt, and fat content were selected according to the amounts derived from the available range of crackers in Austrian stores.

Infants' taste preferences for sweet and salt were assessed at TP3 and TP4. Droplets of aqueous solutions with different concentrations (low and high) of lactose (0.2 and 0.4 mL) and sodium chloride (0.085 and 0.17 mL) were administered by a researcher with a transparent 1 mL pipette while obtaining audiovisual recordings of the infants' reactions to the stimuli. To familiarize the infants with the test setting and method, 2 servings of water were used as the control condition. The infants' reactions were recorded by 2 video cameras (IDS 5241VSE-C-SD32, IDS Imaging Development Systems GmbH; AXIS 211M Network Camera, Axis Communications AB), a 3D camera (Microsoft Kinect), and by a microphone (Sennheiser ME 66, Sennheiser Electronic GmbH & Co. KG). The test setting is shown schematically in Figure 2.

Figure 2. Test setting for recording infants' expressions pertaining to taste stimuli.
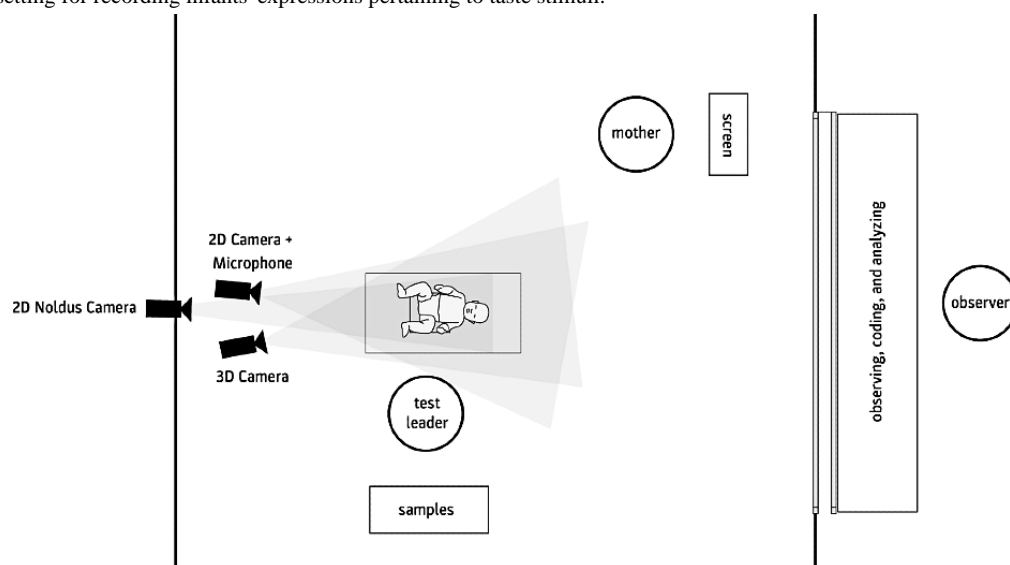
The infants' reactions to the stimuli were coded by 2 trained coders using BabyFACS [21,42] for facial movements as well as the Body Action Posture System for body movements [43,44]. After the 2 coders manually coded and detailed all the distinct facial action units that the infants produced, the correspondence was checked using an intraclass correlation coefficient. Automated emotion recognition using the Noldus FaceReader 5.0 software (Noldus Information Technology) was performed, and correlations with the coders' observations were calculated to validate its results. In addition, the assessments of the coders and FaceReader regarding the infants' reactions to the taste stimuli were validated through additional assessment by the mothers, who were present (yet prevented from interaction) during the testing period.

At FU2 and FU3, the taste preference tests for sweet crackers were performed with the mother-child pairs, as previously described. Additionally, because of the known connection between the perception of bitter taste and the consumption of high-fat or sweet foods [45], the bitter perception of 6-n-propylthiouracil (PROP) was tested with the mother-child pairs at FU2 and FU3. Therefore, a strip of thin filter paper was impregnated with a 0.56 mM PROP solution [46] and placed on the participants' tongue for a maximum of 20 seconds. Afterward, the subjects were asked about the perceived taste of the test strip. The so-called PROP tasters perceived the taste as negative (eg, bitter, sour, disgusting, spicy). Nontasters have no taste sensitivity to PROP [47,48].

The sensory preferences for specific food items rich in salt, sugar, and fat were additionally assessed by a recently developed

and validated questionnaire called PrefQuest [49]. PrefQuest was translated into German, typical food items were adopted to the Austrian region, and it was subsequently used with permission from Deglaire et al [49]. PrefQuest quantitatively recalled the participants' liking for the sensations of fat, fat-and-salt, and fat-and-sweet and includes four types of items: (1) liking for sweet, fatty-sweet, and fatty-salty foods, (2) preferences for the level of seasoning by adding salt, sweeteners, or fat, (3) preferences for the types of dishes on a restaurant menu, and (4) overall questions about sweet-, salt- and fat-related behaviors [49].

Laboratory Analyses of Biochemical Parameters

Maternal plasma and serum samples were taken at TP1 and TP2 during pregnancy and at TP3 and TP4 after delivery. Maternal breast milk was collected at TP3 and TP4. Stool samples from the mothers and children were collected at each of the center visits in the laboratory and from the children at the follow-up visits. Blood and breast milk samples were immediately stored at –20 °C until frozen and were then stored at –80 °C until analysis. Before analysis, all samples were kept at room temperature except the samples for the determination of eicosanoids, which were kept at 4 °C.

Eicosanoids

Blood eicosanoids were analyzed by liquid chromatography and mass spectrometry (DNA). The extraction was performed as described previously [50]. In brief, 500 μL plasma was immediately treated with 500 μL of 5% methanol/0.1% formic acid and spiked with 20 μL of internal standards (ISTDs, Cayman Europe, 95 nM). Compound extraction was performed with solid phase extraction using Oasis HLB (60 mg/30 μm, Waters). Samples were loaded onto the cartridges preconditioned with 2×1 mL methanol and equilibrated with 2×1 mL 5 % methanol/0.1 % formic acid. Each column was washed with 2×1 mL of 5% methanol/0.1% formic acid. The column was dried under vacuum and the eicosanoids were eluted with 2×0.75 mL volumes of methanol. The eluent was reduced to dryness under vacuum at 55 °C. The dried extract was subsequently reconstituted in 0.1 mL of methanol for measurement. Samples were analyzed by liquid chromatography (Agilent 1290, Agilent) coupled to electrospray ionization on a triple quadrupole mass spectrometer (Agilent 6460, Agilent). For analysis, 4 μL of the extract was injected at 5 °C. Chromatographic separation was achieved on a Waters BEH C18 column (Waters) using a flow rate of 0.4 mL/min at 40 °C during a 13-minute gradient (0-13 minutes from 25% B to 75 % B) using the solvents A, 0.1% formic acid, and B, 90:10 v/v acetonitrile/isopropanol. Electrospray ionization was performed in the negative ion mode. To detect the individual eicosanoids, dynamic multiple reaction monitoring (MRM) was performed with individually optimized MRM transitions. Data preprocessing, peak determination, and peak area integration were performed with Mass Hunter Quan (Agilent, Version B.06.00) whereas autointegration was manually inspected and corrected if necessary. The obtained peak areas of targets were corrected using appropriate ISTDs, and calculated response ratios were used throughout the analysis. Breast milk eicosanoids were determined at Lipidomix GmbH using liquid chromatography and mass spectrometry.

Gut Microbiota

Pea-sized human stool samples were collected in stool sample containers (containing 1 mL RNAlater solution) and stored at –20 °C. DNA was extracted using the MagNA Pure Bacterial DNA Kit (Roche) following the manufacturer's recommendations. Next-generation sequencing (Ion Torrent 318, Thermo Fisher Scientific) and phylogenetic as well as statistical analyses were performed in the Laboratory of Diagnostic Genome Analysis at the Institute of Pathology, Medical University of Graz, Austria. In brief, next-generation sequencing was performed with Ion Torrent 318 chips. Sequencing reactions were performed on Ion Torrent PGM using the Ion 400BP Sequencing Kit (all reagents from Thermo Fisher Scientific). Sequences were split by barcode and transferred to the Torrent Suite server. Unmapped BAM files were used as inputs for bioinformatics. All sequences were initially trimmed by a sliding window quality filter with a width of 20 nucleotides and a cutoff of Q20. Reads shorter than 100 nucleotides and reads mapping to the human genome were removed using deconseq [51]. The resulting reads were subjected to error correction using the Acacia tool [52] leading to error correction of 10%-20% of the reads. Subsequently, polymerase chain reaction chimeras were removed by the usearch algorithm in de-novo and reference-based settings [53] and the final sequence files were analyzed using the QIIME 1.8 workflow script [54]. Operational taxonomic unit search was performed using the parallel_pick_open_reference_otus workflow script and the greengenes 13_8 reference database.

Lipid Parameters

Lipid parameters (total cholesterol, high-density lipoprotein, and triglycerides) were analyzed by enzyme immunoassay (DF27, DF48A, and DF69A, respectively) using the Siemens Dimension Xpand Clinical Chemistry Analyzer (Siemens Healthcare GmbH) according to the manufacturer's instructions (Siemens AG). Low- density lipoprotein was calculated according to the formula of Friedewald [55].

Hormones

The hormones estradiol and progesterone were analyzed using an enzyme immunoassay analyzer (Abbot Architect i2000SR, Abbott GmbH) and using reagent kits 7K7225 for estradiol and 7K7725 for progesterone.

Adipokines and Protein

A subset of adipokines (AFABP: BioVendor, RD191036200R; Leptin: BioVendor RD191001100, Modrice; Irisin: Phoenix Ph. Inc, EK_067-52; SFRP: Cloud Clone Corp, SEC842Hu; Hepcidin: DRG Diagnostics, Hepcidin-25-HS EIA) in serum and breast milk was determined by commercially available enzyme-linked immunosorbent assays. Adipokine concentration in breast milk was either expressed per mL of breast milk or was normalized to the protein content. Measurement of the protein concentration in breast milk was performed according to the method described by Bradford [56].

Amino Acid Profile

Amino acid profiles were determined from maternal serum and breast milk via ion exchange chromatography followed by postcolumn derivatization with ninhydrin. The measurement

was conducted at the University of Salzburg (University Clinic for Pediatrics and Adolescent Medicine) with the Biochrom 30+ Amino Acid Analyzer (Physiological System, Biochrom Ltd) according to the manufacturer's recommendations.

Behavioral Variables

Dietary Data

Maternal diet and eating behavior during and after pregnancy were assessed via (1) the valid and reliable Inventory for Eating Behavior and Weight Problems [57] and (2) a recently developed web-based administrable food frequency questionnaire, called the Health Pregnancy Lactation-Food Frequency Questionnaire (HPL-FFQ), before the second and fourth center visits. The HPL-FFQ underwent pretests and expert validation and included the frequency (per day, per week, per month, rarely, or never) and quantity of the consumed food and beverage items during the last 3 months. For validating HPL-FFQ, further data were obtained using a 24-hour dietary recall at TP2 and TP4. The estimation of energy intake and nutritional composition of food items from HPL-FFQ and 24-hour dietary recalls was performed using the nut.s nutritional.software (dato Denkwerkzeuge, version: 1.32.30, 2015). All questionnaires were mailed 3 to 4 days prior to the women's appointments and were checked for completeness during center visits TP2 and TP4. Additionally, the same questionnaires are mailed to the mothers in all follow-up phases.

The children's nutritional behavior is determined by internet-based questionnaires at FU2 and FU3 using (1) the Child Eating Behavior Questionnaire [58], (2) the Food Neophobia Scale [59], and (3) a food frequency questionnaire for children (CFFQ) for the last 3 months [60]. Furthermore, for validation for the CFFQ, mothers are asked to recall all food and beverages consumed by their toddlers in the past 24 hours while visiting the laboratory at FU2.

Feeding Practices

Data on breastfeeding practice and duration were recorded in detail after delivery, according to the definitions of the World Health Organization [61]. Furthermore, for evaluating the exclusivity of breastfeeding, questions were asked to determine the volume of breast milk compared to other fluid intakes. Questions regarding the kind of feeding, duration and frequency of the feeds, and supplement intake, like water, tea, or solid food, were asked in 24-hour and 7-day recalls at TP3 and TP4.

Additionally, maternal feeding characteristics were assessed using the Infant Milk Feeding Questionnaire [62] at TP3 and TP4 and the Child Feeding Questionnaire [63] at FU2 and FU3.

Health Behavior, Physical Activity, and Media Consumption

Dlugosch and Krieger's German-language General Health Behaviour Questionnaire (FEG) [64] was used to measure further behavioral factors of postpartum women regarding alcohol, smoking, sleep, and well-being or psychosocial stress.

To determine physical activity behavior during pregnancy, questions were asked about the frequency (0 to 7 days), duration (1 to 7 hours or more), and intensity (getting out of breath and sweating; every day to never). Physical activity in mothers was assessed using the International Physical Activity Questionnaire (IPAQ), a reliable and validated questionnaire [65]. For FU1, the web-based short version was used. The instrument assesses physical activity in the last 7 days with 7 items and records the activity considering different intensity levels: (1) vigorous-intensity activities, (2) moderate-intensity activities, (3) walking, and (4) sitting. Frequency (days/week) and duration (time/day) are recorded separately for each specific activity type. The long form of the IPAQ was provided at FU2 and FU3, asking details about walking and moderate- and vigorous-intensity physical activity at four intensity levels: sitting, walking, moderate intensity (eg, leisure cycling), and vigorous intensity (eg, running or aerobics). The continuous score is expressed as the median Metabolic Equivalent of Task (MET) minutes per week: MET level × minutes of activity × events per week. Data on the children's physical activity were collected during FU2 and FU3, according to questions from the Health Behavior in School Aged Children Questionnaire [66]. Furthermore, media consumption of children was surveyed through a question about daily use and duration reported by the mothers during FU2 and FU3.

Stress and Coping Assessment

The Stress and Coping Inventory was designed to reliably measure the current stress, the physical and psychological consequences, and its coping. Considering the subjective postpartum stress experience, 7 items were asked, each item covering an important area of life (finance, housing, workplace/training place, partnership, family and friends, disease, and life goals). At FU2 and FU3, the items regarding coping behavior were broadened [67].

Semistructured Interviews

The interviews took place during the period from September 2015 to February 2016 and were conducted face to face at a convenient venue suggested by the participants. After informed consent was obtained, all interviews were recorded with a voice recorder (Philips, Voice Tracer LFH0662). The topics covered in the semistructured interview schedule explored the effects of pregnancy and childbirth on the health behavior of mothers of 1-year-old children. To represent possible changes from prepregnancy to the current life situation, including the first year as a mother, the participants surveyed were asked to provide retrospective descriptions of their health behaviors and lifestyles, focusing on nutrition and exercise.

At the end of each interview, observation memos were written up by the researcher, including subjective impressions of the interview, disturbances, and other framework conditions. Additionally, frequently mentioned key topics were continuously outlined by the researcher. Subsequently, the 24 interviews were transcribed verbatim, following predefined transcription rules. An overview of the major components of the study such as time points, data, and instruments is presented in Table 1.

Table 1. Major components and instruments of the study.

Time point (TP)	TP1[a]	TP2[b]	TP3[c]	TP4[d]	FU1[e]	FU2[f]	FU3[g]
Data: instruments							
Screening for eligibility criteria and obtaining informed consent	✓	✓	✓	✓			
Demographics: structured questionnaire	✓				✓	✓	✓
Maternal health status and smoking: self-reported	✓	✓	✓	✓	✓	✓	✓
Maternal medical history: structured questionnaire	✓						
Maternal weight and height: medical records, weight scale, stadiometer, and self-reported	✓	✓	✓	✓	✓	✓	✓
Paternal weight and height: reported by mother	✓						
Pregnancy history: medical records and self-reported	✓	✓	✓	✓			
Medication treatment of the mother and child: reported by mother	✓	✓	✓	✓	✓	✓	✓
Birth history: medical records				✓			
Feeding practices: structured questionnaire, IMFQ[h], and CFQ[i]			✓	✓	✓	✓	✓
Infant's 24-hour and 7-day dietary intake: food recall reported by mother			✓	✓			
Maternal nutritional behavior: HPL-FFQ[j], IEG[k], and PrefQuest		✓		✓	✓	✓	✓
Maternal 24-hour dietary intake: food recall		✓		✓			
Nutritional behavior of child: CEBQ[l], FNS[m], and CFFQ[n] answered by mother						✓	✓
Anthropometric data of child: medical records, caliper, and reported by mother			✓	✓	✓	✓	✓
Body fat composition of child: ADP[o]			✓	✓		✓	✓
Body fat composition of mother: ADP						✓	✓
Blood and stool of mother: laboratory analyses	✓	✓	✓	✓		✓	
Breastmilk: laboratory analyses			✓	✓			
Blood and stool of child: laboratory analyses			✓	✓	✓	✓	✓
Urine of mother and child: laboratory analyses						✓	✓
Sensory taste perception of mother: threshold, preference, and sensitivity tests		✓	✓	✓		✓	✓
Sensory taste perception of child: threshold, preference, sensitivity tests, and video recording			✓	✓		✓	✓
Health behavior and stress perception of mother: FEG[p] and SCI[q]					✓	✓	✓
Maternal physical activity: IPAQ[r] and structured questionnaire		✓		✓	✓	✓	✓
Physical activity and media consumption of child: structured questionnaire answered by mother						✓	✓
Nutritional behavior: qualitative interview of mother					✓		

[a]TP1: first center visit between 24 and 28 weeks of gestation.

[b]TP2: second center visit in the third trimester of pregnancy, preferably between 32 and 34 weeks of gestation.

[c]TP3: first visit conducted with the same mother-infant pairs between 6 and 8 weeks.

[d]TP4: second visit conducted with the same mother-infant pairs 14 and 16 weeks after delivery.

[e]FU1: first follow-up involving an internet-based questionnaire survey and collection of a stool sample 1 year postpartum.

[f]FU2: a center visit to the laboratory with the mother-infant pairs at 3 to 3.5 years.

[g]FU3: visit 6 years after delivery including an extended web-based questionnaire survey.

[h]IMFQ: Infant Milk Feeding Questionnaire.

[i]CFQ: Child Feeding Questionnaire.

[j]HPL-FFQ: Health Pregnancy Lactation-Food Frequency Questionnaire.

[k]IEG: Inventory for Eating Behavior and Weight Problems.

[l]CEBQ: Child Eating Behavior Questionnaire.

[m]FNS: Food Neophobia Scale.

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[n]CFFQ: food frequency questionnaire for children.

[o]ADP: air displacement plethysmography.

[p]FEG: Dlugosch and Krieger's German-language General Health Behaviour Questionnaire.

[q]SCI: Stress and Coping Inventory.

[r]IPAQ: International Physical Activity Questionnaire.

Data Analysis and Dissemination

Quantitative data analyses will be performed using SPSS Version 27 (IBM Corporation). Baseline data will be presented descriptively. Continuous variables will be presented as means (with standard deviations). Categorical variables will be presented as absolute numbers and rates. Mean nutrition values are derived by participant-individual averaging. Parameters that are not normally distributed will be either log transformed or analyzed using nonparametric methods. Group comparisons will be performed using chi-square tests for categorical characteristics and t tests, ANOVA, or Mann-Whitney U tests for continuous variables. Correlation and regression analyses are used to investigate the association between various exposure variables of interest and the longitudinal outcomes. Furthermore, associations between the aforementioned parameters as well as the BMI of the children, the collected biomarkers, and children's taste perception, sensitivity, and preferences were investigated by explorative data analysis. Associations with maternal weight gain and the children's weight will be analyzed using ANOVA models adjusted for possible confounders. Relationships between the mothers' senses or preferences of taste during and after pregnancy and the children's taste preferences are shown in contingency tables. Univariate models will be established initially to explore the association between the exposure variables and each outcome. Effects of potential confounders are adjusted in the multivariable models.

Qualitative data will be analyzed using f4analyse, a tool for data coding, sorting, and categorizing. A thematic approach and triangulation with the quantitative data (if possible) will be used to identify themes informed by the methods of Braun and Clarke [68].

Analyses on taste-related data and their association with BC, weight, and food intake in mother-infant pairs are scheduled starting with the completion of FU3 by the end of 2022. Subsequently, the dissemination of the results obtained from the newly developed methods should be started first, for example, the validation of the HPL-FFQ. Findings on taste sensory methods related to nutrition, biomarkers, and BC should be published in peer-reviewed journals and presented at high-level conferences by the end of 2023. Therefore, dissemination of results will occur regardless of the outcomes (positive or negative).

Results

Out of the 57 recruited healthy women, 54 participated in the explorative pilot study, whereas 47 mother-child pairs completed data collection from 4 center visits. The follow-up phase is scheduled for the end of 2022. Data analysis and dissemination of the main findings should be completed by the end of 2023. This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the local ethics committee of the Medical University of Graz (EC No 26-066 ex 13/14). Written informed consent was obtained from all subjects. The study was funded by the Austrian Research Promotion Agency (FFG, grant 839098). The study contents have undergone peer review by the funding body and the funding sources were not involved in conducting the research and will not have any role during execution, analyses, interpretation of the data, or in the decision to publish the results.

Discussion

Overview

One of the many factors influencing dietary habits are sensory experiences, with the possibility of shaping and modifying flavor perception and developing strategies for promoting healthy diet in children with a positive food variety [30]. Several studies indicate that prenatal exposure and postnatal feeding practices, especially breastfeeding, have been associated with flavor stimulation and moderately lower childhood obesity [6,8]. To analyze the multifactorial process with respect to overweight or obesity, new methodological approaches that consider different influences are needed to study taste-related data and their association with BC, weight, and food intake in infants and children [34,40].

This paper focuses on the study protocol, providing details on the measurement methods. Assessing the mother's and child's taste perception, including audiovisual data and the BC at several time points, is an innovative approach and can provide insights into a different and scarcely explored field of health-related sensory research to prevent childhood and adult obesity development. Long-term data are collected and analyzed under standardized conditions in the prenatal period from healthy mothers, following strict inclusion and exclusion criteria, and in the postnatal period from mother-infant pairs by an interprofessional team to reveal insights for follow-up studies and provide an interdisciplinary understanding of the factors influencing food preferences and weight development in early life.

The anticipated main findings of the study should address the application of new sensory assessment methods using BabyFACS to identify taste-specific data in infants and its association with diet, BC-related biomarkers with a focus on eicosanoids, and fat-related indices like FMI and FFMI as well as the correlation of breast milk parameters with the infants' intestinal microbiota, which are potentially involved in the early prediction of the development of childhood overweight and obesity.

Potential Strengths and Limitations

This explorative study combines long-term quantitative and qualitative data collection of sensory, anthropometric, nutritional, and biochemical parameters of mother-infant pairs and is characterized by several strengths. First, the study population is small and homogeneous because of selection using strictly defined and comprehensive inclusion and exclusion criteria; the data are thoroughly documented with a follow-up period of 6 years. Nevertheless, the results need to be interpreted carefully, but the sample homogeneity and detailed descriptions provided by the participants are sufficient for exploratory analyses and method development. Thus, the development of an audiovisual test setting for recording infants' expressions pertaining to taste stimuli between the sixth and eighth week after birth and the processing of these data using BabyFACS and the Body Action Posture System is a special innovation in this study. In addition, BC could be measured accurately with ADP. Further, prenatal and postnatal nutrient intakes are assessed via a recently validated but not yet published instrument called the HPL-FFQ. For validation purposes, 2 24-hour recalls were performed as in-depth face-to-face interviews by a trained nutrition expert. Moreover, recall errors and bias in the dietary intake and physical activity assessments cannot be ruled out completely. Another limitation is the fact that the data categories retrieved from the medical records may be not exhaustive and may show heterogeneous quality due to different data collection procedures. Information such as the prepregnancy body weight and body weight during the first trimester could not be objectively measured because the first visit was set from 24 to 28 weeks of gestation. Furthermore, postponements of visits must be expected and may influence the week of pregnancy in the defined visit period.

Future Directions

We assume that the identified parameters in our explorative study could be useful for elucidating connections between maternal metabolic and nutritional status and infant development. Therefore, future studies must focus on determining the relationships between the mother's and child's taste parameters, including audiovisual data, candidate biomarkers from maternal blood or breast milk, infants' fat-related indices, and gut microbiota composition, especially in the first year of life. Additionally, the findings from our study could be an important step toward the establishment of further diagnostic and interventional strategies targeting childhood obesity and early body fat development. Although there are many unanswered questions related to the complex development of obesity, these results might encourage the confirmation of the identified parameters within a larger cohort to quantify the effect of early stimulation of taste and preferences as well as assess potential differences and similarities between population groups.

Acknowledgments

Authors' Contributions

BFN wrote the project grant and was awarded funding for the research. BFN and EP are responsible for the study. BFN, MR, MvdK, and EP contributed to developing the overarching research strategy and study design. WS, MP, AR, NS, AK, and JM designed the details of the study procedure. BFN drafted the manuscript, and WS, MP, AR, NS, AK, JM, MHW, ALA, and IW provided specific content. BS and SH are members of the Advisory Group and offered strategic and academic counseling for the study. AB provided statistical advice and expertise. MK provided expert advice. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report.
[PDF File (Adobe PDF File), 51 KB - resprot_v11i4e37279_app1.pdf]

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Abbreviations

ADP: air displacement plethysmography
BabyFACS: Baby Facial Action Coding System
BC: body composition
FMCFFQ: food frequency questionnaire for children
FEG: Dlugosch and Krieger's German-language General Health Behaviour Questionnaire
FFM: fat-free mass
FFMI: fat-free mass index
FM: fat mass
FMI: fat mass index
GWG: gestational weight gain
HPL-FFQ: Health Pregnancy Lactation-Food Frequency Questionnaire
IPAQ: International Physical Activity Questionnaire
ISTD: internal standard
MET: Metabolic Equivalent of Task
MRM: multiple reaction monitoring
PROP: 6-n-Propylthiouracil

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Protocol

Therapeutic Effect of a Soft Robotic Glove for Activities of Daily Living In People With Impaired Hand Strength: Protocol for a Multicenter Clinical Trial (iHand)

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Abstract

Background: Decline of hand function, especially reduced hand strength, is a common problem that can be caused by many disorders and results in difficulties performing activities of daily living. A wearable soft robotic glove may be a solution, enabling use of the affected arm and hand repeatedly during functional daily activities and providing intensive and task-specific training simultaneously with assistance of hand function.

Objective: We aim to investigate the therapeutic effect of an assistive soft robotic glove (Carbonhand).

Methods: This multicenter uncontrolled intervention study consists of 3 preassessments (T0, T1, and T2), a postassessment (T3), and a follow-up assessment (T4). Participants are patients who experience hand function limitations. For the intervention, participants will use the glove during activities of daily living at home for 6 weeks, with a recommended use of at least 180 minutes per week. The primary outcome measure is handgrip strength, and secondary outcome measures are related to functional arm and hand abilities, amount of glove use, and quality of life.

Results: The first participant was included on June 25, 2019. Currently, the study has been extended due to the COVID-19 pandemic; data collection and analysis are expected to be completed in 2022.

Conclusions: The Carbonhand system is a wearable assistive device, allowing performance of functional activities to be enhanced directly during functional daily activities. At the same time, active movement of the user is encouraged as much as possible,

which has potential to provide highly intensive and task-specific training. As such, it is one of the first assistive devices to incorporate assist-as-needed principles. This is the first powered clinical trial that investigates the unique application of an assistive grip-supporting soft robotic glove outside of clinical settings with the aim to have a therapeutic effect.

KEYWORDS

Introduction

Limitations in hand function are a common issue, with a diverse range of underlying causes. During an open population survey in Rotterdam, the Netherlands, 17% of respondents reported suffering from hand pain, and over 13% presented with hand disability [1]. One particularly debilitating aspect of hand function limitation is decreased hand strength, which occurs with a wide range of conditions, such as arthritis, trauma-induced hand injuries, neuromuscular diseases, orthopedic problems, and neurological disorders. For example, arthritis—inflammation of joints—comes in many forms, of which osteoarthritis, with 13% to 26% incidence [2], and rheumatoid arthritis, approximately 1% incidence [3,4], are most prevalent. Traumatic hand injury is even more common, with incidence rates reported between 57 to approximately 700 per 100,000 [5].

People suffering from loss of hand function experience marked difficulties grasping, holding, and manipulating objects [6] that subsequently lead to difficulties performing activities of daily living independently [7-9]. These limitations can have a negative effect on participation in society and quality of life [10-12]. Depending on the progressive or regressive nature of the limitations of the hand, hand strength and hand function can be maintained or even improved to a certain level of functioning through intensive exercise programs during inpatient or outpatient rehabilitation or community-based physical therapy. For example, strengthening, stretching, and joint mobility exercises are recommended for treating hand osteoarthritis [13]. For rheumatoid arthritis with hand involvement, physical therapy that consists of functional exercises for the hand, ideally integrated in task-specific activities and in a daily regimen, is recommended [14]. Evidence from a randomized controlled trial [15] showed that a tailored hand exercise program for adults with rheumatoid arthritis who had pain and dysfunction of the hands doubled the treatment effect on hand function, activities of daily living, work, satisfaction, and confidence in symptom self-management, in comparison with that of a good-quality usual-care control intervention consisting of joint protection advice and splinting. Similar recommendations are valid for hand limitations due to neurological disorders [16]. Nevertheless, many people suffering from impairments in hand strength do not regain the previous levels of function, even if they are actively involved in exercise programs, or they relapse as soon as they stop exercising [17]. Ideally, people suffering from loss of hand strength should be encouraged to use their

affected hands daily within their abilities [14]. For those left with limited functional independence, all that remains is reliance on assistance for activities of daily living.

Assistive devices can be used to support activities that are hindered by physical limitations. Many assistive devices for activities of daily living are available [18,19]—from simple assistive tools (eg, knife with an adapted handle) to large robotic systems that can act as a substitute for activities performed by people themselves, in the case of very severe limitations (eg, a wheelchair-mounted robotic manipulator) [20,21]. Although the use of assistive technologies allows more autonomy, most often, the devices are a substitute for the function of the person [22-24], instead of stimulating active use of affected limbs. Patients using their affected hands as actively as possible are more likely to maintain or improve hand function; therefore, people have a strong desire to keep using their affected limbs as much as possible, and are not keen to use technology that overrides what little function remains [25].

Recent technological developments in the field of robotics facilitate direct support of motor function for prolonged periods and in environments beyond clinical centers. Soft robotic gloves, constructed of textiles and soft materials (sensors and artificial tendons) that are comfortable to wear and compliant with human movement and which can be used to optimize hand- and finger-related functional abilities, have become increasingly available in the last decade [26]. In a recent review [26], Proulx and colleagues concluded that soft robotic gloves seemed to be a safe and promising technology to improve dexterity and functional performance in individuals with reduced hand function as a result of a neurological event. However, the level of evidence for the effectiveness of these devices needs to be substantially increased before their use in daily life or into neurorehabilitation programs is recommended. One promising approach is robotics with assist-as-needed support, in which the support adapts to the abilities of the user. One particular development is a wearable soft glove (Carbonhand, Bioservo Technologies AG), to enhance a person's grip during activities of daily living. Since the wearable device is equipped with assist-as-needed control and supports meaningful daily activities for the user, the glove not only acts as an assistive device but also provides active, intensive, and task-specific training. This facilitates full integration of the glove in functional activities, allowing a high dose of practice that is highly task-specific, without taking additional time out of the person's daily schedule. Hence, it is possible that unsupported arm and hand function may improve after prolonged use of the glove in daily life. In

a first clinical trial [27], in which one of the intervention groups used a previous version of this system, we discovered that 4 weeks of use of the soft robotic glove at home had a positive effect on hand strength, functional performance, and dexterity (assessed without the glove) in older adults suffering from rheumatoid arthritis or osteoarthritis and in stroke patients; however, the study was not powered sufficiently for a conclusive outcome. Therefore, we aim to investigate whether 6 weeks of use of a state-of-the-art grip-supporting soft robotic glove (Carbonhand) as assistive device during activities of daily living at home results in a therapeutic effect in patients with hand function problems. In accordance with the findings of our pilot study [27], we expect that 6 weeks of use of a grip-supporting

soft robotic glove will result in increased grip strength, improved hand function, and increased hand function abilities in a broad population.

Methods

Study Design

This study is a multicenter uncontrolled intervention trial (iHand). All participants will be assessed 5 times: 3 preassessments, 1 postassessment, and 1 follow-up assessment (Figure 1). SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [28] will be used.

Figure 1. Study flowchart.
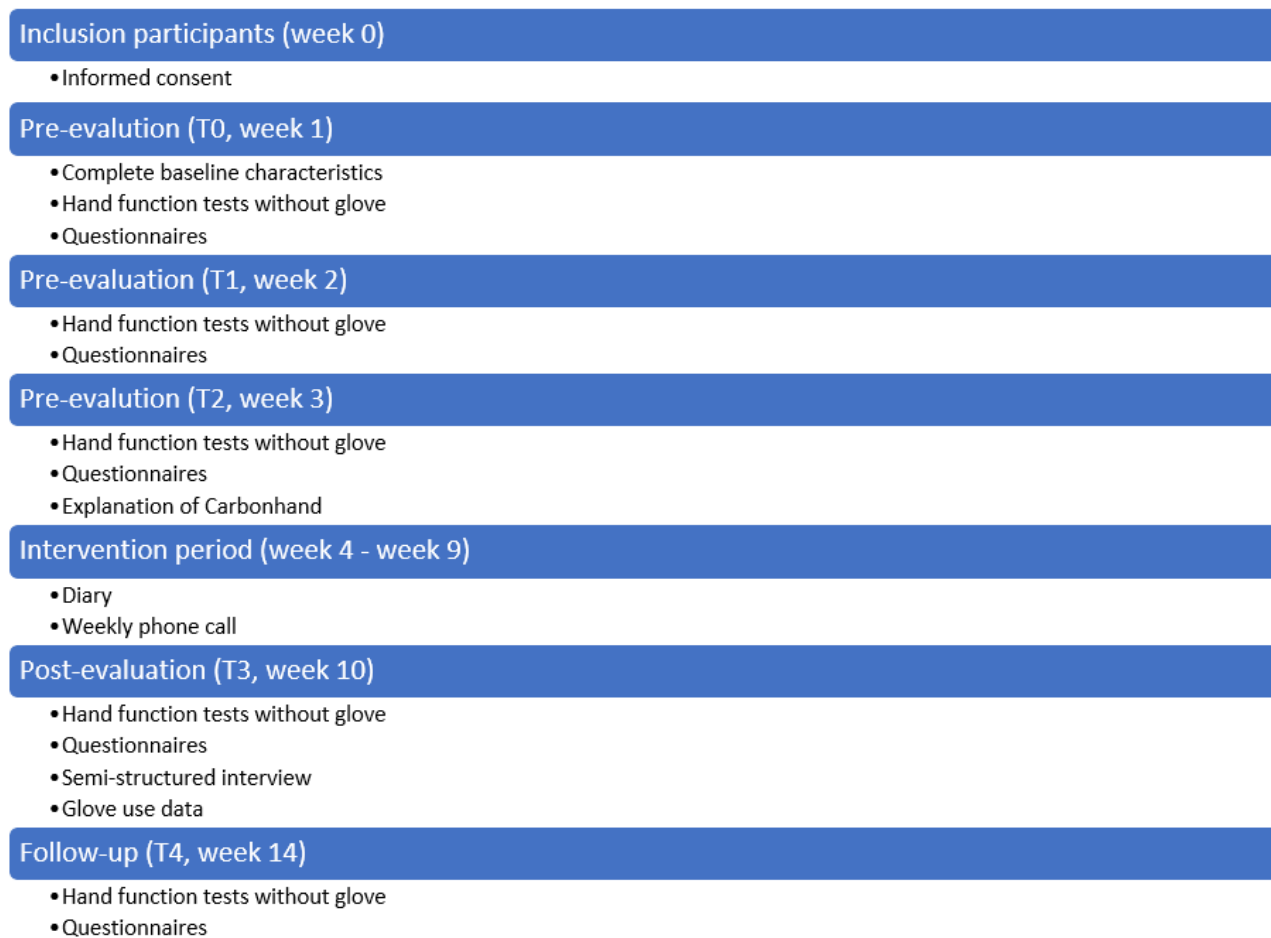
Setting

The study takes place in 8 clinical centers (rehabilitation centers and rehabilitation departments of academic hospitals) in the Netherlands: Roessingh Centre for Rehabilitation in Enschede, University Medical Center Groningen, Isala in Zwolle, Rijndam Rehabilitation in Rotterdam, Reade in Amsterdam, De Hoogstraat Rehabilitation in Utrecht, Sint Maartenskliniek in Ubbergen, and Klimmendaal in Arnhem. Klimmendaal did not participate at the start of the project but was included as center in June 2021.

Study Coordination

Roessingh Research and Development BV is the coordinator of the trial and responsible for the study design, management, data collection, and data analysis. Bioservo Technologies AB is the manufacturer of the Carbonhand system and the project manager and sponsor of the iHand project. Clinical Trial Service BV was contracted as external data monitor, to check that execution of the study in participating centers follows the study protocol and good clinical practice [29].

Ethics

The protocol has been approved by the Medical Ethical Committee of Twente (NL68135.044.19); the Medical Ethical Committee of Twente recently merged with the Medical

Research Ethics Committees United. The study was also registered in the Netherlands Trial Register (NTR NL7561). Since the study includes the use of a medical device outside of its intended use, the study is also registered with the Dutch Health and Youth Care Inspectorate. Although the risk of the study is classified as low, both patient and liability insurance have been obtained. All administrative and protocol-related amendments will be submitted for approval to the Medical Ethical Committee. After receiving their approval, these modifications will be reported to all participating centers and Clinical Trial Service BV via email and made available on a password-secured website (only the latest versions of all study-related documents are posted). If forms such as the study protocol or information letter are changed, the newest version will be sent to the participating centers and they will be asked to use this version from then on.

Participants

We aim to enroll patients with chronic perceived hand function problems, including decreased handgrip strength. Since this impairment is caused by a wide range of disorders, such as acquired brain injury, osteoarthritis, rheumatoid arthritis, spinal cord injury, orthopedic problems or other neurological disorders, we have chosen not to limit the study to a single disorder but rather to focus on the common motor limitation, for which the intervention was developed. Therefore, the study sample is heterogeneous. In each center, a rehabilitation physician or clinical researcher is involved in the identification of potential participants for the study, based on screening of predefined selection criteria. The candidates will be contacted by the professional from that particular center to inform them about the study. When participants are interested, an information letter is sent to them. After 1 week, the health care professional will contact candidates to determine their interest in participating in the study and to answer possible questions. If interested in participating, a physical appointment is scheduled to obtain informed consent form, and then, to complete the screening procedure (some selection criteria require physical tests).

Inclusion criteria are (1) age between 18 and 90 years, (2) being in a chronic and stable phase of disease, (3) having received treatment for limitations in performing activities of daily living due to a decline in hand function (regardless of underlying disorder) at the involved rehabilitation center and department, (4) being capable of at least 10° of active extension of the wrist and fingers and 10° of active flexion of the fingers, (5) having

the ability to make a pinch grip between thumb and middle or ring finger, (6) having the ability to put on the glove, (7) having sufficient cognitive status to understand 2-step instructions (judged by personal contact between participant and experienced health care professional), (8) living at home, and (9) providing written informed consent. To ensure that people are able to meet the recommended amount of use, an initial inclusion criterion was that the most affected hand of the participant was the dominant hand; however, due to support of the glove during mainly bimanual activities, this inclusion criterion was removed.

Exclusion criteria were (1) having severe sensory problems of the most affected hand, (2) having severe acute pain of the most affected hand, (3) having wounds on their hands resulting in a problem when using the glove, (4) having severe contractures limiting passive range of motion, (5) having comorbidities that limit functional use and performance of the arms and hands, (6) having severe spasticity of the hand (≥2 points on Ashworth Scale), (7) participating in another study that can affect functional performance of the arm and hand, (8) receiving arm or hand function therapy during the course of the study, or (9) having insufficient knowledge of the Dutch language to understand the purpose or methods of the study. Reasons for exclusion will be reported.

Eligible candidates participate in a test session, in which the glove system is explained, the size of the glove and straps are determined, and the support of the glove is tested by performing several grasps (10-15 minutes). The aim of this test session is to allow participants to experience the support that can be expected from the glove system and make a well-informed decision about the study.

Carbonhand System

Overview

The Carbonhand system is a soft robotic device, constructed of textiles and soft materials that are comfortable to wear and compliant with human movement. The glove enhances a user's grip based on voluntary, active initiation (Multimedia Appendix 1). The glove is available in several sizes (extra small to extra large) and in both right-hand and left-hand versions. The total weight of the system is approximately 700 grams. Carbonhand is a CE-marked assistive medical device, but CE approval does not extend to the intended use in this study (therapeutic effect). The Carbonhand system consists of a glove and a control unit (Figure 2).

Figure 2. Carbonhand system.

Glove

The main purpose of the glove is to apply the forces generated by the motors in the control unit and to provide the control unit with sensory input from touch sensors at the fingertips. The glove has a slim design and the same look and feel as a regular glove. Three fingers—the thumb, middle, and ring finger—are covered by the glove and are actuated by 3 separate motors to support power grip. The index finger and little finger are left uncovered; the index finger is left uncovered to allow tactile sensing. Actuation finger flexion is triggered by an interaction force between the fingertips and an object through pressure sensors sewn into the glove at the tips of the 3 actuated fingers. The forces are applied by artificial tendons that are sewn into the glove along the length of the fingers, which induce flexion of the fingers when contracted.

Control Unit

The control unit contains a battery, 3 motors, and a microcontroller. It is worn at the waist, on the hip or on the back of the user, using a clip or belt. A cable connects the control unit with the glove, via a detachable connection located close to the glove. An upper and lower arm strap, both available in different sizes, lead the cable along the arm. Embedded software in the control unit proportionally adjusts the amount of assistive force to help the user close the hand—an increase of force induced by the user and recorded at the fingertips will increase the force applied by the actuators and relaxation of active grip reduces the interaction force recorded by the fingertips, resulting in a gradual decline in force supporting finger flexion. Via a smartphone app, the sensitivity and the amount of force produced by the actuators can be adjusted for each finger by the health care professional, and the configuration—which sensors activate which fingers—can be set (eg, activation of the sensor at the middle finger can be set to actuate both the middle and the ring finger simultaneously). Specific useful combinations of a certain amount of sensitivity, force, and configuration of fingers can be saved as profiles. Profiles can be created for specific activities (eg, carrying heavy objects or grasping small objects such as a paintbrush) or general purposes (eg, a low, medium, or high amount of force, to allow the user to switch during the day). Profiles are individually created by the health care professional in consultation with the user, depending on the individual situation and needs. A maximum of 3 custom-designed profiles can be saved under a specific name at the control unit's buttons for use by the patient at home.

The control unit can be used for a new participant after the previous participant has completed the intervention. For hygienic reasons, each participant will receive a new glove. Because the glove is not washable, due to the integrated electronics, participants are advised to wear a rubber household glove on top of the Carbonhand glove during activities that may expose the hand to liquids or dirt. The rubber household glove is also provided to the participant.

Baseline Characteristics

Participant characteristics—age, gender (male, female, nonbinary), impairment or diagnosis, time since diagnosis, most affected side, and dominant side—will be collected from the medical record or from the patient by the health care professionals.

Study Procedure

All health care professionals involved in the study received extensive training prior to the start of the patient recruitment in order to standardize the execution of the study across the different centers. Plenary instruction sessions were scheduled; health care professionals were trained in good clinical practice, execution of the study protocol, in fitting and operating the Carbonhand system, and in explaining (following a standard procedure) the use of the Carbonhand system to the participants. All instructions were also documented in logbooks and manuals, which were provided to the professionals. The latest versions of these documents are maintained on a secure project website.

In total, there are 5 assessments for each participant. Three preassessments (T0, T1, and T2) are scheduled across 3 weeks, as baselines, directly prior to the intervention period. After completing the third baseline session, the Carbonhand system is manually adjusted by the professional to the individual participant. Attention is paid to the correct size of the glove and arm straps, the finger length of the glove, and creating 3 support profiles. In addition, instructions about all aspects of the Carbonhand system are given, demonstrated, and practiced with the participant, until the professionals are confident that the participant knows how to use the system properly at home. In addition to receiving the Carbonhand system, all participants will be provided with a short user manual (in Dutch) and an excerpt from the exercise book [30], in which exercises (functional activities that can be used in the home situation) are described for people with almost complete function of the arm.

During the 6-week intervention period, participants use the Carbonhand system at home. Within 1 week of the end of the intervention period, postassessment (T3) is conducted; 4 weeks later, a follow-up assessment (T4) is conducted, to measure the retention of effects.

Monitoring visits by an independent study monitor are planned for each participating center to ensure the continued protection of participants rights and well-being, to assure protocol adherence, and to verify data integrity during the study in compliance with good clinical practice. All protocol deviations will be filed. We anticipate having 5 monitor visits to each center during the course of the study.

Intervention

Participants wear the Carbonhand glove on their most affected hand. If glove use during the 6-week intervention period is interrupted by unforeseen circumstances (eg, being ill for a few days), the participant is allowed to extend this period to achieve 6 weeks of glove use. The participants are free to choose for which activities, when, and for how long they use the Carbonhand system. However, we will recommend using the system at least 180 minutes per week for 6 weeks during the most common activities of daily living [31], such as lifting and carrying items, performing hobbies, cleaning cooking, and gardening. The recommended intensity of use is based on the findings of a systematic review [32]—a minimum dose of at least 16 hours (which is equal to 960 minutes) is needed to reach

a functional effect in the stroke population. During the period of home use, the health care professional has weekly contact by phone to ask about the participants' experience with the Carbonhand system, to verify adherence to the intervention, to ask if adjustments need to be made to the Carbonhand system's support profiles, and to respond to any potential problems (eg, device deficiencies, adverse events and serious adverse events) that might arise. Extensive notes are made by the health care professional during these phone calls. When adjustments need to be made to the support profiles on the Carbonhand system during the intervention period, an extra visit (either the participant to the center or the investigator to the participant's home) will be scheduled. For each participant, all adverse events and serious adverse device effects are reported by the site investigators in the investigators site file and the web-based clinical database during the entire study period. Roessingh Research and Development BV is responsible for informing the

Medical Ethical Committee about the occurrence of serious adverse device events.

Outcome Measures

Overview

The primary outcome measure of the study is maximal handgrip strength. Secondary outcome measures, related to arm and hand function, functional ability, amount of glove use, pain, and quality of life (Table 1), are only performed on the most affected side. All assessments are estimated to take 1.5 to 2 hours.

During the intervention period, the amount of glove use will be recorded automatically by the Carbonhand system. In addition, participants are asked to keep a diary about daily use of the glove and all activities in which they engage. In order to get a thorough understanding about the experience of the participants of using the Carbonhand system during activities of daily living at home and the user friendliness of the system, semistructured interviews will take place after the intervention period (T3).

Table 1. Overview of outcome measures.

Outcome measure	International Classification of Functioning, Disability and Health component	Domain	Assessment
Maximal handgrip strength	Body function	Grip strength	T0-T4
Maximal pinch strength	Body function	Pinch strength	T0-T4
Static grip endurance	Body function	Grip endurance	T0-T4
Action Research Arm Test	Activity	Upper extremity performance	T0-T4
Jebsen-Taylor hand function test	Activity	Fine and gross hand motor skills	T0-T4
Michigan Hand Outcomes Questionnaire–Dutch version	Activity	Self-perceived health state	T0-T4
Motor Activity Log	Activity	Self-perceived upper limb performance	T0-T4
Numeric pain rating scale	Body function	Self-perceived intensity of pain	T0-T4
EuroQol 5 dimension, 5 level	Participation	Self-perceived health-related quality of life	T0-T4
Short-form 36	Participation	Self-perceived quality of life	T0-T4
Glove use data	Activity	Registered amount of use	Intervention period
Diary	Activity	Self-perceived amount of use	Intervention period
Semistructured interview	Activity	Patient's experiences of Carbonhand use	T3

Primary Outcome Measure

Assessment of maximal handgrip strength will be performed in accordance with American Society of Hand Therapist guidelines [33]: with the participant sitting comfortably and in an upright position with the elbow of the affected arm close to their body, flexed at a 90° angle, and holding the dynamometer (Jamar hydraulic hand dynamometer, Patterson Medical) in their hand. The other parts of the body are not allowed to move or help to give more strength. The handle position of the dynamometer is adjusted for each participant, so that the middle phalanx of the middle finger is at 90° to the handle. The examiner will provide the participant with standardized verbal instructions. Participants will perform 3 maximal contractions for 5 seconds, while the examiner gently supports the base of the dynamometer. A 60-second-duration rest is taken between each contraction. If

the third value is higher than the first and second, a fourth attempt will be added. This will be continued until the last value is lower than the second-to-last value. The mean value of the last 3 attempts will be used as the test score [33].

Secondary Outcome Measures

Maximal pinch strength will be assessed with the Baseline Lite Hydraulic Pinch Gauge dynamometer (Fabrication Enterprises). The pinch strength will be measured in 3 configurations—between the index finger and the thumb, the middle finger and the thumb, and the ring finger and the thumb—with the participant sitting in a straight-backed chair without arm supports, the elbow flexed at 90° and close to the body, the forearm in a neutral position, and the wrist in a neutral position or with slight extension (0°-30°) [33]. The pinch gauge is grasped with the distal segment and ventral side of the thumb

and finger, while the pinch meter is slightly supported by the examiner. The examiner will provide the participant with standardized verbal instructions. Three maximal isometric contractions will be performed for at least 5 seconds, with a 60-second-duration rest period between each contraction. If the third value is higher than the first and second, a fourth attempt will be added. This will be continued until the last value is lower than the second-to-last value. The mean value of the last 3 attempts will be used as the test score [33].

Static grip endurance is measured in the same way as handgrip strength; however, this test determines endurance during a static hold. Participants will be instructed to squeeze and hold the Jamar hydraulic hand dynamometer with full effort for 30 seconds. Participants will not be informed of the time remaining. Relative endurance for this test was calculated as (*mean force during last second*) / (*mean force during first second*), and larger numbers reflect greater relative endurance (ie, less fatigue) [34].

The Action Research Arm Test is a reliable, valid, and sensitive measurement for dexterity that evaluates 19 tasks for distal and proximal arm motor function and is divided into 4 subscales: grasp, grip, pinch, and gross arm motor function [35,36]. The quality of performance on each item is rated on a 4-point ordinal scale that ranges from 0 (can perform no part of test) to 3 (performs test normally). The maximum score of the Action Research Arm Test is 57 points and will be scored as described in [35].

Jebsen-Taylor Hand Function Test is a reliable and valid test to evaluate functional hand motor skills in different patient groups and healthy people of various ages [37]. The test consists of 7 different unilateral hand skill tasks related to activities of daily living: (1) writing a sentence of 24 characters, (2) turning over 7.6 cm × 12.7 cm cards, (3) picking up and moving small common objects (eg, paper clips, coins, and bottle caps), (4) stacking checkers (test of eye–hand coordination), (5) simulated feeding (eg, teaspoon with beans), (6) picking up large empty cans, and (7) moving weighted (450 g) cans. The duration of each task will be recorded in seconds and summed for the test score [38].

Michigan Hand Outcomes Questionnaire–Dutch Language Version (a total of 57 items) assesses patients' opinions their hands and health [39,40]. The questions are used to assess out how patients feel and to what extent they are capable of carrying out daily activities in the past week (with the exception of part 3, in which the last 4 weeks is used). The problem is mapped out within 6 domains: total hand function, activities of daily living, work situation, work performance, pain, aesthetics, and satisfaction. Within each domain, items are scored on a 5-point Likert scale. The scores are normalized to a range of 0 to 100. For the pain scale, higher scores indicate more pain. For the other 5 scales, higher scores indicate better performance.

The Motor Activity Log [41] is a semistructured questionnaire that assesses self-perceived amount of use and quality of movement of the affected arm and hand by stroke patients during activities of daily living. This questionnaire consists of 26 activities and has excellent test-retest reliability for both scores of each activity; each activity is rated by the participant for quality of movement and amount of use of the upper extremity on a 5-point scale.

An 11-point numeric pain rating scale—from 0 (no pain) to 10 (the most intense pain imaginable)—is used to measure the subjective intensity of pain (patients select a value that is most in line with the intensity of pain that they have experienced in the last 24 hours). The numeric pain rating scale has good sensitivity, while producing data that can be statistically analyzed [42].

EuroQol 5D-5L (EQ-5D) index is a standardized instrument that is applicable to a wide range of health conditions and treatments [43]. The first part records self-reported problems in mobility, self-care, usual activities, pain and discomfort, and anxiety and depression domains. Each domain is divided into 5 levels of severity, corresponding to no problems, slight problems, moderate problems, severe problems, and extreme problems. The second part comprises a visual analog scale from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ-5D is designed for self-completion by respondents. In this study, the EQ-5D will be used to calculate a preference-based summary index, based on time trade-off techniques, for which the value 0 represents death and 1 represents perfect health.

Short Form 36 is a 36-item valid and reliable questionnaire to assess the participants' health perception [44]. The questionnaire consists of multi-item dimensions about the physical and mental well-being of the participant. The total and component scores, physical component summary (average score of the domains physical functioning, physical role functioning, bodily pain and general health), and mental component summary (average score of the domains vitality, emotional role functioning, social functioning and mental health) will be calculated. The will be converted to a scale from 0 to 100, where a higher score indicates a better quality of life [45].

Glove-use data will be automatically recorded by the Carbonhand system, such as total time the system is turned on (hours), average session length (minutes), cumulative number of grasps (for thumb, middle, and ring fingers separately), average frequency of grasps per minute (for thumb, middle, and ring fingers separately) and the average grasp force provided by user (for thumb, middle, and ring fingers). The parameters are extracted from the control unit after the 6 weeks of home use using a USB-connection and dedicated Carbonhand software (version LB.09.07; Bioservo Utility Public) by each participating center.

A diary will be kept daily by the participants during the 6-week intervention period. Participants will be asked to report how often and for how long they use the Carbonhand system each day, when they use the system (morning, afternoon, evening), and during which activities. Information from the diaries will be transcribed by the investigator. The study coordinator will perform thematic analyses on those transcriptions to extract qualitative information about glove use and participants' experiences using the Carbonhand system.

A semistructured qualitative interview with open-ended questions will be performed by the investigator at the T3

assessment, to collect participants' experiences about using the Carbonhand system in daily life and the user-friendliness of the system. The interview will last approximately 15 minutes and was developed by Roessingh Research and Development BV in collaboration with Bioservo with the aim of learning about the user experiences and to improve the Carbonhand system. Data extraction (written answers of the interview) will follow the same procedure as that used for the diaries.

If a participant withdraws from the study during the intervention period, we will aim to obtain the reason for stopping, the maximum handgrip strength, and glove-use data and to complete the semistructured interview.

Sample Size

Based on a previous study [27], a mean improvement of 2.16 kg, with an estimated standard deviation of 5.2 kg, in handgrip strength is expected; therefore, a minimum of 56 participants (using power=0.8 and α=.05) are needed. When accounting for 10% dropout, a minimum of 63 participants are needed. Given that 7 participating centers are involved, each center aims to include 9 participants, but centers are allowed to include more if they can, up and until the total target sample size is achieved.

Data Management

Prior to the start of the study, a data management plan that covers all aspects of handling data gathered during and after completion of the iHand project, such as collection, storage, back-up, documentation, access, sharing, reuse, preservation, and archiving (both at the study coordinator's site and participating centers), was devised.

All documents related to this study and all participant data will be collected in the investigators' site files. These files, containing personal and contact information, as well as the screening information from potential candidates, will be safeguarded at the participating center of the corresponding participants. All relevant data (participants' characteristics and clinical assessments) will be copied from the case report form into a web-based clinical database for case report form data (Castor, Castor EDC) by site investigators using unique and anonymous participant codes. All questionnaires (Michigan Hand Outcomes Questionnaire–Dutch Language Version, Motor Activity Log, numeric pain rating scale, EQ-5D, and Short Form 36) are filled in by participants via the web-based clinical database directly on site (ie, these data are not stored in site files). One center will deviate from this procedure—the participants will fill in the questionnaires on paper. These forms are kept in the site file and the data will be entered into the Castor database by the investigator. Transcripts of the weekly phone calls with the participants during the intervention period, copies of the diaries kept by participants, and extracted glove-use data (.csv format) are sent to the study coordinator by email, with participant identification code, after completion of the study. These data will be stored in a secure location on the local computer network of the study coordinator. Personal data of the participants recruited by a particular center will not be reported in the database or in any communication beyond the center and are only accessible by the investigators from that center. If necessary, the participant can be linked to these data

by a participant identification code list, which is safeguarded at each center separately. In the source document agreement, the location of personal data is described by each individual center. Participating centers only have access to their own data set. The study coordinator and monitor have access to the full data set.

All coded data will be stored for 15 years within the clinical database environment and a copy of that database will be stored at Roessingh Research and Development BV for an unlimited time period, backed up daily, after downloading the completed and closed data set from the database.

Statistical Analysis

Outcome measures will be analyzed using SPSS statistical software (version 19; IBM Corp). Data from the 3 baseline assessments (T0, T1, and T2) will be averaged (for overall preassessment values). Statistical analysis of the therapeutic effect will be performed on all participants who completed all assessments up to and including T3 and T4. Data from participants who drop out before or during the intervention period will be analyzed separately to analyze the patient characteristics of dropouts, including the reasons for dropout, to identify potentially relevant information regarding reevaluation of target population, device-related issues, to inform proper interpretation of study outcomes.

Normality of data distribution for each outcome measure will be checked by visual inspection and with the Shapiro-Wilks test, prior to analyzing outcome measures. Descriptive statistics will be used for all outcome measures (mean and standard deviation or median and interquartile range as applicable). The overall level of significance will be set to P<.05.

In order to assess the effect of the intervention over time, linear mixed models will be used to analyze changes in outcome measures over time. If a significant difference is found between sessions, multiple comparisons are performed with Sidak posthoc analysis. If data are not normally distributed, logarithmic transformation will first be applied to potentially achieve normally distributed data and enable use of linear mixed models for analyses. Otherwise, the Friedman test will be used for nonparametric analysis.

In addition, correlations (Pearson correlation coefficient or the nonparametric Spearman correlation coefficient, depending on data characteristics) between amount of use (measured by diary, Carbonhand system, or Motor Activity Log) or baseline patient characteristics and change in hand function outcome measures will be calculated to evaluate whether an increased dose or specific patient characteristics are associated with better outcomes

Results

The study started in June 2019. The first participant was enrolled on June 25, 2019. As of October 2021, we have enrolled 52 participants. As of March 2022, the study is still ongoing due to the COVID-19 pandemic and related restrictions. We expect data collection to be completed in 2022.

Discussion

We aim to conduct a high-quality powered clinical trial, to investigate changes in unsupported hand function after 6 weeks of use of a grip-supporting soft robotic glove during activities of daily living by patients with hand weakness and hand function limitations. It is known that several weeks of training using a robotic device improves activities of daily living performance, hand function, and hand strength to a similar extent as conventional training in stroke and other neurological conditions [46]. Yet, robot-assisted training has not been investigated substantially in disorders such as osteoarthritis, rheumatoid arthritis, neuromuscular diseases, even though the training principles share common ground—providing high-dose exercise training to improve hand function. It is conceivable that robot-assisted training could have a positive effect in a wider range of disorders. Nevertheless, exercise therapy might not be enough to halt deterioration over time or to regain hand function to a level required to achieve independence in activities of daily living.

To support activities of daily living that remain very challenging or impossible, assistive technologies can be used. Assist-as-needed principles have been increasingly incorporated in both assistive and therapeutic technology [47]. The Carbonhand system is one such example that allows the performance of functional activities to be enhanced directly while using the affected arm and hand repeatedly during daily activities, to provide high-dose task-specific training. This combination allows a unique approach, extending direct support of activities of daily living with the possibility to stimulate improvement of hand function over time outside of a clinical setting. Findings may allow high doses of training throughout the day into people's homes, in the most functional task-specific way possible, and possibly prevention of learned nonuse.

To the best of our knowledge, comparison with other studies will be difficult, because this is one of the first user trials that will apply and test a fully wearable robotic system to support hand function at home for unsupervised use during an extended period of multiple weeks. Moreover, other studies [26] that do examine effects of a soft robotic glove focused on examining the direct assistive effect of the glove by comparing performance with and without the glove.

One strength of this powered study is that the sample size calculation was based on results from a previous clinical study [27] that evaluated a similar assistive device. In addition, experiences from the previous study [27] were used in defining the broad range of data collected covering all levels of the International Classification of Functioning, Disability and Health [48], including grip and pinch strength measurements, functional ability measurements of the arm and hand, pain and quality of life questionnaires, semistructured interviews, diaries, and glove-use data. Another strength is the focus on the generalizability of the outcomes for patients with reduced hand strength, by including patients with a wide range of disorders from multiple centers. As a result, we expect that the results of this study will contribute to clinical practice, by identifying the role that assistive devices can play within the rehabilitation

process of a wide range of patient groups. In addition, we pay particular attention to protocol adherence and data collection: all professionals involved in the study received extensive training to standardize the execution of the study in the different centers, in the use of the web-based clinical database for data collection, and in fitting and operating the Carbonhand system. Additional plenary instruction sessions for good clinical practice were scheduled. Each of those aspects are explained in detail in instruction manuals, which are available to all involved persons through a website. In addition, visits to each participating center are conducted by an independent monitor to ensure protocol adherence and data integrity. In this paper, we use the SPIRIT-checklist for transparency and completeness in reporting all key elements. Furthermore, dissemination of the study results is planned through presentations at both scientific and clinical conferences and publications in peer-reviewed scientific medical journals, to reach both health care professionals (medical doctors, occupational and physical therapists) and the academic community. The Vancouver Convention is used as guideline to determine authorship and no professional writers will be involved [49]. Upon reasonable request, data will be available from the corresponding author. In addition, press releases will be issued to web-based media and health care magazines with lay summaries of study outcomes to inform potential end users.

In addition to these strengths, we face some challenges. First, the therapeutic effects of Carbonhand will be assessed using an uncontrolled design because of practical reasons—limited availability of resources in terms of project funding and project duration. Second, some outcome measures, for example those assessed with the Motor Activity Log, Michigan Hand Outcomes Questionnaire–Dutch Language Version, Short Form 36, EQ-5D, and the semistructured interview and diaries, are self-reported, which includes the risk of socially desirable answering. Potential bias is reduced as much as possible by allowing participants to complete the questionnaires by themselves, without interference from the health care professional. Finally, participants that might be disappointed about the effect of the glove may have a higher risk of dropout during or directly after the intervention period. This may influence postintervention (T3) and follow-up (T4) results. In order to prevent this effect as much as possible, professionals were instructed to explain the importance of completing the study to all participants at the start of the study. In addition, the characteristics of the dropout sample will be analyzed to inform proper interpretation of study outcomes. Another limitation is the cumulative collection of glove-use data via the Carbonhand system. This means that the exact amount of use per day per week or per bout of activity cannot be retrieved. In order to obtain insight into day-to-day use of the glove, participants are asked to note this information daily in a diary.

This is the first powered clinical trial to investigate the unique application of an assistive grip-supporting soft robotic glove for use outside of clinical settings with the aim to have a therapeutic effect. Despite the abovementioned challenges, the study will provide a solid knowledge base about the therapeutic effect of 6 weeks of home use of an assistive grip-supporting glove.

Authors' Contributions

AIRK, GBPL, JBB, and JSR contributed to the conception and design of the study. JSR, AIRK, and GBPL were involved in the funding acquisition. AIRK, CDMN, and GBPL jointly coordinate the study and are responsible for data analysis and interpretation. JBB and JSR supervise the study. FPB, CKS, MB, BO, JMSS, SMB, NBMV, and JSR are the local principal investigators and responsible for the project administration and data acquisition at their center. AIRK, CDMN, and GBPL drafted the initial manuscript; all other authors were involved in revising the draft. All authors approved the final manuscript.

Conflicts of Interest

Bioservo Technologies AB is the manufacturer of the Carbonhand system and the project manager and sponsor of the iHand project. Bioservo Technologies AB involved Roessingh Research and Development BV to coordinate the clinical activities within the iHand project; however, Bioservo does not have a direct involvement in the execution of the study and the researchers can publish the study data without restrictions.

Multimedia Appendix 1
General impression of the application of the Carbonhand system.
[MP4 File (MP4 Video), 9769 KB - resprot_v11i4e34200_app1.mp4]

Multimedia Appendix 2
Peer Review Reports.
[PDF File (Adobe PDF File), 192 KB - resprot_v11i4e34200_app2.pdf]

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Abbreviations

EQ-5D: EuroQol 5 dimension, 5 level
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Dexamethasone-Induced Sarcopenia and Physical Frailty in Children With Acute Lymphoblastic Leukemia: Protocol for a Prospective Cohort Study

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Abstract

Background: During treatment for pediatric acute lymphoblastic leukemia (ALL), children receive high doses of dexamethasone for its apoptotic effect on leukemia cells; however, muscle atrophy is a well-known serious side effect. Muscle atrophy (loss of muscle mass) accompanied by a decreased muscle strength may lead to a generalized impaired skeletal muscle state called sarcopenia. Loss of muscle mass is also an indicator of physical frailty, which is defined as a state of increased vulnerability that is characterized by co-occurrence of low muscle mass, muscle weakness, fatigue, slow walking speed, and low physical activity. Both sarcopenia and physical frailty are related to an increased risk of infections, hospitalizations, and decreased survival in children with chronic diseases.

Objective: This study aims to (1) estimate the occurrence of sarcopenia and physical frailty in children during ALL maintenance therapy, (2) evaluate the effect of administering dexamethasone, and (3) explore determinants associated with these outcomes.

Methods: This prospective study is being pursued within the framework of the DexaDays-2 study: a randomized controlled trial on neurobehavioral side effects in pediatric patients with ALL. A total of 105 children (3-18 years) undergoing ALL maintenance treatment at the Princess Máxima Center for Pediatric Oncology are included in this study. Sarcopenia/frailty assessments are performed before and just after a 5-day dexamethasone course. A subset of 50 children participating in the DexaDays-2 trial because of severe dexamethasone-induced neurobehavioral problems were assessed at 3 additional timepoints. The sarcopenia/frailty assessment consists of bioimpedance analysis (skeletal muscle mass [SMM]), handheld dynamometry (handgrip strength), Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (fatigue), Timed Up and Go Test (TUG; walking speed), and physical activity questionnaires. To evaluate potential change in sarcopenia/frailty components after a 5-day dexamethasone administration, a paired Student t test or Mann-Whitney U test will be used. Because of the presence of repeated measurements, generalized linear mixed models will be used to estimate the effect of dexamethasone on sarcopenia and frailty outcomes. Multivariable regression models will be estimated to investigate associations between the assessment scores and patient and treatment-related factors.

Results: Patient accrual started in 2018 and was finalized in spring 2021. From autumn 2021 onward final data analyses will be performed.

Conclusions: This first study combining parameters of sarcopenia and physical frailty is of importance because these conditions can seriously complicate continuation of ALL therapy, independence in physical functioning, reaching motor milestones, and participating in daily life activities. The results will provide knowledge about these complications, the association between dexamethasone treatment and muscle loss and other components of frailty, and therefore insights into the severity of this side

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effect. By exploring potential determinants that may be associated with sarcopenia and physical frailty, we may be able to identify children at risk at an earlier stage and provide timely interventions.

International Registered Report Identifier (IRRID):   DERR1-10.2196/33517

Introduction

Acute lymphoblastic leukemia (ALL) is the most prevalent pediatric cancer worldwide. Advances in treatment strategies and supportive care have resulted in a 5-year survival rate of about 90% in high-income countries [1-3]. Consequently, there is growing attention for adverse health effects, including impairments in physical performance during and after therapy [4-6]. Impairments in physical performance, either transient or permanent, in children with ALL are usually explained by a neurological disorder, fractures, osteonecrosis, general malaise, pain, or severe muscle atrophy [7-11]. Muscle atrophy, in turn, can be caused by malnutrition, inflammation, low physical activity, and can be aggravated by treatment with glucocorticoids [12,13]. Glucocorticoids, which are essential in the treatment of ALL, are known to regulate protein metabolism in skeletal muscle, thereby inducing a catabolic effect and consequent muscle atrophy [14,15].

Dexamethasone is the most potent glucocorticoid and a cornerstone for the treatment of pediatric ALL, because it reduces the frequency of central nervous system relapse [15]. As it is administered in high doses for considerable periods in various ALL protocols worldwide (6 mg/m^2 per day) [16-18], children with ALL carry an increased risk of glucocorticoid-induced muscle atrophy [15].

Muscle atrophy (loss of muscle mass) when accompanied by decreased muscle strength may indicate a generalized skeletal muscle disorder called sarcopenia [19]. Sarcopenia, defined as the combination of low muscle mass and strength or function, is associated with increased adverse health outcomes in various adult populations [20]. The presence of sarcopenia has been investigated to a limited extent in 3 previous studies including children with ALL [4,21,22], which indicated that muscle mass loss in children during ALL therapy was associated with the number and duration of hospital admissions [4], occurrence of invasive fungal infections, other adverse events of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥III [21], and even—when fat mass and body mass index were increased—with impaired survival [22]. However, due to small sample sizes and methodological limitations, which make it difficult to correct for relevant confounders, it is unclear if these results indicate a true causal relationship or coassociation.

Physical frailty is another undesired consequential state, and is characterized by 5 components: unintentional weight loss (due to muscle mass loss), muscle weakness, self-reported exhaustion, slow walking speed, and low physical activity [23]. Physical frailty has been reported as a state of reduced physiologic reserve with increased vulnerability to stressors. It was first defined in the elderly by Fried et al [23], and was shown to be associated with disabilities and early mortality in young adult survivors of childhood cancer [24-27]. The 5 components of physical frailty have all been individually described to occur in children with ALL. For example, higher levels of fatigue were reported in children with ALL compared with children from the general population, and more often during dexamethasone treatment [28,29]. Besides, several studies showed that children with ALL had muscle mass loss [22], muscle weakness [5,6,30], slow walking speed [5,31], and reduced physical activity levels [32-34]. It is therefore relevant to study whether co-occurrence of these 5 physical frailty components may be prevalent in children with ALL, putting them at risk for serious complications.

There is some known overlap between physical frailty and sarcopenia; in fact, sarcopenia has been reported as a precursor of frailty in older adults [23,35-37]. The biological and clinical relationships between these 2 states in pediatric cancer populations are not clear yet.

The development of sarcopenia or physical frailty or both in children during ALL therapy is undesirable because of the consequences it may have for therapy (discontinuation or dose reduction due to clinical state), physical abilities, motor development, and child participation levels in daily life activities, as well as the potential negative effects on the longer term. To our knowledge, physical frailty in children has been assessed in only 2 previous studies, but not yet in pediatric patients with cancer. In both studies the frailty phenotype was associated with severe infections and increased hospitalizations [38,39].

So far, frailty has not been examined in children during ALL treatment nor has the relationship between dexamethasone and sarcopenia/frailty been investigated. Hence, the aims of this study are to estimate the occurrence of sarcopenia and physical frailty in children with ALL during maintenance therapy, to evaluate the effect of administering dexamethasone on sarcopenia and frailty (and their individual components) and to explore potential determinants associated with these outcomes. This paper describes the statistical design and methodology for this study.

Methods

Study Design and Patient Recruitment

This prospective national observational cohort study is taking place at the Princess Máxima Center for Pediatric Oncology,

Utrecht, the Netherlands. The children included in this study are participating in the DexaDays-2 study: a randomized controlled trial on neurobehavioral side effects in pediatric patients with ALL [40]. In that study, Dutch patients with ALL are eligible when they fulfill the following criteria: age 3-18, confirmed diagnosis of ALL, and inclusion in the Dutch Childhood Oncology Group (DCOG) medium-risk group of the ALL-11 protocol. Only patients between 3 and 18 years can participate as this was an inclusion criterion for the DexaDays-2 study, because the questionnaires used in that study are validated only for those ages. Children who reach the age of 3 years during maintenance therapy and are still due to receive 5 dexamethasone courses after their birthday (at least 15 weeks before the end of therapy) are also eligible. Exclusion criteria of that study are anticipated compliance problems, underlying conditions that affect the absorption of oral medication, uncontrolled infections, or any other complications that may interfere with administering dexamethasone treatment, insufficient command of the Dutch language, preexisting mental retardation, and hydrocortisone or risperidone use during the invitation to participate.

Our study on sarcopenia and frailty is being pursued within the framework of the aforementioned DexaDays-2 study. The latter consists of 2 parts: an identification study (including 2 timepoints: T1-T2) and a randomized controlled trial (T3-T11). The prospective observations of the current study are performed at a subset of these time points (Figure 1) during 15 weeks of the maintenance phase of ALL therapy.

A total of 105 patients will undergo a physical frailty assessment before (T1) and after 5 days (T2) of dexamethasone administration (6 mg/m^2 per day in 3 dosages). A subset of 50 children will be assessed at 3 additional timepoints (T3, T7, and T11), to observe the process of sarcopenia and physical frailty longitudinally. This subset comprised children participating in the DexaDays-2 randomized controlled trial based on the severity of their neurobehavioral problems. These 50 patients will receive physiological dosages of hydrocortisone or placebo during a 5-day dexamethasone treatment, and the cross-over will take place after 2 courses of dexamethasone treatment. The sample size is based on the DexaDays-2 study power calculation [40].

Figure 1. Timeline for sarcopenia and physical frailty assessment during the study. [a]Patients continue with this part of the study when they have significant dexamethasone-induced behavioral problems, based on the study design of the DexaDays-2 study. ALL: acute lymphoblastic leukemia; MR: medium risk; Dexa: dexamethasone.
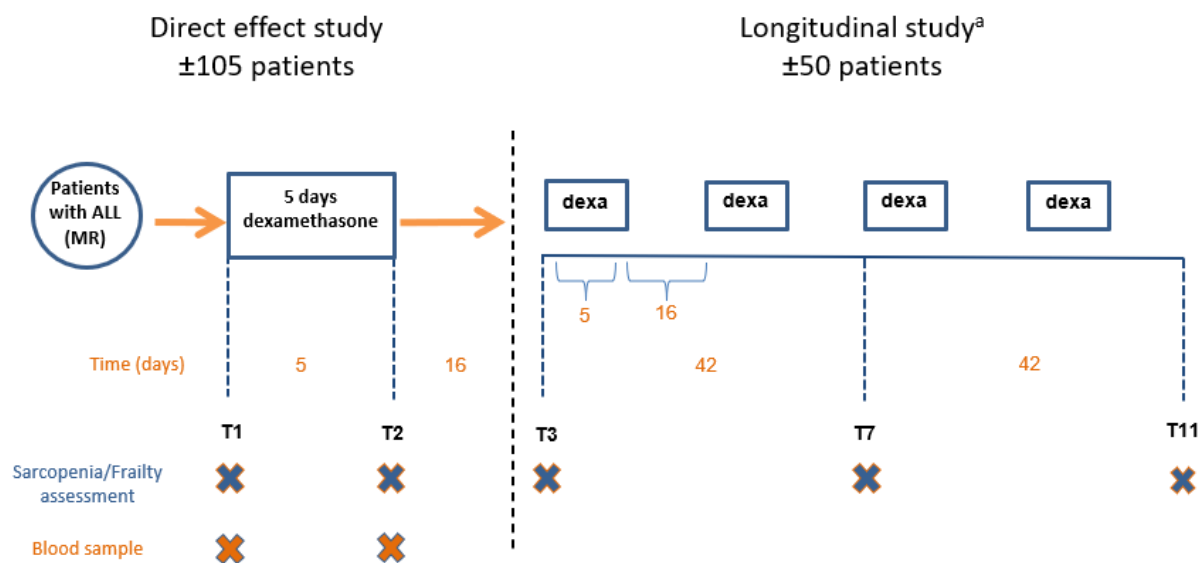
Ethics Approval

The study was approved by the Medical Ethics Committees of the Erasmus Medical Center Rotterdam (reference number: NL62388.078.174).

Outcome Definitions: Sarcopenia and Physical Frailty

Sarcopenia

We will use the most widely cited definition of sarcopenia as proposed by the European Working Group on Sarcopenia [19,39], that is, the combination of low muscle strength or function, and impaired muscle mass [19]. For decades, the term sarcopenia had been used to describe muscle loss alone without reference to function. However, recent updates and consensus definitions state the importance of including muscle function in the concept of sarcopenia [39]. Therefore, in this study, sarcopenia is defined as a combination of impaired muscle mass and low muscle strength.

These components are also separately included in the frailty definition (Table 1, Figure 2).

Table 1. Short overview of definition and measurements used to assess sarcopenia in children with ALL[a].

EWGSOP[b] sarcopenia definition	Concept used in previous pediatric ALL studies	Method used in our study
Loss of muscle mass	Psoas muscle area loss evaluated using computed tomography [20].	Skeletal muscle mass evaluation by bioimpedance analysis.
	Skeletal muscle mass or lean body mass evaluated using dual-energy X-ray absorptiometry [4,21].	
Muscle weakness	N/A[c]	Handgrip strength evaluation using handheld dynamometry.

[a]ALL: acute lymphoblastic leukemia.

[b]EWGSOP: European Working Group on Sarcopenia in Older People.

[c]NA: not applicable.

Figure 2. Physical frailty and sarcopenia definitions and the individual components.
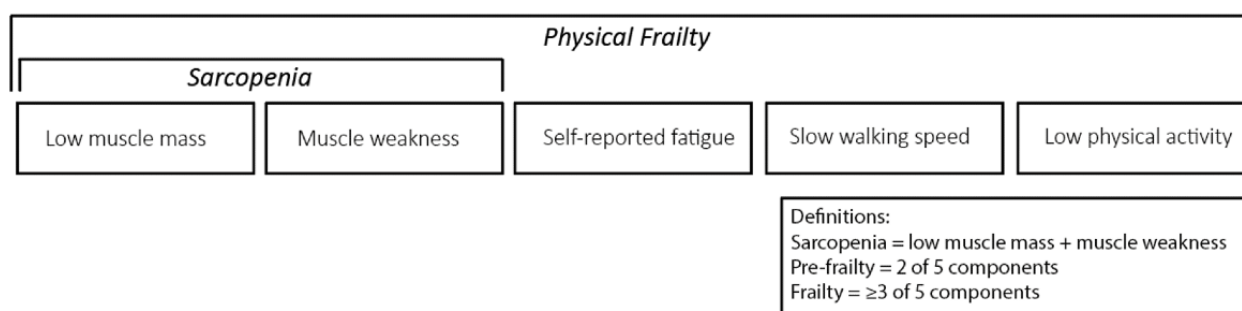
Physical Frailty

In accordance with the original definition of Fried et al [23] and previous clinical frailty studies in childhood cancer survivors, we will define frailty using the following components: low muscle mass, muscle weakness, self-reported fatigue, slow walking speed, and low physical activity [24,25]. Prefrailty and frailty will be defined, respectively, by the presence of 2, or 3 or more of the 5 components [22]. Assessments are excluded if 3 or more components are missing.

The outcome measures to examine sarcopenia and physical frailty components are selected based on suitability for children with an age range of 3-18 years (Table 2).

Table 2. Short overview of measurements used to assess frailty in childhood cancer survivors and in this study.

Frailty components	Concept used in CCS[a]	Method used in the current study in children with ALL[b]
Shrinking/weight loss	Lean muscle mass evaluated using DXA[c] [24,25].	Skeletal muscle mass evaluation by bioimpedance analysis.
Weakness	Handgrip strength evaluated using handheld dynamometry [24,25].	Handgrip strength evaluation using handheld dynamometry.
Exhaustion	Self-reported exhaustion assessed using the SF-36[d] [25] or during a semistructured interview [24].	Self-reported fatigue assessment using PedsQL-MFS[e].
Slowness	Slow walking speed evaluated based on cut-off points for 15 ft [25], or by using the 6-Minute Walk Test [24].	Slow walking speed evaluation using the Timed Up and Go Test.
Low physical activity	Energy expenditure during leisure time physical activity based on the NHANES[f] Physical Activity [25] and based on frequency and duration per week derived from a semistructured interview [24].	Energy expenditure evaluation based on physical activity questionnaires.

[a]CCS: childhood cancer survivors.

[b]ALL: acute lymphoblastic leukemia.

[c]DXA: dual x-ray absorptiometry.

[d]SF-36: 36-item Short Form Survey.

[e]PedsQL-MFS: Pediatric Quality of Life-Multidimensional Fatigue Scale.

[f]NHANES: National Health and Nutrition Examination Survey.

Skeletal Muscle Mass

Total body SMM will be measured using multifrequency segmental bioimpedance analysis (Tanita MC-780; Tanita Corporation) [41]. The measurement procedure requires the child to stand in bare feet on the analyzer and to hold a pair of handgrips, 1 in each hand for approximately 15 seconds. Subsequently, the Skeletal Muscle Index (SMI) will be calculated by dividing the individual SMM (kilogram) by height (m^2; ie, SMI=SMM/height). The Tanita device has shown excellent test-retest reliability [42]. High significant correlations (correlation coefficients ≥0.85) were shown for body composition values in children and adolescents, between bioimpedance analysis and dual-energy X-ray absorptiometry (which is the golden standard for the measurement of muscle mass) [43].

Muscle Strength

Handgrip strength (kilogram) will be measured in sitting position with the elbow flexed at 90° using a hydraulic Jamar handheld dynamometer (Sammons Preston). During the measurement the child will be verbally encouraged to achieve a maximum performance. For both the dominant and nondominant hand the mean score of 3 repeats will be calculated. Raw results will be compared with population-based age- and sex-specific reference values [44]. Handgrip dynamometry showed good validity (intraclass correlation coefficients [ICCs] 0.73-0.91) with high reproducibility in children from the age of 4 years and has excellent test-retest reliability (ICC 0.91-0.93) [45,46], and the measurement was feasible in children with leukemia [47].

Fatigue

Fatigue-related complaints will be assessed using the validated Dutch version of the Pediatric Quality of Life Inventory (PedsQL)-Multidimensional Fatigue Scale (MFS) [48,49]. This questionnaire consists of 3 scales: General Fatigue, Sleep/Rest Fatigue, and Cognitive Fatigue, resulting in subscores and in a total fatigue score. We will use parent proxy reports for children aged 2-4, 5-7, 8-12, and 13-18 years, as well as self-report versions for children aged 8-12 and 13-18 years. The results of PedsQL-MFS will be compared with Dutch normative values from the general population [48]. The internal consistency of the Dutch version of the PedsQL-MFS has been reported as satisfactory (Cronbach coefficient α >.70), test-retest reliability was good (ICC 0.68-0.84), and the interobserver reliability varied from moderate to excellent (ICC 0.56-0.93) [48]. The original version of PedsQL-MFS has been validated in patients with pediatric cancer, 50% of whom had ALL [49], and the Dutch version has been used previously in studies in children with ALL [28,50].

Walking Speed

The TUG will be used to asses walking speed. A chair, without arm rests, allowing the child to sit with his feet flat on the floor and his hip and knees flexed at 90° will be used. The chair will be positioned at a 3-m distance from a wall. The child will be asked to get up from the sitting position and walk "as fast as he can, without running" to the wall and touch a self-chosen picture on the wall, turn around without using the wall for support, walk back to the chair, and sit down. During the test verbal instructions will be repeated and encouragements are made. Time is recorded from the "go" cue to when the child is sitting down in the chair. The mean time of 3 trials will be considered as the test result [51]. The results of the test will be compared with age-specific reference values [52]. The TUG has shown excellent test-retest reliability (ICC 0.80-0.98) and interobserver reliability (ICCs 0.86 to 0.99) in the pediatric population [53], and the measurement was feasible in children with leukemia [47].

Physical Activity

Physical activity will be estimated using parent and self-reported questionnaires. We will use questionnaires generated in a Dutch population–based prospective cohort study investigating the development of a cohort of newborn children until young adulthood [54]. We will use parent proxy-reported versions for children aged 3-11 years, and child-reported versions for children aged 9-11 years [55,56]. These questionnaires comprise questions regarding frequency and duration of outdoor playing, sports participation, and active transport to/from school, as well as sedentary behavior such as watching television and computer use. Children aged 12-18 years will be asked to fill in the modified Baecke questionnaire, which consists of 3 components: school activity, sports activity, and leisure activity [57]. The results of the physical activity questionnaires (type of activity, frequency, and duration) will be compared with the Youth Compendium of Physical Activities [58]. The age-specific metabolic equivalent of the specific activity (either leisure or sports) will be used to estimate the energy expenditure in calories of an individual participant.

In addition, we hypothesized that generalized muscle weakness might be better expressed in a functional performance test, which is currently not a part of the frailty assessments. To explore the potential value of a functional muscle strength measurement in the concept of sarcopenia and frailty, we will use the "Time to Rise From the Floor Test" (TRF) [59]. The child will be asked to sit in the cross-legged position on the floor and to get up as fast as possible. The TRF will be performed 2 times, and for both performances, the quantitative performance (time in seconds) and a quality grade will be scored. We will use the "Gowers maneuver" as a quality performance by grading the amount of support needed to rise [60]. This is a standardized method to quantify on a 1-7 scale, where 1 means normal rising and 7 means unable to rise (Table 3).

All assessments will be performed by a pediatric physiotherapist (EV) or a trained medical doctor (AvH).

Table 3. Gowers maneuver grade: to quantify the ability to rise from the floor[a].

Performance	Grade
Normal rising	1
Butt-first maneuver, 1 hand on floor	2
Butt-first maneuver, 2 hands on floor	3
Unilateral hand support on thigh	4
Bilateral hand support on thighs	5
Arises only with aid of an object (table, chair)	6
Unable to arise	7

[a]Standardized method to quantify the quality of rising by grading the amount of support needed to rise.

Potential Determinants

We will explore the following potential determinants for the components of sarcopenia and physical frailty: sex, age, weight Z-scores at diagnosis, time since the start of treatment, registered toxicity and serious adverse events in induction therapy, cumulative vincristine dosage, dexamethasone pharmacokinetics, and carrier of relevant genetic variants (candidate single-nucleotide polymorphisms). Information regarding these factors will be extracted from the electronic patient files or is collected in the DexaDays-2 study. Dexamethasone kinetics are measured through peak levels (2-3 hours after the first dexamethasone administration on day 1 of the dexamethasone course) and trough levels (measured on day 6, at least 12 hours after the last dexamethasone dose administered on the previous evening). A peripheral blood sample to extract germline DNA, for evaluation of carrier status of relevant candidate single-nucleotide polymorphisms related to sarcopenia and physical frailty, is taken on T1 as part of the DexaDays-2 study. As a complete array (Illumina GSA) will be run, we will be able to select the most relevant specific additional single-nucleotide polymorphisms of interest, based on evidence from the most recent literature (Figure 1).

Statistical Analysis

The results of the physical frailty assessments, that is, SMI, handgrip strength, self-reported fatigue, walking speed, and physical activity (component scores), will be reported as means and SDs, or as median and interquartile ranges if data are non-normally distributed. The frequency of sarcopenia and physical frailty, as well as the individual components at all timepoints will be reported in percentages and schematically visualized. A correlation matrix will be built to explore coherence between the additional measure TRF and the other frailty components.

To evaluate the potential change in frailty components after 5 days of dexamethasone administration, a paired Student t test or Mann-Whitney U test will be used depending on the distribution of the data.

To evaluate whether the mean scores from the frailty components change between T1, T3, T7, and T11, 1-way ANOVA will be employed.

To study the effect of dexamethasone administration at T1, T3, T7, and prior to T11 on sarcopenia, physical frailty, and each individual components, generalized mixed models will be estimated. These models incorporate correlations between repeated responses on the same individual. Patient-specific random intercept, age, weight, time since the start of therapy, and cumulative vincristine dosage will be included in the model.

Multivariable linear regression model will be estimated to investigate associations between the potential determinants (patient- and treatment-related factors, pharmacokinetics, and genetics) and the assessment scores at T1 and T2 (SMI, handgrip strength, self-reported fatigue, walking speed, TRF, and physical activity). Results will be presented as regression coefficients along with 95% CI.

Multivariable logistic regression models will be estimated to explore associations between the aforementioned potential determinants and the occurrence of sarcopenia and physical frailty at T1 and T2. Odds ratios along with 95% CIs will be estimated.

Statistical analyses will be performed using software packages R Statistics (version 1.0.143; R Foundation) and SPSS (version 26.0.0.1) for Windows (IBM).

Results

Patient accrual started in 2018 and was finalized in spring 2021. A total of 105 children undergoing ALL therapy will participate in this study. From autumn 2021 statistical analyses will be performed.

Discussion

This paper describes the design of the first study on sarcopenia and physical frailty in children during maintenance therapy for ALL. The results of this study will provide information and create awareness on the magnitude and severity of sarcopenia and physical frailty in this specific group of children, which may help us understand which factors are associated with the large variations in physical ability between children receiving similar treatments. With this knowledge we may be able to identify physically vulnerable children at an earlier stage. This is important because being vulnerable to sarcopenia or frailty can complicate continuation of ALL therapy, independence in physical functioning, reaching motor milestones, and participation in daily life activities.

In this study we will assess sarcopenia involving a combination of low muscle mass *and* low muscle strength for the first time in patients with ALL. The SMM will be estimated using the Tanita MC-780 multifrequency segmental body composition analyzer, which is a validated, reliable, low-cost, fast, and non-invasive device to estimate body composition in the pediatric population [43].

None of the previous studies in children with ALL concerning muscle mass loss incorporated functional muscle strength assessments. We expect this to be of additional value because recent updates and consensus definitions state the importance of including muscle function in the concept of sarcopenia [61], as reduced muscle mass in combination with normal muscle strength may suggest malnutrition rather than sarcopenia [62]. Besides, in children, impaired muscle function directly influences motor development and is therefore relevant [63].

To explore this aspect further, we added a functional strength measurement to the assessment: the TRF. Although the handgrip dynamometer is a reliable instrument to measure handgrip strength in children [46], this may not be the first sign of reduction of muscle strength. We suspect that a generalized reduction in muscle strength (such as in sarcopenia and physical frailty) might be better shown by a functional performance test. The time and degree of support needed to rise from the floor are standardized measures to quantify deterioration and are associated with walking ability in children with muscular dystrophy [64].

The results of this study will provide knowledge about the effect of treatment with high doses of dexamethasone on muscle loss and other components of physical frailty, and therefore insights into the severity and risks of these side effects. Furthermore, through exploring potential determinants that could influence the occurrence of the sarcopenia or frailty, we might be able to identify children at risk for substantial problems at an earlier stage. As a result, we might be able to start targeted interventions and clinical studies on reducing the dexamethasone-induced components of physical frailty with, for example, nutrition and exercise.

This study has a number of strong points. First, because care for children with ALL in the Netherlands is centralized, a national cohort of Dutch children can be screened on eligibility for this study, rendering a large and hopefully unbiased population. Second, all children will have a physical frailty assessment by a skilled pediatric physiotherapist or a trained medical doctor, which benefits the validity and reliability of the performed physical assessment. Third, the burden of the study will be minimal because the assessments are performed during maintenance therapy of ALL, in which children experience less toxicities, fewer hospital admissions, and therapy is mainly administered at home and in the outpatient clinic. Fourth, we selected sarcopenia and frailty endpoints in accordance with previous research and the official definitions. Furthermore, we added 1 functional strength measurement, the TRF, based on expert opinion and on particular feasibility in children with ALL.

Some possible study limitations have to be taken into account as well. We will only include children participating in the DexaDays-2 study, which could potentially lead to selection bias, as patients who experience dexamethasone-induced neurobehavioral problems could be more motivated to participate because in that trial they will receive a drug to potentially reduce these problems. Furthermore, the subset of 50 children that will be measured longitudinally comprises children participating in the DexaDays-2 randomized controlled trial based on the severity of their neurobehavioral problems. These patients will receive physiological dosages of hydrocortisone or placebo during a 5-day dexamethasone treatment, and the cross-over will take place after 2 courses of dexamethasone treatment. We do not know if this affects the occurrence of sarcopenia and physical frailty in this cohort, for example, whether children with dexamethasone-induced clinically relevant neurobehavioral problems also show more physical side effects. Besides, within the DexaDays-2 study patients aged 3-18 years were selected, which complicated selecting outcome measures suitable for all participants. We succeeded in selecting measurements that have previously been used and validated in pediatric populations indicating their usefulness; however, with the exception of the PedsQL-MFS, none of the measurements has been validated in pediatric oncology patients.

In conclusion, this study is designed to determine the occurrence and severity of sarcopenia and frailty components in children during the maintenance phase of ALL therapy, and to determine the effects of administration of high doses of dexamethasone on physical vulnerability. With this study we aim to create awareness about these potential risks in children with ALL, as well as expanding our knowledge for reducing further side effects.

Acknowledgments

Conflicts of Interest

None declared.

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Abbreviations

ALL: acute lymphoblastic leukemia
CTCAE: Common Terminology Criteria for Adverse Events
DCOG: Dutch Childhood Oncology Group
ICC: intraclass correlation coefficient
PedsQL-MFS: Pediatric Quality of Life Inventory-Multidimensional Fatigue Scale
SMI: Skeletal Muscle Index
SMM: skeletal muscle mass
TRF: time to rise from the floor
TUG: Timed Up and Go Test

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Protocol

Community Opioid Dispensing After Injury (CODI): Protocol for a Population-Based Data Linkage Study

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Abstract

Background: There is an urgent need to reduce preventable deaths and hospitalizations from prescription opioid harms and minimize the negative effect opioid misuse can have on injured individuals, families, and the wider community. Data linkage between administrative hospitalization records for injured patients and community opioid dispensing can improve our understanding of the health and surgical trajectories of injured persons and generate insights into corresponding opioid dispensing patterns.

Objective: The Community Opioid Dispensing after Injury (CODI) study aims to link inpatient hospitalization data with opioid dispensing data to examine the distribution and predictive factors associated with high or prolonged community opioid dispensing among adults, for 2 years following an injury-related hospital admission.

Methods: This is a retrospective population-based cohort study of adults aged 18 years or older hospitalized with an injury in Queensland, Australia. The study involves the linkage of statewide hospital admissions, opioid prescription dispensing, and mortality data collections. All adults hospitalized for an injury between January 1, 2014, and December 31, 2015, will be included in the cohort. Demographics and injury factors are recorded at the time of the injury admission. Opioid dispensing data will be linked and extracted for 3 months prior to the injury admission date to 2 years after the injury separation date (last date December 31, 2017). Deaths data will be extracted for the 2-year follow-up period. The primary outcome measure will be opioid dispensing (frequency and quantity) in the 2 years following the injury admission. Patterns and factors associated with community opioid dispensing will be examined for different injury types, mechanisms, and population subgroups. Appropriate descriptive statistics will be used to describe the cohort. Regression models will be used to examine factors predictive of levels and duration of opioid use. Nonparametric methods will be applied when the data are not normally distributed.

Results: The project is funded by the Royal Brisbane and Women's Hospital Foundation. As of November 2021, all ethics and data custodian approvals have been granted. Data extraction and linkage has been completed. Data management and analysis is underway with results relating to an analysis for blunt chest trauma patients expected to be published in 2022.

Conclusions: Little is currently known of the true prevalence or patterns of opioid dispensing following injury across Queensland. This study will provide new insights about factors associated with high and long-term opioid dispensing at a population level. This information is essential to inform targeted public policy and interventions to reduce the risk of prolonged opioid use and dependence for those injured. The novel work undertaken for this project will be vital to planning, delivering, monitoring, and evaluating health care services for those injured. The findings of this study will be used to inform key stakeholders as well as clinicians and pain management services.

International Registered Report Identifier (IRRID): RR1-10.2196/36357

Introduction

Prescription opioids are responsible for a large proportion of the preventable mortality, morbidity, and health care burden in many countries. This is a global and escalating issue. Canada, the United States, and Australia have some of the highest per capita opioid consumption in the world [1,2]. In the United States, overdose deaths involving prescription opioids have significantly increased yearly from 1999 to 2017 and again in 2020 [3]. In 2020, at least 72% of all overdose deaths involved opioids [4].

The Australian Institute of Health and Welfare reports that, each day in Australia, there are almost 150 hospitalizations, 14 emergency department presentations, and 3 deaths involving harm from pharmaceutical opioids [2,5]. In Australia, there has been a 3-fold rise in deaths with opioids present from 2010 to 2019 [6]. In 2018, opioid deaths accounted for 64.5% of all drug-induced deaths in Australia [7]. While opioids are commonly prescribed to injured patients to treat pain, their continued use can be controversial as taking opioids for longer periods of time or in higher doses can increase the risk of addiction, overdose, and death [8]. Characteristics of initial opioid prescription including higher dosage, long-acting opioids, and duration of prescription [9,10], as well as individual patient characteristics such as anxiety, prior opioid exposure [11], and higher self-reported levels of pain [12], are associated with long-term opioid use. There is an urgent need to reduce these preventable hospitalizations and deaths and the negative effect they have on injured individuals, families, health care providers, and the wider community.

Data linkage between administrative hospitalization records for injured patients and community opioid dispensing provides an important opportunity to improve our understanding of opioid use and inform opioid use reduction and harm minimization measures. Through data linkage, we can map patterns and identify demographic and health predictors of high or long-term opioid dispensing and evaluate the feasibility of routine linking of hospital data into existing regulatory prescription medicine monitoring processes. In a new and unique contribution to this field of research, our study will link inpatient hospitalization data with community opioid dispensing data to examine community opioid dispensing among adults for 2 years following an injury-related hospital admission in Queensland, Australia. These data are vital to planning, delivering, monitoring, and evaluating health care services and are essential to inform targeted public interventions to reduce the risk of prolonged opioid use and dependence for those injured.

The overall study objective is to examine the distribution and predictive factors associated with high or prolonged community opioid dispensing among adults for 2 years following an injury-related hospital admission in Queensland. The specific aims are as follows: (1) determine the prevalence of community opioid dispensing following injury-related hospitalizations in Queensland; (2) examine the patterns of community opioid dispensing during the 2 years following an injury-related hospital admission among adults, in terms of frequency, quantity, time post injury, and geographic distribution, as well as for different injury types, injury mechanisms, and population subgroups; and (3) identify predictors of high-level and long-term community opioid dispensing in adults following an injury-related hospital admission, for different injury types, mechanisms, and population subgroups.

Methods

Study Design

This is a retrospective population-based cohort study of adults aged 18 years or older hospitalized with an injury in Queensland, Australia, using linkage of statewide hospital admissions, community opioid dispensing, and mortality data collections. We anticipate there will be approximately 150,000 patients included in the analyses.

Study Population

Queensland is a large state in Northeastern Australia covering an area of 1,852,642 km^2, with a total population of 5.2 million people in 2021 [13]. Injured patients often must travel large distances to specialist trauma care, and for rehabilitation and follow-up with pain management services.

Data Sources and Linkage

This study will link and analyze data extracted from three Queensland data collections, which are as follows: (1) admitted patient data from the Queensland Hospital Admitted Patients Data Collection (QHAPDC), (2) community opioid prescription and dispensing data from the Queensland Monitoring of Drugs of Dependence System (MODDS), and (3) Queensland Deaths data, from the Registry of Births, Deaths, and Marriages (BDM). At the date of the data request, the most recent data available for linkage were up to and including December 31, 2017.

Linkage will be undertaken by the Statistical Services Branch within Queensland Health, which enables linkage services to be conducted in a secure environment, ensuring compliance with strict security, privacy, and confidentiality requirements [14]. Using their Master Linkage File, individuals are matched across multiple health-related data collections and registries in Queensland using probabilistic and deterministic techniques followed by clerical review to manually inspect uncertain matches in probabilistic linkage [14]. Each person is then assigned a unique patient ID, which is appended to each data set to aid in ongoing linkage.

The MODDS data collection system has never been used for any record linkage before. Statistical Services Branch will undertake the new linkage of MODDS using the abovementioned principles. Once the data linkage has been completed, the Master Linkage File will be able to use the appended unique patient IDs in the MODDS database to enable

future research to be streamlined. However, a new real time online prescription monitoring system (QScript) was introduced in Queensland in 2021 and will contain the prescription monitoring data moving forward [15].

All adults hospitalized for an injury in Queensland, between January 1, 2014, and December 31, 2015, will be included in the cohort (Figure 1). The first injury-related hospital admission meeting the specified inclusion criteria described below will be identified as the "index injury admission." Admission to hospital for any cause will be extracted for 2 years following the index injury separation (discharge) date. Opioid dispensing data for each injured person will be linked and extracted for the period 3 months prior to the index injury admission date through to 2 years following the index injury separation date. Deaths data will be linked and extracted for the 2-year follow-up period. The study covers a maximum period from October 1, 2013, to December 31, 2017.

Figure 1. Community Opioid Dispensing After Injury (CODI) study design and data sources. ICD: International Classification of Diseases; MODDS: Monitoring of Drugs Dependence System; Q-BDM: Queensland Births, Deaths, and Marriages; QHAPDC: Queensland Hospital Admitted Patient Data Collection.
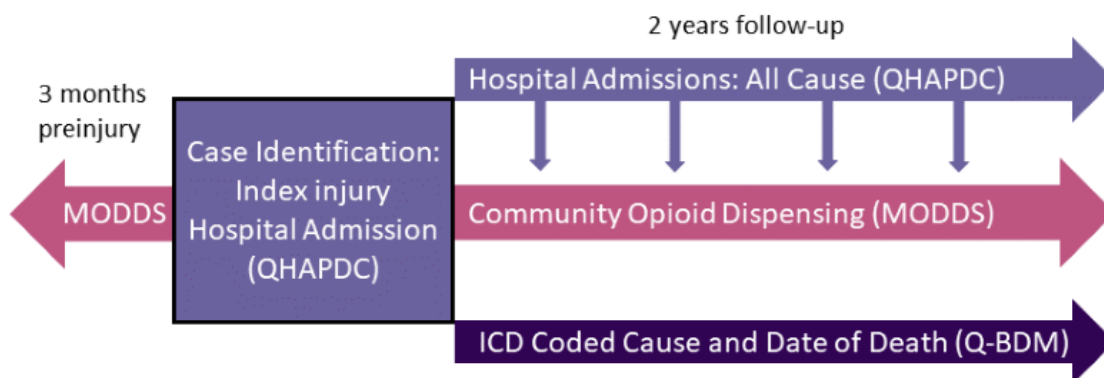
Hospital Admission Data: QHAPDC

Information collected on hospital admissions from the QHAPDC will include the hospital type (public or private) and health service area location; patient demographic details including age, sex, Aboriginal and/or Torres Strait Islander status, and area of residence. Patient admission details will include admission date, discharge date, care type, funding source, as well as International Classification of Diseases, 10th Revision, Australian Modification (ICD-10-AM) diagnosis codes, Australian Classification of Health Interventions procedural codes, length of stay in an intensive care unit, and separation destination.

Community Opioid Dispensing Data: MODDS

Community opioids dispensed for the cohort will be extracted from the MODDS data collection system. Medicines and poisons are classified into schedules according to the level of regulatory control over the availability of the medicine or poison required to protect public health and safety [16]. Opioids are included under Schedule 8 and are subject to monitoring in Queensland [16,17]. Schedule 8 are controlled drugs and are the highest level of control for prescription medicines.

Information extracted from the MODDS database will include the prescribed drug name, formulation, quantity prescribed, as well as prescribing and dispensing dates. Postcode of prescribing

doctor and dispensing pharmacy will also be obtained for geographic analysis. The MODDS database also includes a classification code based on confirmed diagnosis of drug dependence or notifications of long-term treatment, which will also be extracted alongside prescription data.

Mortality Data: Registry of Births, Deaths, and Marriages (BDM)

Mortality data for the injured cohort will be extracted from Queensland BDM including dates and cause of death. While the date of death is available in near real time, International Classification of Diseases (ICD)-coded cause of death is only available to Queensland Health when it has been processed by the Australian Bureau of Statistics. Coded cause of death data can take several years to become available, and until that time the cause of death is uncoded, but date of death is available.

Cohort Inclusion and Exclusion Criteria

The cohort will be identified from QHAPDC. Subjects will be included if they meet all the following criteria: aged 18 years and over; admitted to any Queensland hospital for injury-related acute care between January 1, 2014, and December 31, 2015 (all public and private hospitals will be included); and had a principal diagnosis from ICD-10-AM codes, S00-T98.

After extraction, cohort subjects will be excluded from the analysis if their place of residence is outside Queensland, or they died during index injury admission. Non-Queensland residents would be lost to follow-up because our data are for Queensland only, and patients dying in hospital will not have subsequent prescriptions.

Data Management and Classifications

Admitted Patient Data

It is possible for an individual to have multiple related or unrelated hospital admissions over the study period, so data sequencing logic is needed to distinguish records as (1) part of the same hospitalization (eg, a transfer); (2) a readmission or follow-up care related to the original index injury; (3) a new injury; or (4) a hospital admission for a reason other than injury. The study will apply data sequencing principles, logic, and definitions developed by Vallmuur et al [18], who use coded diagnoses, external causes, admission and discharge dates, transfer, and care type codes to distinguish between these records.

International Classification of Injury Severity Score (ICISS)

Injury severity for the index injury admission will be estimated using the International Classification of Injury Severity Score (ICISS), which is an ICD-based injury severity measure [19]. The ICISS is derived for each injured subject in the cohort by multiplying the probability of inpatient survival (ie, survival risk ratio) for each injury diagnosis (primary and all other diagnoses for the index injury admission). Using previously calculated survival risk ratios for Australia and New Zealand, ICISS can also be categorized into three severity categories: minor (≥0.99), moderate (>0.914 to <0.99), or serious (≤0.941) [20].

Accessibility/Remoteness Index of Australia

A measure of geographic remoteness is assigned to each subject in QHAPDC using their place of residence, mapped to the Accessibility/Remoteness Index of Australia [21]. Geographic areas are coded based on their road distance to service centers. Remoteness areas are classified as Major Cities, Inner Regional, Outer Regional, Remote, and Very Remote.

Socio-Economic Indexes for Areas (SEIFA)

A measure of socioeconomic status is assigned to each subject in QHAPDC using their place of residence and the Socio-Economic Indexes for Areas (SEIFA), developed by the Australian Bureau of Statistics [22]. SEIFA ranks areas in Australia according to relative socioeconomic advantage and disadvantage. The indices are based on information from the National five-yearly Census. In QHAPDC, SEIFA deciles are ranked from 1st decile for least advantaged through to the 10th decile for most advantaged.

Opioid Data

To enable comparisons across opioid prescriptions of different types, formulations, and strengths, prescription data will be converted to oral morphine equivalents (OME). The OME of a drug is the dose of oral morphine that would produce the same level of pain relief. OME is the preferred method for analysis of opioid use for research purposes because it adjusts for the difference in potency across available types and formulations of opioids, via conversion factors [2]. The conversion factors available from the Australian and New Zealand College of Anaesthetists Faculty of Pain Medicine will be used for this study [23].

Person-Years at Risk

A study end date will be created for all individuals in the cohort. The end date will be either the registered date of death, or if no death record exists, an individual will be deemed alive and therefore censored at the end of their 2-year follow-up period. Person-years at risk during the study period will be calculated individually as the time between the index injury separation date and the study end date.

Ethics Approval

Ethics approval and a waiver of consent was obtained from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/2018/QRBW/48236). Additional approval was obtained for the release of confidential information for the purposes of research under the provision of Section 280 of Public Health Act 2005, Queensland (QCOS/033343/RD007954). As part of this Public Health Act application, the data custodians of each data source (QHAPDC, MODDS, and BDM) were required to provide authorization for use of the data source. No patients, prescribers, or dispensers of opioids will be identifiable in this study, and only nonidentifiable data will be obtained.

Analysis Plan

Data analyses will be conducted using SAS 9.4 (SAS Institute). Appropriate descriptive statistics (frequencies, percentages, means, medians, standard deviations, and interquartile ranges) will be used to describe the injured cohort in terms of demographics, distribution of injury types, and mechanisms. Demographic and injury factors will be based on the characteristics recorded at the time of the index injury admission. Parametric and nonparametric tests will be used depending on the normality of the data.

While there are no agreed clinical guidelines for classifying opioid misuse, consideration will be given to classification of levels of opioid use based on total OMEs and duration or frequency of dispensing, informed by a review of the literature and applied consistently across the cohort. Regression models to examine demographic and abovementioned admitted patient factors predictive of levels and duration of opioid use will be applied. The opioid dispensing outcome data is not expected to be normally distributed. Logistic regression will be used for binary outcomes (eg, prolonged opioid use, yes/no), and either Poisson or Negative Binomial regression for counts of scripts and total OMEs, with an exposure time offset based on individual person-years at risk. Multinomial logistic regression will be used to examine opioid dispensing patterns, dependent on data and model parameters.

Results

As of November 2021, all ethics and data custodian approvals for the study have been granted. This included approval under the Queensland Public Health Act 2005 for the release of patient information. Data extraction and linkage has been completed by the Statistical Services Branch. Deidentified data have been provided to the research team. Data management and analysis is underway. The first results relating to an analysis of opioid dispensing patterns following blunt chest trauma are expected to be published in 2022, with subsequent papers planned.

Discussion

Findings

Little is currently known of the true prevalence or patterns of opioid dispensing following injury in Queensland. While we know there is a significant escalation in opioid dispensing in Australia and worldwide [24,25], we do not know if there is an escalation for injured persons, or the demographic, injury, and health factors that may contribute to high or long-term use, or how frequently this occurs. Information about patterns of prescription opioid use beyond the acute in-hospital phase following injury is needed to inform policies and to enable targeted interventions to address pain management and reduce harmful opioid use.

The data in MODDS provide information on all public and private opioid dispensing in the community across the state. It will show frequency and quantity of dispensing and duration. However, there is no health information in MODDS around the circumstances for prescribing. Understanding the health circumstances for opioid prescribing is important for appropriate interpretation of individual opioid use. Many people who are hospitalized for an injury experience repeat admissions in the months or years following the injury, which may include multiple surgical procedures that can be planned or unplanned [26,27], all of which may necessitate intervals of opioid analgesia. Additionally, independent health conditions may develop (eg, cancer) that also warrant opioid analgesia and need to be identified to avoid attributing opioid patterns to the injury event, rather than other comorbidities. Thus, linking all-cause hospitalization data longitudinally can help to better map the health and surgical trajectories of injured persons and provide insights to the corresponding opioid dispensing patterns during the same period.

No previous research projects have linked to the MODDS data set. Without this data linkage, the new information generated in this project would require a lengthy, costly, and logistically challenging prospective cohort study, individually following up thousands of injured people in Queensland over several years. The most recent data available for linkage at the time of the current study data requests were December 31, 2017. Since that time, there have been more proactive strategies for opioid stewardship at varying stages of implementation in many countries, including Queensland, Australia [28]. Such strategies are aimed to reduce prescribing and provide alternative pain management and monitoring for patients. While this study will provide important information for a particular point in time, it will be important to revisit similar data systems beyond the time period of this study for surveillance purposes to identify any changes in long-term trajectories of opioid dispensing for injured populations. The Opioid Advisory Committee of Queensland will provide expert guidance on the data interpretation, which will be an invaluable additional external review process.

Limitations

This is a retrospective observational study and will be limited to interpretations of association rather than causation. The data will be drawn from a defined period, and it will not be known if other societal factors or changes in the broader context of opioid prescribing in the same period may have influenced the results. The study sample is limited to persons hospitalized in Queensland; it will capture public and private hospitals but will not include injury-related presentations to emergency departments if patients are not admitted to the hospital, or injuries seen by general practitioners or community medical clinics.

There is no measure of pain severity in administrative patient data collections, and it will not be known if the opioid medications dispensed were administered in the prescribed manner by the person prescribed to. However, the data collection is statewide, and small sample deviations are unlikely to substantially affect population outcomes. Our data will not include some codeine-containing products that were available over the counter (Schedule 3) prior to 2018, or those in Schedule 4. All codeine preparations are now only either Schedule 4 or 8 medicines, and under new regulatory arrangements, are now included in prescription monitoring systems [25,29].

The linkage will not include hospitalization data prior to the study period, and therefore some people may have experienced prior injuries or previous hospital admissions that may have influenced opioid dispensing and will not be captured in the study. However, ongoing health issues are likely to be identified in the hospitalization database across the study period via primary and other diagnostic codes.

Although administrative data lack complex details on individual risk factors, they enable measurement of health service use longitudinally and comprehensively for the whole cohort. It will not be possible to identify persons who leave the state of Queensland; however, small sample deviations are unlikely to substantially affect population outcomes. While the quality of the Queensland Health linkage and data is considered high and manual clerical reviews are conducted, probabilistic and deterministic record linkage will always result in some false matches and mismatches; thus, the potential for error must be recognized [14].

Conclusion

This study will provide a comprehensive statewide profile of opioid dispensing for 2 years following an injury-related hospitalization. It will provide new insights about factors associated with high or long-term opioid dispensing, including patient demographics, injury types, injury causes and severity, as well as comorbidities and subsequent admissions and procedures. This information will aid planning and monitoring health care service provision and inform harm reduction

interventions for injured Queenslanders. This study will also inform the potential for routinely incorporating additional health data into the newly implemented real time monitored drug reporting system in Queensland to identify opportunities to reduce preventable mortality and morbidity.

Conflicts of Interest

None declared.

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Abbreviations

BDM: Births, Deaths, and Marriages
CODI: Community Opioid Dispensing after Injury
ICD-10-AM: International Classification of Diseases, 10th Revision, Australian Modification
ICD: International Classification of Diseases
ICISS: International Classification of Injury Severity Score
MODDS: Monitoring of Drugs Dependence System
OME: oral morphine equivalent
QHAPDC: Queensland Hospital Admitted Patient Data Collection
SEIFA: Socio-Economic Indexes for Areas

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Protocol

Improving Viral Load Suppression Among Men and Children Active in Care Through Community-Designed and Led Solutions: Protocol for Retrospective Closed Cohort Study in Eastern Uganda

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Abstract

Background: In collaboration with facilities, communities, district local government, and the United States Agency for International Development (USAID) implementing partners, the iDARE methodology was implemented at the community level to address root causes of low HIV antiretroviral therapy adherence among men and children actively enrolled in care, resulting in low viral load suppression (VLS) in two districts in the eastern region of Uganda. The methodology encourages the use of cocreated sustainable solutions addressing gender, youth, and social inclusion issues to reduce barriers to care and reach the 95-95-95 Joint United Nations Programme on HIV/AIDS target for HIV epidemic control. We aim to measure the impact of iDARE on VLS for men and children active in care and investigate the practical scale up of the solutions designed using the iDARE methodology.

Objective: The primary objective of this study will be to measure the implementation impact of the iDARE methodology at the facility and community levels on VLS for people living with HIV. The secondary objective is to investigate the practical scale up of the iDARE methodology using evidence-based gender, youth, and social inclusion social behavior change packages to rapidly meet the Ugandan Ministry of Health targets for VLS.

Methods: A retrospective cohort study design will be used to analyze program data that aims to increase the rates of VLS in men and children who are classified as active in care using community engagement and quality improvement techniques. We will examine 3 pilot health centers' data from a USAID-funded program aimed at social behavior change to increase health-seeking behavior in Uganda. Based on the iDARE process and results, change packages were developed to highlight lessons learned and best practices in order to share with subsequent implementation sites.

Results: The USAID-funded Social and Behavior Change Activity began implementation of iDARE in September 2020, with baseline data collected in August 2020.

Conclusions: Data on viral load suppression was collected from facilities on a monthly basis to record progress toward the 95-95-95 goal. The expected primary outcome is an increase in actively enrolled men and children reaching VLS in order to meet the Ugandan Ministry of Health target of 95% VLS among those active in care.

International Registered Report Identifier (IRRID): DERR1-10.2196/32784

KEYWORDS

XSL•FO

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Introduction

Background

Despite the immense global effort, the HIV epidemic remains a threat and a leading cause of morbidity and mortality. Persistent disparities by geographic region and demographics, including age and sex, have led to an unbalanced burden of disease. Globally, there is a 10% difference in antiretroviral therapy (ART) rates between males and females, 68% and 79%, respectively [1]. There are also regional disparities, especially in Sub-Saharan Africa (SSA) [2]. Globally, more than 37 million people are living with HIV, and two-thirds of those individuals are in SSA despite only having 15% of the global population [1,2]. Furthermore, in SSA, there is more than a 20% difference between adults and children classified as active in care for ART treatment, 74% of adults (aged ≥15 years) and 53% of children (aged <15 years) [1].

In Uganda, there are roughly 1.46 million people living with HIV, and HIV prevalence among adults aged 15-49 years is 6%, and among children aged 0-14 years, it is 0.5% [3]. While rates are dropping, HIV incidence continues to outpace morbidity; therefore, the overall prevalence of HIV in Uganda remains high [3,4]. Of the people living with HIV, 86% are enrolled in treatment and are active in care, meaning they are receiving ART [3]. Of those active in treatment, 89.8% have achieved viral load suppression (VLS) [3]. However, Uganda did not meet the 90-90-90 goals as set by the World Health Organization's 2020 Global Health Sector Strategy on HIV, but the country is now working towards the new 95-95-95 goals to control the HIV epidemic. The 95-95-95 goal states that 95% of people living with HIV know their HIV status; 95% of people diagnosed with HIV receive ART, and 95% of people living with HIV on ART treatment achieve VLS [2,5]. Complicating the Ugandan response to the epidemic is the disparities in burden across geographical areas and between socio-economic and social demographic subpopulations.

In 2020, the United States Agency for International Development's Social and Behavior Change Activity (USAID SBCA) in Uganda began with the vision of Uganda where individuals and communities are healthy, resilient, and supported by strong and adaptable systems and institutions to lead productive lives. SBCA works across Uganda in HIV, malaria, tuberculosis, gender-based violence, family planning, maternal newborn child health, and nutrition. Under this project, WI-HER began the application of the iDARE methodology to address gaps in VLS. iDARE, developed by Dr. Taroub Harb Faramand, was implemented to support the locally-led improvement of HIV VLS rates under the USAID SBCA program by focusing on gender, youth, and social inclusion (GYSI) gaps across subpopulations with a disproportionate burden of poor health outcomes. During a formative data review on HIV VLS in the eastern region of Uganda, WI-HER, in partnership with district local governments in Tororo and Kapachorwa districts, identified men and children as key subpopulations with the largest gap in VLS that was impacting district and overall national efforts in achieving 95-95-95 targets.

A detectable viral load in people living with HIV is associated with increased morbidity, mortality, and transmission [2]. Strong adherence to ART suppresses viral load to undetectable levels for people living with HIV, greatly reducing the risk of transmitting HIV to others. According to the Ugandan Ministry of Health (MOH) 2019 HIV Epidemiological Surveillance Report, VLS is 89.8% for people living with HIV who are on ART and 75% for all people living with HIV [3]. However, this is not consistent across age and sex-disaggregated data; 48% of children (aged <15 years) active in care for HIV have achieved VLS; for men, the rate is 68% [3]. In Uganda, low ART adherence for children and men has been associated with food insecurity, stigma, lack of caregivers for support, and forgetting [6-9].

As the third goal for achieving the 95-95-95 targets, VLS requires quality services from the facility but also adherence to treatment, including appointment keeping and clientele taking medication in a timely manner. In order to increase adherence, this requires the clientele to shift their behavior and/or mindset. For newly diagnosed individuals living with HIV, in addition to adjusting to life living with a chronic disease, GYSI factors impact an individual's perceptions, beliefs, attitudes, and decisions, which impact their behavior and, ultimately, health outcomes, namely VLS. Social and behavior change (SBC) programs have a history of increasing VLS, especially among high-risk populations in Uganda [10,11]. SBC is rooted in Social and Behavior Theories that support the necessity of interventions aimed at improving health behaviors [12]. Community-based SBC interventions to improve the delivery of ART have been shown to reduce the disparities between males and females in VLS in SSA [13-15]. Additionally, SBC has been effective in increasing ART adherence for youth living with HIV in Uganda [16]. The Ugandan MOH and USAID SBCA have taken steps to streamline SBC efforts to increase VLS [10,11].

Rationale

This study will provide practical evidence of the feasibility and efficacy of SBC to increase the rate of VLS within male and children subpopulations that bear a disproportionate burden of unsuppressed cases for those active in care. In addition to the efficacy of the iDARE methodology at improving VLS rates, the study will examine the feasibility and the scalability of the iDARE approach through the staggered timing of the clustered cohort design.

Evidence provided in this study will support the scaling of the iDARE methodology within Uganda, in partnership with the MOH, district local government, and implementing partners, to meet the 95-95-95 target set by the UNAIDS Global Health Sector Strategy on HIV. In addition to meeting the 95-95-95 target, improving adherence and increasing VLS will avoid the development of HIV antiretroviral drug resistance (HIVDR) in the Ugandan context. An early warning indicator assessment in Uganda indicated a high potential for HIVDR [3]. Raising numbers of HIVDR cases would lead to the need to shift ART strategies, which could result in cost increases for the MOH and international pharmaceutical support organizations. In the Ugandan 2019 HIV Epidemiological Surveillance Report, the MOH stated the need to improve the efficiency of HIV services

to reduce morbidity and reduce the incidence of HIV so that Uganda may achieve control of the HIV epidemic [3].

Aims

The primary aim of this study will be to examine the implementation impact at the facility and community levels of the iDARE methodology on VLS for people living with HIV. The secondary aim is to investigate the practical scale up of the iDARE methodology using evidence-based GYSI social behavior change packages to rapidly meet MOH targets of VLS.

Methods

Study Design

This is a retrospective closed cohort study reviewing program data collected directly from facilities from WI-HER SBC efforts through USAID SBCA. The cohorts are the pilot 3 facility catchment areas for implementation of iDARE to address VLS in men and children. iDARE implementation was staggered using lessons learned and best practices in the form of GYSI social behavior change packages from the preceding facilities to inform subsequent facilities. We hypothesize that the iDARE methodology will lead to a marked improvement in HIV VLS and will be rapidly scalable using GYSI social behavior change packages as guides. The actions taken and data collected were for the implementation of public health and clinical programs for those intended purposes.

Ethical Considerations

Data analyzed for the retrospective study are public health program data; data were not collected for the purpose of research. Therefore, this study does not require IRB approval [17].

Setting

Implementation of the iDARE methodology to increase VLS for men and children active in care took place at 3 pilot facilities across 2 regions in Uganda. Sites were selected based on accessibility, burden of disease, and local resources.

The Bukedi subregion, with a population of 2,296,686, is in the eastern region of Uganda at the border of Kenya [4,18]. Within the Bukedi subregion, implementation took place in Tororo District, with an estimated population of 607,803 [4,18]. The iDARE coach, along with the district health team, selected the Nagongera Health Center (HC) IV and Mulanda HC IV based on low levels of VLS among men and children for those classified as active in care at the baseline assessment using DHIS2 data in August and September 2020, respectively. Implementation of iDARE began in September of 2020 in the Nagongera HC IV and in October 2020 for Mulanda HC IV.

The Sebei subregion is also in the Eastern Region of Uganda, north of Bukedi subregion. Within the Sebei subregion, implementation took place in Kapachorwa District, which has an estimated population of 125,785 [4,18]. The iDARE coach, along with district health team and local implementing partners, selected Kabeywa HC III from a baseline assessment using DHIS2 data in December 2020, and implementation of iDARE

to address low levels of VLS in men and children began in January 2021.

iDARE

Grounded in behavior theory and human-centered design, the iDARE methodology is based on improvement science and drives locally-led solutions. The methodology, developed by Dr. Taroub Harb Faramand, draws from classic theories and concepts that have a robust evidence base and application in the field, such as the theory of planned behavior, the social cognitive theory, and the diffusion for innovations, as well as innovative approaches from parallel fields including behavioral insights, behavioral economics, and consumer/marketing research [19-21]. The iDARE methodology is a results-driven and inclusive methodology for supporting community-designed and led solutions and engagement to achieve SBC. It helps local stakeholders identify a shared goal, think through gaps, and together come up with sustainable, locally-owned solutions. iDARE promotes GYSI at its core to determine root causes of any gap or challenge and thinks through locally (contextually and culturally) appropriate ways to overcome the root causes and drive sustainable social and behavior change. The steps are as follows:

1. Identify challenges and/or gaps in achieving an overall goal or outcome with particular emphasis on identifying GYSI issues, gaps, or barriers.
2. Design effective local solutions for achieving the intended outcome alongside stakeholders and ensure inclusive participation from program constituents using a vast toolbox of best practices, resources, and methodologies.
3. Apply and assess activities with clear indicators and feedback loops for continuous improvement;
4. Record performance against indicators as well as successes, failures, and additional gaps and challenges that have arisen during implementation.
5. Expand and scale successful solutions to realize the greater impact and share activity experiences widely for learning.

Used as an implementation framework, iDARE emphasizes close partnerships with stakeholders and clear sustainability metrics for achieving an exit strategy to ensure that initiatives are locally-owned, sustainably delivered, responsibly managed, and properly documented. For the USAID SBCA program in Uganda, iDARE is used to bring together community and district-level stakeholders to support their communities to improve health outcomes.

Social and Behavior Change Packages

Across the 3 pilot sites, implementation of iDARE was staggered to build upon lessons learned and best practices from the preliminary sites. Successful iDARE solutions were recorded into Social and Behavior Change Packages, categorized for the target populations, men and children. The change packages were then used in subsequent sites in order to rapidly share lessons learned.

iDARE teams use their iDARE journal to record existing and new gaps, barriers, and issues impacting their targeted goal/outcome. With the WI-HER coach's support, iDARE teams transfer successful solutions recorded in the iDARE journal to

develop the Social and Behavior Change Packages. These packages are a tool for iDARE teams to have a resource guide of successful solutions that led to social and or behavior change, with qualitative and quantitative data as evidence to justify the successful change. They indicate the clinical area of iDARE implementation, target population, GYSI barrier being addressed, solutions that have been implemented, including step-by-step guidance on how the solutions were implemented, and the results. These packages may then be used at subsequent sites to drive scale up and cross-site learning in order to direct iDARE teams towards useful solutions from other sites. While these solutions have worked in one site, it is important to note that iDARE is a process, and solutions must be tailored to the culture, resources, and priorities for every context.

iDARE Teams

An iDARE coach supported the implementation of iDARE across all 3 sites. iDARE coaches are experts in SBC, GYSI, and improvement science trained by WI-HER on the iDARE methodology. iDARE implementation for improved VLS was supported by one iDARE coach across all 3 pilot sites. The iDARE coach across these 3 sites was directly trained by Dr. Faramand almost 10 years ago and has been working in the field using iDARE since.

The iDARE coach met with the district health teams and a local implementing partner to identify local facilities based on the epidemiological data for VLS within the Tororo and Kapachorwa districts. District health teams and local implementing partners were incorporated into the implementation process to build sustainable coaching and supervision within the local context after the exit of the iDARE coach. The district-level health team and local implementing partners make up the district-level iDARE teams.

The district-level iDARE team identified facility stakeholders for inclusion in the community-level iDARE teams through their direct role in HIV care and treatment or data management at the facility. For example, the lead nurse of the HIV clinic may be selected due to their direct interaction with HIV clients in the facility. District-level iDARE team members worked together with facility stakeholders to conduct semistructured interviews with nonsuppressed actively enrolled men and children (and their caregivers) to identify community influencers to add to the community-level iDARE team. Influencers were selected by the target populations themselves (in this case, the nonsuppressed actively enrolled men and children) through rapid analysis of interviews with existing target health facility patients and with the target populations at large. Examples of community influencers are priests, teachers, and local administration, but it is not necessary to have an official position to be a community influencer.

The facility team members and community influencers together make up the community-level iDARE teams. Across all 3 pilot sites, district and community-level iDARE teams were formed for the clinical health area of HIV VLS. At the community level, the iDARE coach worked with each community-level team to assign key roles, including community lead, clinical lead, and data focal person, based on the role of the team members within the facility and consensus from the wider community-level iDARE team.

iDARE teams are flexible in their design and setup in order to rapidly address ongoing and/or newly identified gaps and challenges (Figure 1). At Nagongera HC IV, in the initial iDARE team, there were 3 facility health workers and 6 community influencers. However, during implementation, an additional 4 influencers were identified to join the team. In the initial Mulanda HC IV iDARE team, 3 facility health workers and 8 community influencers were included. During the iDARE process, an additional 2 influencers and 1 health worker were added to the team. At the Kabeywa HC III, 4 facility health workers and 10 community influencers were on the initial iDARE team, with an additional community influencer added since implementation.

Figure 1. Community level iDARE teams from Nagongera, Mulanda, and Kabeywa Health Centers.
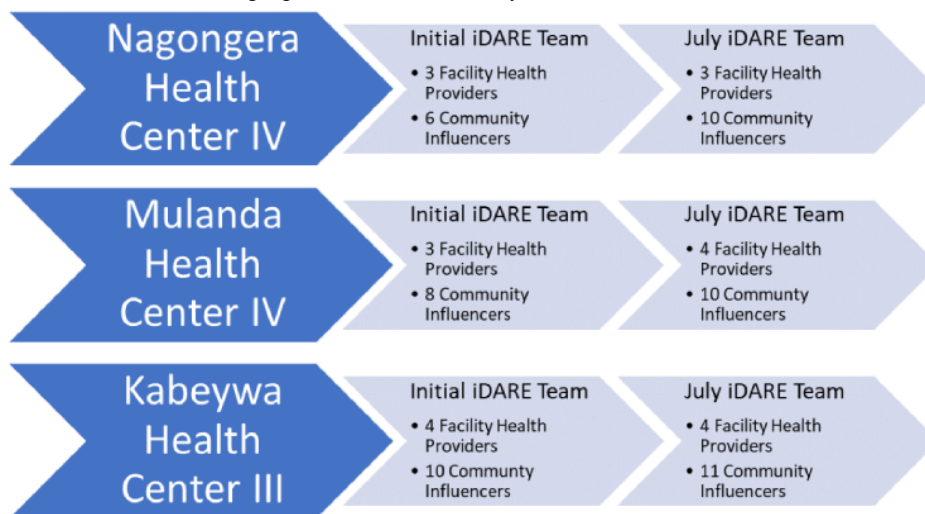
iDARE Implementation

The initial step in the implementation of iDARE at the community level is orientations facilitated by the iDARE coach with the community-level iDARE teams. With support from the coach, iDARE teams identify a SMART (specific, measurable, attainable, relevant, time-bound) goal and agree upon an indicator to measure progress in achieving the SMART

goal. Orientations are followed by monthly check-ins between the iDARE coach, the district-level iDARE teams, and community-level iDARE teams to gather data and support the ongoing iDARE process to achieve the target goal. During these visits, additional coaching is done on topics of GYSI, data management, and continual root cause analysis. Continued coaching sessions are intended to support and build capacity in the iDARE teams, specifically in data management and continuous improvement in the iDARE team's indicator. Within 6 months of iDARE implementation, in-person site visits drop from monthly to quarterly with monthly virtual data checks.

Facility orientations took place over 2 days and were conducted by the iDARE coach. The iDARE coach was consistent across all study sites. The focus of day 1 is GYSI concept sensitization and the introduction of the iDARE methodology. The second day focuses on the first 2 steps in the iDARE process. Namely, identifying root causes of low adherence to ART in the GYSI context. This is done through interviews and rapid analysis of people living with HIV and additional stakeholders within the community. Once the root causes of low adherence are identified, the community-level iDARE teams design SBC solutions to address the root causes. They then complete an action plan for implementation, including assigning roles and responsibilities within the iDARE team and developing indicators to measure success based on the clinical goal. For VLS, the facility used the 95-95-95 USAIDS goal; therefore, the indicator target was set to 95% VLS for those active in care. After the iDARE orientation, the solutions and action plans were applied by the responsible persons to address the GYSI gaps impacting health outcomes. The implementation process included the ongoing collection of the data to measure the impact of the solutions against the indicator target. In this process, the community-level iDARE teams assessed the solutions for the successes and failures. Data were recorded, along with processes, into the social and behavior change packages to share best practices and lessons learned with subsequent facilities that face similar GYSI gaps in VLS; in doing so, facilities can expand on the successful solutions across new implementation sites.

Due to the ongoing COVID-19 pandemic, lockdowns restricted movements between districts and led to adjustments to the iDARE implementation. During the first government lockdown in 2020 and the second in June to July 2021, monthly coaching visits were switched to a hybrid approach, and community-level iDARE teams came together at the facility for virtual support from the iDARE coach. Facilities practiced social distancing as well as mask and handwashing protocols to mitigate the risk of COVID-19.

Regular learning sessions were held to support the continuous learning and adaptation among iDARE teams within each site and across facilities. Through these meetings, lessons learned and best practices were shared; this process aided in the development of comprehensive Social and Behavior Change Packages for scaling up.

Participants

There was no recruitment; all persons who qualified as having not achieved VLS despite being active in care at baseline were included from all 3 pilot catchment areas in closed cohorts. Recently diagnosed people living with HIV were encouraged to initiate ART. Six-months post-ART initiation, individuals were classified as active in care if they had been up taking ART at a 95% adherence and were eligible for viral load testing. Collecting data on all individuals active in care within the catchment greatly reduced sampling bias, as no samples were taken. This method also provided practical, real-world evidence for the implementation of iDARE at the community level.

Respectively, men and children active in care at the time of baseline were included in the study as distinct closed cohorts. All people living with HIV, active in care at the time of implementation within the iDARE catchment area, constitutes having been exposed to the iDARE intervention. Therefore, they are included in the population-level analysis.

Outcomes

After an individual active in care reaches 95% adherence in the facility health records and maintains appointments for 6 months, they were then tested for VLS using serum and dried blood samples for a PCR test. Viral load suppression refers to the proportion of HIV RNA within the individual's blood. To meet the criteria to be VLS, the individual must have HIV RNA <1000 copies per milliliter of plasma. The data was dichotomous, either confirmed as virally suppressed or not, and presented as a rate of the population level.

The primary outcome was the rate of VLS for those active in care at each of the 3 pilot facilities. The focal data person on the community-level iDARE team reviewed and reported from the facility records on people living with HIV that were active in care. Facility HIV registries were the source document; they hold de-identified client records on HIV, ART, and VLS. VLS data was shared with the iDARE coach for data collection purposes to track the process of improving health outcomes. Data was then verified by the iDARE coach by examining the registries during site visits.

Program data was collected and maintained on the secured organization drive. The data was never paired with individually identifiable markers, which were not collected by the program teams.

Data will be analyzed using R for descriptive and inferential statistics (version 4.1.2; R Foundation for Statistical Computing).

Results

Implementation began in September 2020 for iDARE in Tororo District at Nagongera HC IV, followed by Mulanda HC IV in October 2020, then in Kapachorwa District at Kabeywa HC III in February 2021. The baseline was assessed the preceding month before implementation at each of the sites to determine the total number of men and children classified as active in care and the total number of those that were active in care that had achieved VLS. The average across all sites at baseline indicated 72% (668/992) of males and 63% (103/163) of children active in care had achieved VLS. Baseline data across all 3 pilot sites are provided in Table 1 below.

Table 1. Cohorts by group and facility at baseline.

Cohorts	Nagongera HCIV (August 2020)	Mulanda HCIV (September 2020)	Kabeywa HCIII (January 2021)	Total
Children (male and female, 0-19 years)				
Virally suppressed, n (%)	62 (60%)	38 (73%)	3 (38%)	103 (63%)
Active in Care, n	103	52	8	163
Men (20 years and over)				
Virally Suppressed, n (%)	357 (65%)	296 (85%)	15 (60%)	668 (72%)
Active in Care, n	550	347	25	922

Discussion

Data on VLS was collected from facilities on a monthly basis to record progress towards the 95-95-95 goal. The expected primary outcome was increasing actively enrolled men and children reaching VLS to meet the Ugandan MOH's target of 95% viral suppression among those active in care. Solutions identified as successful are to be shared as an evidence base for scale up at the national level through leveraging information sharing through the social and behavior change packages developed over the course of implementation. Due to the high level of contextualization of solutions, social and behavior change packages will need to be continually updated to track lessons learned, highlight best practices, and include up-to-date data on the ongoing implementation of iDARE to address GYSI gaps in HIV care, including in VLS.

Conclusions

The data collected on the iDARE implementation as a means to increase VLS among men and children will aid in the contribution to the evidence base of addressing GYSI issues impacting access and uptake of services. Additionally, anticipated results will reflect the necessity of using locally-led, inclusive quality improvement techniques that GYSI based barriers to care, such as iDARE, are a key element in the global goal to end the HIV pandemic.

Limitations in the design include the nonexperimental comparison. To support Uganda's goal to close the gap in achieving the HIV 95-95-95 goals, next step recommendations include comparison site data on VLS for men and children as a means to determine a more accurate effect size for iDARE.

Conflicts of Interest

None declared.

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Abbreviations

ART: antiretroviral therapy
CCP: Johns Hopkins Center for Communications Program
GYSI: gender, youth, and social inclusion
HC: health center
HIVDR: HIV antiretroviral drug resistance
MOH: ministry of health
SBC: social and behavior change

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SBCA: Social and Behavior Change Activity
SSA: Sub-Saharan Africa
USAID: United States Agency for International Development
VLS: viral load suppression

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Protocol

Schwartz Rounds for Staff in an Australian Tertiary Hospital: Protocol for a Pilot Uncontrolled Trial

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Abstract

Background: Schwartz Rounds are a unique, organization-wide interdisciplinary intervention aimed at enhancing staff well-being, compassionate care, teamwork, and organizational culture in health care settings. They provide a safe space wherein both clinical and nonclinical health staff can connect and share their experiences about the social and emotional aspects of health care.

Objective: Although Schwartz Rounds have been assessed and widely implemented in the United States and United Kingdom, they are yet to be formally evaluated in Australian health care settings. The purpose of this study is to evaluate the feasibility and impact of Schwartz Rounds on staff well-being, compassionate care, and organizational culture, in a tertiary metropolitan hospital in Brisbane, Australia.

Methods: This mixed methods repeated measures pilot study will recruit 24 participants in 2 groups from 2 departments, the intensive care unit and the gastroenterology department. Participants from each group will take part in 3 unit-based Schwartz Rounds. Primary outcomes will include the study and intervention feasibility measures, while secondary outcomes will include scores on the Maslach Burnout Inventory–Human Services Survey, the Schwartz Centre Compassionate Care Scale, and the Culture of Care Barometer. Primary and secondary outcomes will be collected at baseline, after the Rounds, and 3-month follow-up. Two focus groups will be held approximately 2 months after completion of the Schwartz Rounds. Descriptive statistics, paired t tests, chi-square tests, and analysis of variance will be used to compare quantitative data across time points and groups. Qualitative data from focus groups and free-text survey questions will be analyzed using an inductive thematic analysis approach.

Results: The study was approved by the Mater Hospital Human Research Ethics Committee (reference number: HREC/MML/71868) and recruitment commenced in July 2021; study completion is anticipated by May 2022.

Conclusions: The study will contribute to the assessment of feasibility and preliminary efficacy of the Schwartz Rounds in a tertiary Australian hospital during the COVID-19 pandemic.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12621001473853; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=382769&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/35083

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Introduction

Background

Employees working within health care settings are at greater risk of mental health concerns compared with the general public. Health care workers have been found to experience high rates of work-related stress, burnout, depression, anxiety, and suicidal ideation [1-3]. This has also been shown to impact the quality of patient care and compassionate care [4]. Furthermore, the current COVID-19 pandemic has brought into focus the well-being of health care staff and compassionate care with unprecedented challenges across health care settings, increased workload, uncertainty, and stress [5]. It has highlighted the need for interventions aimed at preventing and treating psychological distress and disorders in health care workers and improving organizational support and culture [5].

Recently, an Australian framework, named "Every Doctor, Every Setting," has been designed to support the mental health and well-being of doctors and medical students [6]. Its guiding principle is that improving the well-being of doctors and medical students is a key enabler of good patient care. The framework outlines that, in addition to strategies to increase the well-being of health professionals, strategies that focus on improving team and system cultures are to be promoted, as individual-level approaches often fail to be translated into practice benefits due to organizational cultural barriers. This is supported by the literature on the importance of health care worker support, within an environment that is conducive to open discussions about the social and emotional aspects of their work [7].

Various interventions have been implemented within health care settings to increase empathy and improve patient care, reduce work stress and burnout, and improve staff well-being [6-8]. While many interventions have been evaluated, few allow for organization-wide involvement (ie, multiple disciplines, both clinical and nonclinical staff), most might be one-off events, that rely solely on individual involvement (ie, counseling), and require all attendees to participate. Therefore, there is a pressing need for interventions in health care that are focused on the social and emotional aspects of care, that are ongoing, allow all staff to attend and choose to participate, and require engagement by both individual staff and the larger institution. One such format that provides a safe space for both clinical and nonclinical health care staff is Schwartz Rounds [9,10].

Schwartz Rounds in Health Care Settings

Schwartz Rounds have been developed by the Schwartz Centre for Compassionate Care as a unique intervention where health care workers can share and reflect on their experiences of the social and emotional aspects of health care [10]. Schwartz Rounds (hereafter the Rounds) were inspired by the late Kenneth Schwartz who recognized that his own cancer care was improved through authentic, individualized, and compassionate care by health care workers from all professions.

To facilitate Hospital staff attendance and participation, the Rounds were designed to follow the Hospital medical rounds structure in that they have a topic, a panel, and an audience; they are conducted monthly (for approximately 1 hour), and usually during the lunch time and with food provided for the participants. The key distinguishing features of the Rounds are that their content is focused on the emotional and social aspects of care rather than the clinical aspects, and that they are open to all staff, clinical and nonclinical. The purpose of the Rounds as an intervention aimed at exploring and sharing the emotional and social challenges of providing care, rather than solving problems or debriefing, is stated at the outset of every Round. The Rounds start with a brief introduction of their history and purpose. This is followed by 2-4 panelists sharing their stories about the emotional aspects of care for about 5 minutes each, and a facilitated, reflective discussion where the participants share their thoughts and reflections on the content heard.

There is evidence that the Rounds have a positive impact within hospital and educational settings for staff, patients, and organizations [11,12]. They have been reported to increase compassionate patient care; improve teamwork and staff relations; improve organizational and institutional culture (ie, enhanced patient-centered care and shared purpose); normalize and validate emotional reactions and eradicate the stigma of emotional responses within a health care setting; and positively impact staff through reducing their work-related stress, and improved psychological well-being and ability to respond to challenges [13-25]. The Rounds have been shown to be sustainable with organizational support, strong leadership, and a committee designed to run and organize the Rounds. They have been widely implemented in the Unites States and United Kingdom and are starting to be implemented in other countries including Canada, Ireland, New Zealand, and Australia.

Despite the considerable evidence regarding the benefits of the Rounds, a recent systematic review has identified that the overall level of evidence is low to moderate with many of the studies lacking methodological rigor [8]. Furthermore, the review did not find any research examining the feasibility and efficacy of Schwartz Rounds in Australian health care settings. This study protocol is based on the known process and features of the Rounds but it was developed to suit an Australian metropolitan tertiary hospital. The protocol incorporates a COVID-19 safety plan as the Rounds will be delivered in the context of the COVID-19 pandemic restrictions. It describes the delivery of the Rounds in the unit-based format that may provide additional benefits in the areas of team cohesion and sense of a shared purpose for participating units.

Study Aims and Objectives

The primary study objective is to examine the feasibility of the Rounds in an Australian setting through the assessment of participant feedback provided via postround evaluation surveys and focus groups, Rounds' attendance, and fidelity.

The secondary study objective is to evaluate the impact of Rounds on improving staff well-being, compassionate care, and organizational culture.

The research questions we explore within the study are as follows:

- What are the factors that underpin feasibility of Rounds?
- What impact does Rounds have on staff well-being, compassionate care, and organizational culture?

Methods

Study Design and Setting

This prospective pilot study will utilize a mixed methods, uncontrolled, repeated measures design. This design was selected to test the feasibility and preliminary efficacy of the Rounds and inform possible adaptations of their content and structure that may be needed in future larger studies. The study will be conducted in Mater Hospital, an Australian tertiary metropolitan hospital that offers a wide range of medical, surgical, and mental health services for adolescents and adults.

Participant Selection and Recruitment

As this is a pilot study of Schwartz Rounds in hospital settings, main eligibility criteria for participation in the study will include being employed at Mater Hospital and willingness to participate in all aspects of the study (focus group participation is not mandatory). Members of the research team and planning committee will be excluded from participation in the study to avoid any risk of bias. Participants will include both clinical staff (ie, nurses, doctors, allied health) and nonclinical staff (ie, administrative/managerial, catering and ward services, health security, pastoral care) employed at Mater Hospital.

Staff interested in participating in the Rounds will receive an email from the department head that will include the research flyer and the participant information and consent form, and they will be asked to return the signed consent form to the research team via email. Potential participants will be given the opportunity to receive further information and ask questions to the research team regarding the study over the phone or via email. Once consent forms have been received, participants will be sent a link to the online baseline survey to complete prior to commencement of Rounds. The surveys will be distributed by the study research assistant, via email, 1-2 weeks prior to each Round and returned by the day of the Round. Facilitators will meet with the panel members 2-3 weeks prior to each Round, for 1-2 hours, to discuss the topic and familiarize them with the Rounds processes.

During the study planning, the research team liaised with several Mater Hospital departments, and based on the staff interest and teams' needs, selected 2 teams to participate, the intensive care unit (ICU) and the gastroenterology department. The study participants will therefore be recruited in 2 groups, the ICU group and the gastroenterology group, who will complete 3 unit-based Rounds each. The participants will complete a quantitative survey focusing on staff well-being, compassionate care, and organizational culture at baseline, after the Round, and 3 months' follow-up. They will also complete a short postround feedback form after each Round that incorporates both Likert scale questions and an open-ended comment section. During consenting, participants will be invited to participate in a focus group session to provide detailed feedback on the Rounds. The flow of participants in the study is shown in Figure 1.

Figure 1. Flow of participants through the study. PICF: Patient Information Consent Form.

Schwartz Rounds Intervention and the Rounds Process

Each Round will follow the format outlined by the Schwartz Centre [10]. A steering committee will be made up of the research team members (facilitators, clinical leads, an administrator, and a research assistant/project manager), the members of Mater HR, and other Mater staff champions (ie, team leaders/department heads, executive committee). The research team will meet fortnightly to discuss the planning and delivery of the Rounds and other research-related activities. A steering committee will meet monthly to quarterly, depending on the need. Each member of the research team will be trained in how to run the Rounds in alignment with the standard

procedure provided by the Schwartz Centre for Compassionate Health Care [10].

Facilitators will emphasize that the purpose of the Rounds is not to solve organizational problems or clinical management issues, but to provide a psychologically safe space where staff can speak freely about the social and emotional aspects of working within health care settings. Patient and staff confidentiality will be highlighted, and participants will be informed that they are to maintain confidentiality of the content of Rounds. To ensure the privacy and confidentiality of the staff, confidentiality will be discussed at the beginning and closing of each Round as well as in the panelists' preparatory sessions and focus groups. Each Round will take approximately 1 hour. Facilitators will allow time for participants to ask

questions and engage in open discussion, to provide opportunity to reflect on the stories shared, and to discuss their experiences of hearing the stories of their colleagues.

The Rounds will be held in-person during lunch or another time suitable for participating staff. Staff will also be invited to participate as Round panelists. A panel of speakers, usually 2-4 staff members from different work areas, will spend a combined 15 minutes presenting a patient story or talking about a topic related to their work. Panelists will have an opportunity to practice their story with the facilitators before the Round is conducted. They will be debriefed after each Round to help achieve closure and identify any immediate feedback or concerns.

Immediately after the completion of each Round, participants will be required to complete the Schwartz Centre Evaluation. After each Round, facilitators will complete a brief fidelity checklist and the research team will meet to discuss any immediate feedback. After the completion of 2 Rounds, an online survey link for the postrounds survey will be emailed to participants with a request to be completed within 1-2 weeks. Participants will be asked to complete surveys at baseline, after completing the Rounds, and at 3 months after the Rounds; attend at least two out of three Rounds; and provide immediate postround feedback. In addition, 3 participants per Round will be invited to participate as a panelist and share their stories and experiences in health care, making up the content of the Round.

To test the recruitment, delivery, and assessment procedures and inform any necessary adaptations prior to commencement of the study, the research team conducted an in-house pilot Round with the consultation liaison team. The 3 panelists, a psychologist, psychiatrist, and a psychiatric registrar, in discussion with the facilitators, agreed on the Round topic "When compassion is hard to find when caring for patients and their families." The pilot Round was attended by 21 participants from a variety of nonclinical and clinical disciplines and their feedback on the Round as well as the study procedures was used to fine-tune the recruitment and data entry processes and incorporated in the study protocol. The participants' feedback was overwhelmingly positive with 100% (21/21) of attendees reporting that the pilot Round gave them new insights into the perspectives and experiences of their co-workers, 86% (18/21) reporting new insights into the perspectives and experiences of their patients, 67% (14/21) reporting feeling better prepared to handle tough or sensitive situations, 76% (16/21) feeling less isolated in their work, and 95% (20/21) stating that they planned to attend future Rounds.

Data Management and Analysis

Qualitative and quantitative data will be collected by the research team through the self-report questionnaires, Rounds attendance sheets, postround feedback forms, and focus groups transcripts. Data will be deidentified and each participant will be given a number or pseudonym. All deidentified and identifiable data will be stored electronically on REDCap and Griffith University Research Space, where only the research

team will have access to the data. All hard copy documents will be stored in a locked cabinet at Griffith University where only those that require direct access will be able to access it. Electronic information will be kept on encrypted devices. All data will be stored for 5 years and then destroyed in compliance with Griffith University and Mater Health policies. Upon study completion, deidentified data will be kept on the Griffith University repository after the final ethics report has been submitted.

Qualitative data from the open comment section of the standard postround evaluation form and focus groups transcripts will be thematically analyzed by 2 members of the research team [26]. Quantitative data will be analyzed using SPSS (IBM). Descriptive statistics, paired t tests, chi-square tests (or other suitable nonparametric tests), and analysis of variance will be used to compare survey data across time points and groups. Post hoc analyses will be conducted to compare differences between specific time points.

Outcome Measures

Participants will complete an online survey via REDCap at preround, postround, and 3-month follow-ups, which will collect demographic information and measures of staff well-being, compassionate care, and organizational factors. Demographic data will include age, sex, ethnicity, profession, length of time in profession, workload and typical roster, and length of employment at the Hospital.

Staff well-being will be measured using the Maslach Burnout Inventory–Human Services Survey (MBI-HHS) [27]. The MBI-HHS is a reliable and validated 22-item measure that measures burnout using 3 subscales: Emotional Exhaustion (α=.90), Depersonalization (α=.79), and Personal Accomplishment (α=.71), on a 7-point scale ranging from "never" to "everyday." Compassionate care will be measured using the Schwartz Centre Compassionate Care Scale (SCCCS) – provider version [28,29]. The SCCCS consists of 12 items answered on a 10-point scale and has been shown to be reliable and valid for use with patients (α=.98) [29]. Organizational culture will be assessed using the Culture of Care Barometer – version 2 (CoCB-v2) [27]. The CoCB-v2 is a reliable and valid measure that consists of 30 items across 4 subscales: Organizational Values (α=.93), Team Support (α=.93), Relationships With Colleagues (α=.84), and Job Constraints (α=.70) [30,31].

In addition to these outcome measures, participants will be asked to complete the standard Schwartz Rounds Evaluation Survey at the end of each Round. This survey includes 10 questions answered with no, yes, or not sure; a question asking the participants to rate the Round overall as either poor, fair, neutral, good, or excellent; a free text question asking the participants to list 2 ways in which the Rounds will change how they related to or communicate with patients or colleagues; and an open comment section. Textbox 1 shows the Schwartz Rounds evaluation survey.

Textbox 1. Schwartz Rounds evaluation.

- During this session, attendees discussed challenging social and emotional aspects of patient care.

- Today's discussion gave me new insights into the perspectives and experiences of my co-workers.

- Today's discussion gave me new insights into the perspectives and experiences of patients or families.

- As a result of this discussion, I feel better prepared to handle tough or sensitive patient situations.

- As a result of this discussion, I feel less isolated in my work with patients.

- As a result of this discussion, I feel more open to expressing thoughts, questions, and feelings about patient care with colleagues.

- I plan to attend Schwartz Center Rounds again.

- The discussion was well-facilitated.

- Today's discussion suggests that changes may be needed in departmental or institutional policies or practices.

- Today's program was free of commercial bias.

- Please rate today's program overall.

- List 2 ways in which today's discussion will change how you relate to or communicate with patients or colleagues (if any):

    1. (Example)

    2. (Example)

- Additional comments, including ideas for future topics: (If you would like to share input with the Planning Committee member about your ideas, please provide your name and contact info.)

Focus groups will be conducted after the completion of the Rounds, to give participants the opportunity to provide detailed feedback on the Rounds. Focus groups will be facilitated by an external member of the research team with prior experience in facilitating groups and adequate knowledge of the topic and the purpose of the group. Conversation openers developed by the research team will be used [14-16]. Focus groups will be conducted approximately 2 months after the third Round for each group. Qualitative data will be analyzed thematically by 2 researchers (GH and AT) independently to ensure validity.

COVID-19 Risk Mitigation Plan

The impact of conducting Rounds in the context of COVID-19 challenges was discussed regularly during the study conception and planning. Research team considered the use of virtual Rounds in the planning stage but decided to proceed with the in-person Rounds, in view of the confidentiality and sensitivity and strong participants' preference for in-person attendance that was indicated after the pilot Round.

Rounds planning included considerations of the reduced staff participation due to COVID-19–related quarantine, sick and family leave, low staffing levels on Hospital wards, and difficulties in accessing adequate room space to conduct the Rounds safely in accordance with COVID-19 social distancing requirements. The study COVID-19 risk mitigation plan specifies the personal safety and hygiene measures to be followed by the research team and participants, in compliance with Queensland Government and Mater Health COVID-19 guidelines. The measures include social distancing and may include mask wearing and rescheduling of the Rounds during acute lockdowns, in keeping with the government and organizational directives at the time the Rounds are scheduled.

Safety Considerations

Possible risks to participants include a potential risk of unintended psychological harm to some participants, if they experience emotional distress in response to Rounds content. This risk will be minimized by having 2 researchers (GH and TE) facilitate the Round and 2 members of the research team (JM and AT) attend each Round to focus on participants and monitor for emotional distress. Contact information of the research team will be provided to discuss issues and, an external advisor, experienced in the running of Rounds in Australia, will be engaged in a consultative role. Prior to Rounds, all participants will be given brochures on the Hospital employee assistance program to access counseling and support if needed. In the event of harm occurring through damaged networks with peers or the organization, confidentiality will be emphasized.

Sample Size and Statistical Power

Participants will be recruited via a convenience sample. The required sample size was calculated using a power calculation for a repeated measures analysis of variance (one group measured across three time points) study using G*Power with effect size of 0.25 (f), α level of .05, power of 0.80, and correlation among repeated measures of 0.5. Therefore, it is calculated that a total sample size of 24 will be required for the study to be adequately powered to detect a significant difference ($P<.05$) between the time points. Approximately 10-15 participants will be selected from interested staff, to participate in 2 focus groups. This number of participants will ensure that 5-8 participants will take part in each focus group, in keeping with the recommended size for focus groups, and to ensure an even spread between professions, consistent with previous research recommendations [15,22].

Reflexivity to Improve Robustness

Prior to commencing the research, each member of the research team wrote and shared with the team a reflexive statement describing their prior experiences, assumptions, and beliefs about the research process and Schwartz Rounds. These statements will be discussed and revisited in regular research team meetings to enhance the individual researchers and team reflexivity, and the research integrity of the study [32].

In sharing their reflexivity statements, all members of the research team identified that they believed that the Rounds would enhance staff well-being and contribute to more sustained compassionate care and rejuvenated progressive organizational culture. Some members of the research team considered how their dual roles of being a health professional/clinical leader and a member of the research team might affect the research process. It was also acknowledged that, because of the hierarchical nature of the health care system, staff could feel pressured to participate in the Rounds when an operational or clinical manager was promoting the Rounds. Furthermore, concerns about the busy Hospital staff being released to attend the Rounds were identified. These concerns highlighted the importance of the research team members and steering committee communicating regularly with the Hospital executive team and directors of the departments involved in the study to promote the value of the Rounds. Finally, research team members acknowledged that changing organizational culture would take time and that this pilot project would ideally be a springboard for establishing ongoing Rounds in the Hospital.

Patient and Public Involvement

Views on the study design were obtained during the study conception from the clinical staff working in different departments as well as the nonclinical staff including administrative staff, security workers, human resources staff, and pastoral care. Patient views on the potential benefits of Hospital staff participating in an intervention facilitating compassionate care and staff well-being were elicited through the Hospital Consumer Consultancy Group members. Although the study participants were not formally involved in the recruitment or data analysis, department leaders and other staff members were consulted regarding their departments' participation.

Ethics Approval

The study was approved by the Mater Hospital Human Research Ethics Committee (reference number: HREC/MML/71868).

Results

This study was funded by the Griffith University Health Group collaboration grant in October 2020 and approved by the Mater Hospital Human Research Ethics Committee on January 13, 2021. Recruitment commenced in July 2021 and was completed in September 2021. Data collection commenced in July 2021, with projected completion by March 2022. Data analysis will commence in April 2022 and the results are expected to be published in the second half of 2021. The trail has been registered in the Australian New Zealand Clinical Trials Registry (ACTRN12621001473853).

Discussion

The key goals of this study are to evaluate the feasibility and efficacy of the Rounds in improving compassionate care, staff well-being, and organizational culture in a tertiary, metropolitan Australian hospital where the cultural background might be different to that of the North American or United Kingdom settings. Although the Rounds are currently being conducted in several other Australian locations, this study is, to our knowledge, the first pilot research study of Schwartz Rounds in Australia.

Another important feature of the study is the Rounds delivery during the current COVID-19–related challenges where this type of staff wellness intervention could be crucial in mitigating staff burnout and improving patient care and organizational culture. Furthermore, the implementation of the Rounds in unit-based format may demonstrate the feasibility and benefits of the Rounds in the most acutely affected departments such as the ICU as well as those with secondary overflow and staffing issues such as the gastroenterology department. Unit-based Rounds may also be more acceptable to staff and more likely to enhance teamwork and sense of shared purpose than the hospital-wide Rounds due to their smaller size and more cohesive group composition.

The use of the mixed methods, combining qualitative data from 2 different sources with quantitative data from the MBI-HHS, SCCCS, and CoCB-v2, will enhance the methodological rigor of the study and the confidence in its findings. The study findings have the potential to provide novel insights into the factors underpinning the feasibility and efficacy of the Rounds and their mechanism of action, and may inform the refinements of the Rounds in future studies.

Key limitations of the study are related to the relatively small sample size and a lack of a control group, which may lead to statistically insignificant findings in some outcome measures and limit the study's generalizability. However, given the pilot and exploratory nature of the study, its primary role is the assessment of the feasibility of the intervention and study procedures, with qualitative data providing additional valuable insights into these areas.

The results of the one-off pilot Round conducted in January 2021 provided a promising early indication of the potential value of Rounds in Australian settings, and during significant COVID-19–related challenges. The study is, to our knowledge, the first to evaluate Schwartz Rounds in a unit-based format during the COVID-19 pandemic and the first to include the departments potentially acutely affected by COVID-19. We anticipate that the results of the study will have a more wide impact as Schwartz Rounds are increasingly being adopted in different health care settings as well as in universities and other educational settings.

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Acknowledgments

Authors' Contributions

The study protocol was conceived and designed by AT, TE, JM, PP, CH, and GH, and critically revised by AT, TE, JM, PP, CH, GH, and LW. Drafting of the paper was completed by TE and GH. All authors edited the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CoCB-v2: Culture of Care Barometer – version 2
ICU: intensive care unit
MBI-HHS: Maslach Burnout Inventory–Human Services Survey
SCCCS: Schwartz Centre Compassionate Care Scale

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Protocol

Oral Health Status and Practices, and Anthropometric Measurements of Preschool Children: Protocol for a Multi-African Country Survey

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Abstract

Background: Oral diseases are among the most prevalent conditions with significant impact on the growth and development of young children. Data are required to plan effectively for the management of early childhood caries (ECC) and other oral diseases in this age. There are currently very few African countries with updated and nationally representative data on ECC prevalence, and risk indicators and regional data on ECC and other oral diseases are scarce.

Objective: We aim to determine the oral health status and practices, dietary intake, and anthropometric measurements of preschool children in several African countries.

Methods: A cross-sectional study will be conducted in several African countries using a standardized questionnaire and clinical examination for data collection from healthy preschool children in kindergartens and primary health care facilities. The clinical examination will assess ECC using the decayed, missing due to caries, and filled teeth (dmft) index according to the World Health Organization (WHO) criteria, dental erosion (using the Basic Erosive Wear Examination Index), deciduous molar hypomineralization (using the European Association of Paediatric Dentistry criteria), dental fluorosis (using Dean's Index), oral hygiene status (using the Oral Hygiene Index Simplified), and oral mucosal lesions. Oral hygiene habits and dental visits will be assessed using the WHO child questionnaire, and dietary intake will be assessed using the Food and Agriculture Organization method. Anthropometric measurements will be obtained following the International Society for the Advancement of Kinanthropometry standard protocol, and the children's nutritional status will be assessed following the WHO child growth standards. To train and calibrate examiners, educational resources and electronic forms will be used to reach interexaminer and intraexaminer reliability with κ>0.6. Descriptive analysis will determine the prevalence of clinical conditions by age and sex. Bivariate analysis and multivariable regression will assess associations between the clinical conditions and sociodemographic factors, and oral health behaviors.

Results: Data collection will begin after approvals and ethical clearance are obtained. The first stage will include 3 countries, namely Egypt, Nigeria, and South Africa, and collaborators from other African countries will join afterward.

Conclusions: This study will lay down the foundations for using validated tools to collect data on the oral health of young children in Africa, allowing researchers from different countries across Africa to collect standardized data on ECC and other oral conditions. This will facilitate comparisons and analysis of risk factors that might be unique to the African continent. The results will provide baseline data on the prevalence of oral diseases and enable planning to address the treatment needs of young African children and design programs to prevent oral diseases in the African continent.

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KEYWORDS

oral health; early childhood caries; oral hygiene; dietary intake; Africa; preschool children; dentistry; oral disease

Introduction

Oral diseases and dental caries are public health problems [1,2]. Early childhood caries (ECC), caries in children younger than 6 years of age, is one of the most common childhood diseases globally affecting up to 70% of children from disadvantaged communities and developed countries [3,4]. In addition, 8% of children worldwide are affected by untreated ECC [5].

Most African countries have no or outdated ECC data. According to available data, ECC prevalence ranges from 14.9% in Nigeria to 86% in Gambia [6]. Caries is multifactorial with many factors implicated including bacteria, poor diet (such as excessive consumption of refined carbohydrates), and poor oral hygiene [7].

The consequences of ECC include pain, loss of appetite, loss of school days, and poor quality of life [3,8]. Children with ECC are more likely to have caries in their adult lives, and hence, prevention of caries is essential for the well-being of children [3,4]. Data on the presence and severity of ECC have been mainly reported using the decayed, missing due to carries, and filled teeth (dmft) index of the World Health Organization (WHO). However, this index does not report on the clinical consequences of ECC [9]. The pufa index addresses this gap by assessing visible extension of caries to pulp (p), ulcerations of the oral mucosa due to root fragments (u), fistulae (f), and abscesses (a) [9].

In addition to caries, children's hard dental tissues may be affected by other diseases such as dental erosion (DE) and developmental defects of enamel (DDE) such as fluorosis and deciduous molar hypomineralization (DMH). DE is caused by extrinsic (ingestion of acidic food, drinks, and acidic medications) and intrinsic (regurgitation of gastric contents into the mouth through gastroesophageal reflux) factors [10]. DE affects the enamel, dentine, and even pulp resulting in pain, sensitivity, and discomfort [10]. Its prevalence is increasing [10] with current prevalence among young children ranging between 20% to 70% [11].

DDE such as fluorosis, enamel hypoplasia, and DMH are childhood oral lesions. Dean's Index has been used to measure fluorosis across the globe and is recommended by the WHO [12]. Approximately 12% of children aged 4 to 5 years have fluorosis in 1 or more teeth [13]. Data from Africa about DMH are sparse with little information about the relevant risk factors, and this limits the design and implementation of risk prevention programs for these lesions.

Diet is a risk factor for ECC and DMH [14]. Night-time bottle feeding, intake of sweetened juice, nocturnal breastfeeding after 12 months of age, and prolonged use of a pacifier covered in sweetened substances increase the risk of developing ECC [14]. Dietary diversity measured by the number of consumed food groups over a specified period is an indicator of diet quality, micronutrient adequacy, and micronutrient density [15]. The nutritional status of children can be assessed by anthropometry [16] including height-for-age, weight-for-age, weight-for-length, and weight-for-height z-scores and the mid-upper arm circumference [16-18].

Data about oral diseases, oral health practices, and dietary intake in young children in Africa are scarce. A situational analysis is needed to shed light on these conditions in different African countries to identify oral health needs and help plan oral health services based on evidence in addition to the provision of advice about dietary and oral hygiene practices. The aim of the study is to assess the prevalence of ECC and its severity using the pufa index, DDE, DMH, DE, oral health practices including oral hygiene habits, and the diversity of dietary intake in addition to anthropometric measurements of preschool children in several African countries.

Methods

Design, Setting, and Participants

A cross-sectional study will be used to collect data from children aged 1 to 5 years, who are free from diagnosed physical or intellectual disabilities and whose parents or guardians consent to join the study. These children will be recruited from wellness centers, kindergartens, early childhood centers, vaccination sites, and other primary health care facilities depending on the country-level context.

Sample Size

The required sample size can be determined [19] using a 5% margin of error, 95% CI, and the estimates of prevalence of oral diseases based on the literature with accommodation of design effects because of stratification and clustering of the sample [20], as shown in Table 1.

The maximum calculated sample size is 766 and with 20% expected nonresponse, the required sample size ranges from 334 at 10% prevalence to 920 at 50% prevalence. Researchers in each country or location will adapt these estimates based on which oral health outcomes they are studying and the previous estimates of prevalence at their site. In the absence of previous estimates, the working prevalence for sample size estimation would be 50%.

Table 1. Estimates of prevalence of oral diseases and required sample size.

Oral disease prevalence (%)	Sample size based on simple random selection	Sample size considering design effects because of clustering and stratification
10	139	278
20	246	492
30	322	644
40	368	736
50	383	766
60	368	736
70	322	644
80	246	492
90	139	278

Sampling Technique

Multistage stratified cluster sampling will be used, including stratification by the area of residence (rural and urban) according to the population distribution of each country and by age into the following five age groups: 12-23 months, 24-35 months, 36-47 months, 48-59 months, and 60-71 months. All participants in a facility or at a site (cluster) will be included. Participants and facilities will be randomly selected per stratum.

Data Collection Tools

Clinical Examination

Plaque will be recorded using the Simplified Oral Hygiene Index as described by Green [21]. The following teeth and surfaces will be included: 55 buccal surface, 51 labial surface, 65 buccal surface, 75 lingual surface, 71 labial surface, and 85 lingual surface. Each tooth will be scored as follows: 0-no plaque; 1-plaque less than a third of the tooth surface; 2-plaque more than a third but less than two-thirds; and 3-plaque covering more than two-thirds of the tooth surface. The average individual score will be calculated by adding the scores of each tooth and dividing by 6, which is the number of teeth.

ECC examination will be performed under natural or fluorescent lighting with the participant sitting on a chair according to the WHO method of examination [12]. The examination is visual-tactile, conducted through visual observation and using a blunt probe such as the ball-ended WHO probe or a periodontal probe. When in doubt, examiners should assign lesser scores. Tooth surfaces should not be routinely probed. The probe should be used only to confirm possible enamel breakdown. The dmft index will be used to record the ECC status in primary teeth. Only teeth with cavitated caries will be diagnosed as decayed, whereas those with early white spot lesions or fissure sealants will be recorded as sound. The mesial and distal surfaces with tight contacts and no obvious signs of ECC lesions shall be coded as sound. Code x is to be used for a tooth that cannot be seen because it is unerupted, when a primary tooth has exfoliated, or when a permanent incisor is about to erupt or has already erupted. An examination form will be used to capture the clinical findings (see Multimedia Appendix 1).

The pufa index will be used to assess the severity of dental caries [9]. Decayed teeth will be classified as "p" if pulp is visible, "u" if there is ulceration of the oral mucosa due to root fragments, "f" if there is a fistula, and "a" if an abscess is present. Soft tissue lesions from the surrounding tissue that are not related to a tooth or ECC will not be recorded. Only 1 score will be assigned per decayed tooth.

The prevalence and severity of DE will be measured using the Basic Erosive Wear Examination Index [22]. The buccal, occlusal, and palatal surfaces will be examined, and the highest score for each sextant will be recorded. The sum of the scores from each sextant will be added to obtain the individual score. The sextants will be classified as follows: Sextant 1: tooth #54-55, Sextant 2: #53-63, Sextant 3: #64-65, Sextant 4: #74-75, Sextant 5: #73-83, and Sextant 6: #84-85.

To assess DMH, teeth will be examined wet after debris removal using a piece of gauze. Each surface of all primary teeth will be screened for the following based on the European Association of Paediatric Dentistry's diagnostic criteria for (DMH): score 1-absence of demarcated opacities, score 2-posteruptive enamel breakdown, score 3-atypical restoration reflecting the distribution of hypoplastic enamel, and score 4-extracted teeth owing to DMH [23].

Dental fluorosis will be recorded using Dean's Index as recommended by the WHO [12,24]. All primary teeth will be included in the examination. The scoring includes normal: smooth, glossy, pale creamy-white translucent enamel surface; questionable: a few white flecks or white spots; very mild: small opaque, paper-white areas covering less than 25% of the tooth surface; mild: opaque white areas covering less than 50% of the tooth surface; moderate: all tooth surfaces affected, marked wear on biting surfaces, and with possible brown staining; and severe: all tooth surfaces affected, discrete or confluent pitting, and brown stain present.

Oral lesions not associated with dental caries will be identified and recorded according to the WHO classification [25], including leukoplakia, lichen planus, necrotizing ulcerative gingivitis, and candidiasis in addition to others. The type and location of the condition will be recorded.

To obtain an acceptable level of data reliability for ECC, DMH, and DE among examiners, a reference calibrating examiner (gold standard) in each country will be selected, who is a dentist with a record of publishing studies on ECC, DDE, or erosion in preschool children. The gold standard examiners will later calibrate the examiners in their respective countries. Training of the gold standard examiners will be conducted using photographs of lesions followed by an internet-based quiz asking examiners to assign diagnostic codes that will be compared to predefined diagnoses set by consensus within the core study team (authors of this paper: MET, MOF, and AB). The technique of using photographs for training and calibration has been used previously and has proved valid [21]. In addition, this method is also recommended by the WHO [12]. Once trained using the photographs, the gold standard examiners will conduct a field-based calibration exercise for the other examiners comparing the examiners' diagnostic codes to those of the gold standard per country. Reliability will be assessed between a group of examiners (interexaminer reliability) and between the same examiner at different time points (intraexaminer reliability). This is done by comparing the results of examining the teeth of 5 or more children among examiners and duplicates of the examination of the same children, respectively. Discrepancies are resolved by discussion and the exercise will be repeated until reaching at least 90% agreement with $\kappa>0.6$, indicating substantial to perfect agreement [26]. The Bangdiwala (B) statistic may be a suitable alternative to use in case of low prevalence of oral health outcomes [27].

Questionnaire

A standardized questionnaire (see Multimedia Appendix 2) will be used to collect data on oral hygiene habits [12] and dietary intake [28]. The questionnaire consists of the following sections:

Section 1 assesses the sociodemographic background including the children's age, sex, and familial factors such as parental education and occupation, as well as the children's rank, weight at birth, and history of breastfeeding.

Section 2 pertains to the history of several medical conditions and childhood illnesses. These include the history of medical conditions that may predispose children to malnutrition, enamel hypoplasia, and an increased risk of prolonged use of sweetened medication.

Section 3 assesses caries risk behaviors. These include the frequency of eating refined carbohydrates between meals, oral hygiene habits, history of dental visits, and parental assessment of child health based on the WHO questionnaire [12].

Section 4 is a 3-day food diary [29]. The diary takes notes of the food consumed at mealtimes and in between meals, including a weekend. Parents are expected to write down everything the child eats and drinks including how much was eaten using an estimate of portion sizes.

Section 5 is the Minimum Dietary Diversity Questionnaire assessing whether the child had eaten any of the 15 food groups in the last 24 hours [28]. Section 6 assesses the frequency and quantity of intake of 12 categories of sugary foods and oils [30].

The questionnaire will be completed before the oral examination is conducted and after written consent for participation in the study is obtained. The questionnaire can be translated into local languages and pilot tested to ensure accuracy and cultural appropriateness.

Anthropometric Measurements

Anthropometric measurements will be taken according to the standard guidelines [16,17]. Nutritional status will be determined using the WHO AnthroPlus software, which contains the WHO child growth standard for children aged 0 to 5 years [31]. Data on height and weight will be collected in line with the standard protocol of the International Society for the Advancement of Kinanthropometry [32]. Children will remove shoes and any heavy clothes before having their height and weight measured. Height will be measured to the nearest 0.1 cm with a portable stadiometer (Seca 217) and weight will be measured to the nearest 0.1 kg using a portable digital scale with remote display (generic electronic digital weighing scale) and the weighing scale will be zero-balanced before each child steps onto it. Measurements will be recorded after the fluctuations on the digital screen stop. Records will be taken after 2 consistent readings are obtained.

Ethical Considerations

Approval for the study will be obtained from the ethics and research committee of each country. Consent will be sought from caregivers for their participation and the participation of their children in the study. Where culturally appropriate, permission for the mother's participation in the study and consent for child's participation will be sought from the husband or father. The child's caregiver will be provided with the researchers' names and affiliations, detailed contact information of the principal investigator and the institutional research and ethics committee, study title, objectives, methods, risks, and benefits. Participants will also be informed that they have the right to withdraw from the study and will be provided with explanations regarding how the confidentiality of the provided information will be ensured. The signed consent form will be duplicated. One of the copies will be given back to the mother, whereas the other will remain with the principal investigator. Only those who give their consent to participate in the study will be enrolled.

At the end of the study, participating caregivers shall be given an information sheet that provides details on the causes and prevention of oral diseases. Participating children will receive oral hygiene instructions once the screening is completed. Parents or legal guardians will be notified of their child's oral health status, anthropometric status, and dietary intake diversity. If treatment is required, a referral letter will be given to them.

Statistical Analysis

Data Management

Data will be entered directly into an electronic form constructed using SurveyMonkey (Momentive Inc). Alternatively, a recorder may enter data on paper forms and later transfer them to the database. The examination form will show that the surfaces of each tooth are arranged in the same order for all teeth on the

right and left sides of the mouth, namely occlusal, mesial, distal, buccal, and lingual, rather than the usual mirror image system displayed on dental charts. This arrangement is designed to make it easier for recorders to enter data in a systematic manner. The master database will be backed up each day and converted to PDF. However, data will be maintained as Excel (Microsoft Corporation) files for analysis. Deidentification of the records will be done by removing any personal identifiers that can be used to trace the data to specific participants.

Data Analysis

Data will be imported into SPSS (IBM Corporation) for analysis. Descriptive analysis will be conducted to determine the prevalence of clinical conditions by age and sex. Bivariate analysis will be conducted to test associations between the presence of clinical conditions and sociodemographic factors as well as oral health habits. Anthropometric data will be analyzed using the WHO AnthroPlus software [16]. Dietary diversity scores will be calculated. Minimum dietary diversity will be included when children complete the survey on 5 or more out of 7 possible food groups.

Multivariable regression will be used to determine the associations controlling for confounders with calculation of regression estimates and their 95% CIs. The goodness-of-fit statistics of the models will be calculated. Significance will be set at 5%.

Results

This study is not funded and principal investigators at each site or in each country are expected to secure the funds needed to conduct the study. Egypt, Nigeria, and South Africa will participate in the first stage of data collection with more countries to be invited to join in the next stage(s). Participant recruitment is expected to begin once ethical clearance is obtained in the respective countries.

Discussion

Study Objectives and Outcomes

This study will provide information about the oral health of preschool children in African countries where oral health data are scarce. Several mother and child health programs are instituted in many African countries through governmental efforts in addition to developmental assistance for health. Generating evidence about the oral health needs of young children can support the integration of oral care for children into these existing programs.

It is expected that the prevalence of dental caries will be high in most of the countries in Africa, especially those with transitional economies. The improved financial ability of citizens increases access to high-carbohydrate diets. However, health system development may be slower than the rate of economic growth, thereby reducing the possibility of providing preventive and curative care to children. Macrolevel factors are important in understanding the risk of children to oral diseases including ECC. Country context is needed when reflecting on the

prevalence of ECC and the proposals for ECC-related policies and guidance.

Household risk factors for oral diseases and ECC are also important when discussing the study findings. Socioeconomic status may increase the risks related to nutrition, dental service use, neighborhood, and residential location in addition to risks associated with knowledge, attitude, and practice. In addition, cultural practices are critical factors that may affect dietary practices of infants and children. Discussions about the prevalence of ECC will take this into cognizance.

At the individual level, each child may have risk factors for oral diseases and ECC including defective dental enamel (enamel hypoplasia, DMH, and fluorosis). Collecting data on dietary intake and obtaining anthropometric measurements help assess the nutritional status of each child and identify how nutritional factors may be a risk factor for oral diseases. This is especially important for Africa where malnutrition is still a major risk factor for under-5 mortality and morbidity. The prevalence levels are 5.3%, 30.7%, and 6% for overweight, stunting, and wasting, respectively [33]. Understanding the relationships between malnutrition and oral health diseases will facilitate the development of integrated health programs that can address the oral and general health of children [34]. Such integration will likely occur at minimal costs, as it will likely fit into the targets of many existing country programs that address malnutrition as a developmental problem.

The study also aims to systematically collect data using standardized forms and methods. The developed calibration methods can be used to support data collection in future projects. The study would be the first to provide comparisons across African countries in the field of oral health, especially in young children. In addition, the study will help many countries in Africa to provide more recent data on young children's oral health and ECC. The findings would be generalizable to entire countries because the used sampling strategy ensures representation of different regions and subgroups.

The study findings will be disseminated through the publication of the first regional profile of ECC, focusing on the prevalence of ECC in Africa. This will provide evidence to support or dispel assertions about the high prevalence of ECC in the region. Moreover, countries will be able to publish and disseminate country-specific data generated using the methods described in this protocol.

The study may have some limitations. First, there may be language barriers when answering the dietary survey. This can be addressed by translating the survey into different languages where required. The survey tool also includes photographs of food items to help parents understand the meaning of the used terms. Country-level researchers can change these photographs and replace them with those of similar local items. Second, there may be challenges in accessing rural populations due to transportation or logistic issues. In these cases, researchers can send the survey forms beforehand to be collected on the day of the examination, when the anthropometric assessments will be done. Third, the cross-sectional design of the study is suitable for exploring population parameters and program planning but cannot support causality, and longitudinal studies would be

needed to overcome this limitation. Fourth, data collection about oral hygiene habits and dietary intake is subject to recall and social desirability biases, as is the case with all studies using questionnaires to elicit information. The use of standardized and validated tools such as those used by us reduces these biases. Fifth, recruiting nationally representative samples may be difficult and external funds would be needed to help cover the associated expenses. Furthermore, focusing on selected indicators of oral health outcomes and practices may help tailor the protocol to fit available resources in different countries.

Conclusions

The methods described in this protocol provide guidance for researchers in Africa to gather data on oral diseases and anthropometric scores in young children using a standardized and validated data collection tool. The data can help generate descriptive information on prevalence and risk indicators for oral health diseases in preschool children in the region.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Clinical examination form.
[DOCX File , 31 KB - resprot_v11i4e33552_app1.docx]

Multimedia Appendix 2
Questionnaire.
[DOCX File , 1527 KB - resprot_v11i4e33552_app2.docx]

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Abbreviations

DDE: developmental defects of enamel
DE: dental erosion
dmft: decayed, missing due to caries, and filled teeth
DMH: deciduous molar hypomineralization
ECC: early childhood caries

pufa: pulp, ulcerations of the oral mucosa due to root fragments, fistulae, and abscesses
WHO: World Health Organization

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Original Paper

Adult Vaccine Hesitancy Scale in Arabic and French: Protocol for Translation and Validation in the World Health Organization Eastern Mediterranean Region

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Abstract

Background: The world as we know it changed during the COVID-19 pandemic. Hope has emerged with the development of new vaccines against the disease. However, many factors hinder vaccine uptake and lead to vaccine hesitancy. Understanding the factors affecting vaccine hesitancy and how to assess its prevalence have become imperative amid the COVID-19 pandemic. The vaccine hesitancy scale (VHS), developed by the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization, has been modified to the adult VHS (aVHS) and validated in English and Chinese. To our knowledge, no available aVHS has been designed or validated in Arabic or French.

Objective: The aim of this research is to translate the aVHS from its original English language to Arabic and French and validate the translations in the WHO Eastern Mediterranean region.

Methods: The study will follow a cross-sectional design divided into 5 phases. In phase 1, the original aVHS will be forward-translated to Arabic and French, followed by backward translation to English. An expert committee will review and rate all versions of the translations. Expert agreement will then be measured using the Cohen kappa coefficient (k). In phase 2, the translated aVHS will be pilot-tested with 2 samples of participants (n=100): a group that speaks both Arabic and English and another that speaks French and English. Participants' responses to the English version will also be collected. In phase 3, responses will then be compared. Descriptive statistics and paired t tests or one-way analyses of variance (ANOVA) and Pearson correlation coefficient will be used in the preliminary validation. In phase 4, prefinal versions (Arabic and French) will be tested with larger sample sizes of Arabic speakers (n=1000) and French speakers (n=1000). Sociodemographic information and vaccination status will be collected and used for further analysis. In phase 5, the scale's statistical reliability and internal consistency will be measured using Cronbach alpha. An exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) will be used to examine the model fit resulting from the EFA. ANOVA and regression models will be constructed to control for confounders. All data will be electronically collected.

Results: As of January 2022, the scale had been translated to Arabic and French and was undergoing the process of back translation. All data collection tools have been prepared (ie, sociodemographics, vaccination status, and open-ended questions) and are ready to go into their electronic formats. We expect to reach the desired sample size in this phase by June 2022.

Conclusions: This study will provide researchers with a validated tool to assess adult vaccine hesitancy within populations that speak Arabic and/or French and provide a road map to scale translation and ensure cross-cultural adaptation.

International Registered Report Identifier (IRRID):   PRR1-10.2196/36928

Introduction

Background

The world as we know it changed during the COVID-19 pandemic. Although hope has emerged with the development of new vaccines against the disease, public health providers still face a significant challenge in ensuring uptake of those vaccines by the larger public. To achieve herd immunity to COVID-19, a substantial proportion of the population would need to be vaccinated [1]. However, there are many factors hindering vaccine uptake, including logistic and economic factors and misinformation leading to a lack of public confidence in the effectiveness and safety of the vaccines [1,2]. These are all factors that contribute to what has been termed vaccine hesitancy. Vaccine hesitancy is defined as the "refusal or delay of the uptake of vaccines despite the availability of services" [3,4]. Vaccine hesitancy is a global problem that has negatively impacted public health. The World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) established a working group to address this issue [3].

Understanding the factors affecting vaccine hesitancy and how to assess its prevalence have become imperative amid the COVID-19 pandemic. Developing new vaccines utilizing existing or new technologies spurred public scrutiny regarding the need, safety, and efficacy of such vaccines [1,2]. This prompted a need for a tool to help assess vaccine hesitancy among adults. Before this, vaccine hesitancy scales (VHS) available in the literature focused on parental attitudes and perceptions regarding vaccinating their children [5]. Various attempts were made to develop or adapt parental VHS tools for adults, but very few went through the rigor of being validated [5-8]. The need for such a validated scale has only increased with the COVID-19 pandemic.

Various scales have been developed to measure hesitancy among parents or health care workers [5]. The WHO SAGE Working Group on Vaccine Hesitancy developed a 10-item VHS that is widely used in different countries and settings [9]. The VHS has been modified to the adult VHS (aVHS) and has been adapted and validated in English and Chinese [5].

The aVHS is a 10-item scale with a 5-point Likert scale ranging from "Strongly disagree" to "Strongly agree." The Likert scale items have scores ranging from 10 to 50, where 50 represents the highest degree of vaccine hesitancy and 10 represents the lowest. The scores on 7 items on the scale will be reverse coded so that the highest scores reflect the highest degree of vaccine hesitancy. A cut-off score of 24 is used to dichotomize the outcome into "vaccine hesitant" and "not vaccine hesitant" categories. The score range and cut-off score have been proposed and validated by the research team developing the scale [5].

Objective

To our knowledge, no available aVHS has been designed or validated in Arabic or French.

Both of these languages are widely used in the countries included in the WHO Regional Office of the Eastern Mediterranean (EMRO) [10], with Arabic being the most commonly used language in EMRO and French being a commonly used language in EMRO countries such as Algeria, Tunisia, Morocco, and Djibouti. For the aVHS to be valid for these populations, the scale must undergo translation and cultural adaptation prior to validation and reliability testing. This study will adopt a rigorous methodology to translate and validate the aVHS and conduct a proper psychometric evaluation of the translated version to make the scale available to all scholars in the EMRO region and beyond. In addition, we plan to survey a representative sample of the region to assess the aVHS' structure, internal consistency, and validity across different social and demographic settings. Therefore, this research aims to translate the aVHS from its original English language to Arabic and French and validate the translations in the WHO Eastern Mediterranean region.

Methods

The study will follow a cross-sectional design divided into 5 phases inspired by the methodology proposed in the "Guidelines for developing, translating, and validating a questionnaire in perioperative and pain medicine" [11]. Study phases are detailed in the following sections and illustrated in Figure 1.

Figure 1. Flow diagram of study phases. aVHS: adult vaccine hesitancy scale.
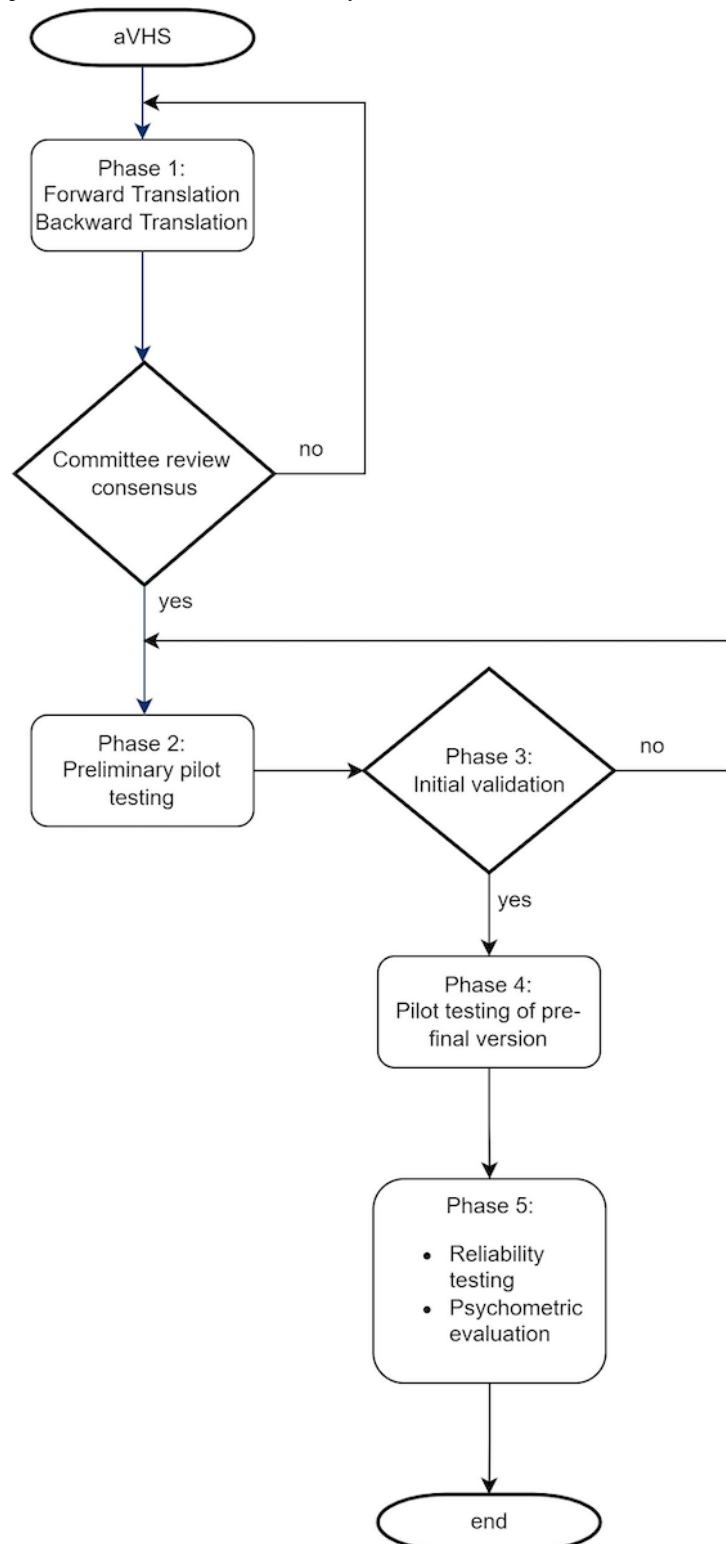
Study Phases

Phase 1: Translation

The original aVHS will be forward translated to Arabic by individuals who are bilingual in Arabic and English and translated to French by individuals who are bilingual in French and English. Translators' mother tongues are the language of translation in order to capture the target language's nuances better. Backward translation will be conducted to reveal any

misunderstanding or miswording in the forward translation. A different set of bilingual individuals (Arabic and English; French and English) will conduct the back translation into their mother tongues. To avoid bias, back-translators will not be aware of the intended purpose of the scale and will be blinded to the English version. A review of all versions of the translations and any discrepancies will be reviewed and resolved by an expert review committee of 6 to 10 members [12]. The committee will be required to rate each item for relevance, representativeness,

and technical quality on a scale of (accept—reject—modify). Expert agreement will then be measured using the Cohen kappa coefficient; a cut-off of ≥0.70 will be deemed acceptable [13].

The translation and back-translation process will be repeated until a satisfactory agreement is reached.

The data collection tools for this study will include both the English and translated versions of the aVHS (Table 1).

Table 1. Data collection tools for each testing phase.

Data collection tool	Preliminary pilot testing phase	Testing of prefinal version
aVHS[a] (Translated)	x[b]	x
aVHS (English)	x	—[c]
A set of open-ended questions	x	—
Sociodemographics	—	x
Vaccination status	—	x

[a]aVHS: adult vaccine hesitancy scale.

[b]Tool will be used.

[c]Tool will not be used.

Phase 2: Preliminary Pilot Testing

The translated aVHS will be pilot tested with 2 samples of participants: a group that speaks both Arabic and English and another that speaks French and English. Based on previous studies, at least 5 participants per scale item are required for testing [5,14]. As such, our sample size will be 100, equally divided between the Arabic and French translations. A convenience sampling approach will be utilized. Participants will be approached on the Mohammed Bin Rashid University (MBRU) campus and screened for inclusion criteria. They will be asked to complete the translated scale and subsequently requested (verbally by an interviewer) to elaborate on what they thought each scale item meant. This process helps ensure that the translated items retain the same meaning as intended in the English scale and ensure there is no confusion regarding the translated scale. After participants complete this process using the translated aVHS, participants will be asked to complete the aVHS in English. Items on the original English scale will be in a different order from that of the translated version [12]. Therefore, participants will be asked to complete the translated version first without seeing the original scale.

Phase 3: Initial Validation Phase

Responses to both the English and translated versions of the scale will then be compared. Statistical analyses will be conducted to test the reliability of the translation against the original scale. Descriptive statistics and paired *t* tests or 1-way analyses of variance (ANOVA) will be used to analyze the data

collected. The Pearson correlation coefficient will be used in preliminary validation of translated versions against the original version of the scale. If reliability is not achieved, then phase 2 will be repeated. If the translated versions are statistically reliable, these will become the prefinal versions for phase 4.

Phase 4: Testing of the Prefinal Version

Prefinal versions (Arabic and French) will be tested with a larger sample. Generally, there is a lack of consensus on the sample size required for validity testing of a scale [15]. A review of the research in this area found it has been recommended to use at least 10 participants per item when doing a comprehensive psychometric analysis [12,16] and that between 300 and 500 participants are required to perform an exploratory factor analysis (EFA) [12], which will be conducted in this study. A sample size of 1000 participants was deemed "excellent" for scale validation [12,17]; therefore, our proposed sample size is 1000 Arabic speakers and 1000 French speakers. This sample size is set to avoid sampling errors that may reduce the statistical power needed to validate the scale [18]. Data about participants, such as sociodemographic information and vaccination status, will also be collected (as detailed in Table 2) and used for further analysis.

Data will be collected anonymously via a link to an online survey hosted locally at MBRU. The link will be posted on different social media platforms. A series of questions to determine participant eligibility will be asked. Those who meet the inclusion criteria will be able to proceed to data collection.

Table 2. Variable names and types.

Variable name	Measurement level	Description/parameter
Age (years)	Categorical	18-25, 26-35, 36-45, 46-55, 56-65, 66-75, ≥76
Gender	Categorical	Male, female, other
Occupation [19]	Categorical	1. Managers; 2. Professionals; 3. Technicians and associate professionals; 4. Clerical support workers; 5. Services and sales workers; 6. Skilled agriculture, forestry, and fishery workers; 7. Craft and related trade workers; 8. Plant and machine operators and assemblers; 9. Elementary occupations; 0. Armed forces occupations
Nationality	Categorical	Based on the World Bank list of countries [20]
Income (US $)	Numerical	Annual
aVHS[a]	5-point Likert scale	Strongly disagree to strongly agree

[a]aVHS: adult vaccine hesitancy scale.

Phase 5: Validation of the Prefinal Version (Psychometric Testing)

The scale's statistical reliability and internal consistency will be measured using Cronbach alpha; values range from 0 to 1, where a value of 0 indicates no internal consistency and a value of 1 reflects perfect internal consistency. A Cronbach alpha cut-off of 0.70 will indicate adequate internal consistency [21]. An EFA will be conducted to examine the structure of the scale as well as reliability of the items. Confirmatory factor analysis (CFA) will be used to examine model fit resulting from the EFA. ANOVA or regression models will be constructed to evaluate potential confounding effects arising from variations in sociodemographic factors of the participants. Continuous variables will be further categorized after data visualization to avoid groups with sparse data. Mean, medians, IQRs, and SDs will be used to describe continuous variables. For categorical or non-normally distributed variables, the Wilcoxon Signed Rank test will be used. Frequency distributions, percentages, and chi-square tests will describe binary and categorical variables and identify significant differences between groups. The correlation between vaccine hesitancy scores and the vaccination status reported by participants will also be explored. Analyses will be conducted and reported for both Arabic and French versions independently.

All data will be electronically collected (ie, templates, devices) to ensure the standardization of the data collection process and minimize errors from manual data entry.

Privacy, Confidentiality, and Data Storage

No identifying information will be collected from participants in any of the study phases. Data will be collected and stored on local MBRU servers. Data collected for the validation of the prefinal version phase will be anonymously collected via a link to an online survey hosted on a website hosted locally. The link will be posted on different social media platforms, and only the research team will have access to the data.

The study is part of the research project titled "Addressing Vaccine Hesitancy through Targeted and Personalized Mobile Educational Interventions for Different Populations in the Eastern Mediterranean region."

Ethical Approval

The study has been reviewed and approved by the institutional review board of Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU IRB-2021-87).

Data Analysis

Data analysis in each phase will follow the steps explained in the preceding paragraphs. Statistical analysis software will be used to analyse the data set. A complete case analysis approach will be adopted. Data will be tested for normality, visually using histograms and statistically using the Shapiro-Wilk test. The significance level cut-off will be set at $P<.05$, and exact P values will be reported.

Results

As of January 2022, the scale had been translated to Arabic (Multimedia Appendix 1) and French (Multimedia Appendix 2) and was undergoing back translation. The original English version can also be found in Multimedia Appendix 3. All data collection tools have been prepared (ie, sociodemographics, vaccination status, and open-ended questions) and are ready to go into their electronic formats.

This project includes 3 stages of data collection and analysis: (1) expert agreement on translation; (2) initial validation phase where responses on both versions of the scale will be compared; and (3) psychometric testing of the prefinal version in which internal consistency, validity, and model fit will be explored and tested. We expect to reach the desired sample size in this phase (2000 participants) by June 2022.

All translated versions of the scale will be publicly available to scholars free of charge.

Discussion

Overview

This study is part of a group of studies conducted by the Institute for Excellence in Health Professions Education (ieHPE) at MBRU, located in Dubai, United Arab Emirates. These studies are all taking different approaches to address vaccine hesitancy. The original, English-language version of the aVHS is being used as part of these studies (unpublished). We selected the

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aVHS as it is one of very few tools to have undergone validation prior to implementation. In this project, we will be translating and validating the scale for countries included in the WHO EMRO [10], in which most of the population speak Arabic and/or French. We reviewed the literature and found existing VHS in Arabic; however, none of them have undergone a rigorous validation process [22-25]. Such a process is needed to clarify the underpinnings of the scale factor loadings, structure, and stability. For example, suppose we aim to understand vaccine hesitancy in our region. In that case, we cannot simply rely upon scales that have been validated in a different setting; surveys, questionnaires, and scales, in general, cannot be validated unless they have been validated and tested on the population in which they are planned to be used [26]. Our objective is to adopt a rigorous methodology to ensure validity and reliability of the tool.

Sample size assessment was also an issue we encountered while planning the study. There is no clear consensus in the literature for the sample size calculation required for scale validation. For example, published studies mentioned that 1000 was an ideal sample size [12,17], while others reported that 10 subjects per item would be sufficient [11]. This would have reduced the proposed sample size from 1000 to 100 for this 10-item scale study. It was also previously mentioned that 300 to 500 subjects are required to perform an EFA [12]. We chose the sample size for this study because it ensures we will be able to conduct the analysis proposed.

Our literature review also uncovered that sociodemographic factors and differences in the political climate are potentially reflected in vaccine hesitancy status [3,26,27]. Interestingly, although overall health in general has commonly been associated with higher educational level [3], those with higher educational levels have been shown to have a greater hesitancy to vaccinate [3], even among health care providers [27], demonstrating that underlying social determinants are different than with overall health. The sociodemographic factors that are correlated with vaccine hesitancy have been explored in some studies in the region [28]. Still, most have focused on a single country [25],

while other studies did not address these factors [24,29]. This study aims to explore those factors across different countries in the region. In addition, the relationship between vaccine hesitancy and actual vaccination will be explored and reported in this study. Although some countries mandate vaccination for their citizens and some pose some restrictions on unvaccinated individuals, vaccine hesitancy as a perspective might be independent of actual vaccination. This is a meaningful relationship to explore to understand the population's attitude toward vaccines and actual behaviors potentially influenced by governments' mandates.

Limitations

One of the limitations of the protocol is the convenience sampling approach utilized. Although convenience sampling could potentially introduce bias to the study results, it is still a practical approach utilized by various studies, especially in the absence of a sampling frame. We expect this to be a minor issue in phase 3 of the study as this phase aims to test the translation only. As for phase 4, data stratification and regression models will allow us to elucidate and control for potential bias. Another limitation is posting the survey online. We are aware that this impacts the generalizability of the results, since only people with electronic devices, internet connection, and a degree of digital literacy will be able to access the survey and may not be representative of the rest of the population. But since this protocol proposes translating and validating the scale and does not aim at measuring the prevalence of vaccine hesitancy, we hypothesize that the impact should be minor.

Conclusions

This study will provide researchers with a validated tool to assess adult vaccine hesitancy within populations that speak Arabic or French and provide a road map on how to scale translation and ensure cross-cultural adaptation. We aim at supporting our approach with statistical evidence.

Any work resulting from this project will be disseminated nationally and internationally through submission to academic journals and international conferences.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Arabic translation of the adult vaccine hesitancy scale (aVHS).
[DOCX File , 17 KB - resprot_v11i4e36928_app1.docx]

Multimedia Appendix 2
French translation of the adult vaccine hesitancy scale (aVHS).
[DOCX File , 17 KB - resprot_v11i4e36928_app2.docx]

Multimedia Appendix 3

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Original English version of the adult vaccine hesitancy scale (aVHS).
[DOCX File , 14 KB - resprot_v11i4e36928_app3.docx]

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Abbreviations

ANOVA: analysis of variance
aVHS: adult vaccine hesitancy scale
CFA: confirmatory factor analysis
EFA: exploratory factor analysis
EMRO: Regional Office for the Eastern Mediterranean
ieHPE: Institute for Excellence in Health Professions Education
MBRU: Mohammed Bin Rashid University
SAGE: Strategic Advisory Group of Experts on Immunization
VHS: vaccine hesitancy scale
WHO: World Health Organization

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Protocol

A Study on Prevalence and Determinants of Ototoxicity During Treatment of Childhood Cancer (SOUND): Protocol for a Prospective Study

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Abstract

Background: Some children with central nervous system (CNS) and solid tumors are at risk to develop ototoxicity during treatment. Up to now, several risk factors have been identified that may contribute to ototoxicity, such as platinum derivates, cranial irradiation, and brain surgery. Comedication, like antibiotics and diuretics, is known to enhance ototoxicity, but their independent influence has not been investigated in childhood cancer patients. Recommendations for hearing loss screening are missing or vary highly across treatment protocols. Additionally, adherence to existing screening guidelines is not always optimal. Currently, knowledge is lacking on the prevalence of ototoxicity.

Objective: The aim of the Study on Prevalence and Determinants of Ototoxicity During Treatment of Childhood Cancer (SOUND) is to determine the feasibility of audiological testing and to determine the prevalence and determinants of ototoxicity during treatment for childhood cancer in a national cohort of patients with solid and CNS tumors.

Methods: The SOUND study is a prospective cohort study in the national childhood cancer center in the Netherlands. The study aims to include all children aged 0 to 19 years with a newly diagnosed CNS or solid tumor. Part of these patients will get audiological examination as part of their standard of care (stratum 1). Patients in which audiological examination is not the standard of care will be invited for inclusion in stratum 2. Age-dependent audiological assessments will be pursued before the start of treatment and within 3 months after the end of treatment. Apart from hearing loss, we will investigate the feasibility to screen patients for tinnitus and vertigo prevalence after cancer treatment. This study will also determine the independent contribution of antibiotics and diuretics on ototoxicity.

Results: This study was approved by the Medical Research Ethics Committee Utrecht (Identifier 20-417/M). Currently, we are in the process of recruitment for this study.

Conclusions: The SOUND study will raise awareness about the presence of ototoxicity during the treatment of children with CNS or solid tumors. It will give insight into the prevalence and independent clinical and cotreatment-related determinants of ototoxicity. This is important for the identification of future high-risk patients. Thereby, the study will provide a basis for the selection of patients who will benefit from innovative otoprotective intervention trials during childhood cancer treatment that are currently being prepared.

Trial Registration: Netherlands Trial Register NL8881; https://www.trialregister.nl/trial/8881

Introduction

Each year around 600 children are newly diagnosed with cancer in the Netherlands [1]. Over the past decades, cancer diagnostics and treatment have improved, resulting in an overall survival up to about 80% in high-income countries [2]. Due to the increased survival, more awareness has been raised for sequelae of childhood cancer treatment. A serious direct and late effect of treatment includes ototoxicity, which involves the destruction of cochlear structures leading to hearing loss, tinnitus (ear ringing), or vertigo (dizziness) [3,4]. Ototoxicity in childhood may seriously affect speech development and social and neurocognitive skills, subsequently leading to a reduced quality of life [5-7].

It is known that certain types of cancer treatment including platinum agents, cranial irradiation, and brain surgery can induce or enhance ototoxicity [3,8]. Platinum agents have been used successfully for treatment of solid and central nervous system (CNS) tumors [8]. Platinum accumulates in the inner ear and resides here for months to years after treatment [9]. It forms crosslinks with DNA, leading to a transcription and replication blockage and extensive production of reactive oxygen species (ROS). ROS cause inflammation and apoptosis, especially in the outer hair cells, stria vascularis, and spiral ganglion cells [10,11]. Up to 70% of platinum-treated children develop irreversible hearing loss and eventually 40% of them even need hearing aids at an early stage [12-14]. During cancer treatment aminoglycosides, glycopeptides, and diuretics are often prescribed as supportive care therapy [15-18], but knowledge is lacking on their contribution to hearing loss development in pediatric patients. Until now, the relation between supportive care treatment and ototoxicity has only been studied in small pediatric cancer patient cohorts with a retrospective design.

Children diagnosed with CNS tumors or head and neck tumors are often treated with high irradiation doses or surgery [19]. Irradiation of normal ear structures cannot always be avoided, leading to middle and inner ear damage or vascular insufficiency of the ear [20-22]. Mechanical damage of ear structures caused by surgical resection of tumors may also lead to hearing loss [23]. It may also be possible that the tumor itself causes hearing loss. Currently, standardized approaches for audiological monitoring during and shortly after therapy are lacking in clinical practice. Beside this, adherence to scheduling of audiological examinations is sometimes flawed, as the focus of clinicians is on cancer diagnostics and rapid start of treatment, rather than on monitoring side effects. Sometimes patients are too ill to undergo audiological testing. Furthermore, age-appropriate audiological tests are often not applied, and standardized tinnitus and vertigo screening is often not implemented. Standardized audiological monitoring is important as it will aid in the timely detection of symptomatic or asymptomatic hearing loss and early referral to an audiologist. In certain circumstances, alternative cancer treatment options may be considered depending on the child's diagnosis and evidence-based alternative treatments.

In the Princess Máxima Center for Pediatric Oncology, the Study on Prevalence and Determinants of Ototoxicity During Treatment of Childhood Cancer (SOUND) was started in January 2021. We intend to invite 600 patients in this study over a period of 24 months. This number is based on the number of children diagnosed with solid and CNS tumors at our institute. The results of the SOUND study will provide information on the prevalence of hearing loss, tinnitus, and vertigo in a prospective cohort of children with solid and CNS tumors. It will also give insight into the determinants of ototoxicity, especially the contribution of aminoglycosides, glycopeptides, and diuretics. Furthermore, the results will indicate whether it is at all feasible to perform standardized audiological examinations in every childhood cancer patient with a potential risk of ototoxicity. Eventually, this study may serve as a solid basis for the selection of patients at risk that will benefit from innovative otoprotective interventions in the future.

Methods

Study Objectives

The primary objective of the study is to investigate the prevalence of hearing loss after cancer treatment in a prospective cohort of pediatric CNS and solid tumor patients. Secondary objectives focus on examining the prevalence of tinnitus and vertigo after cancer treatment, identifying clinical determinants for ototoxicity, and investigating the feasibility of testing patients at risk for ototoxicity with standardized audiological examinations.

Study Design and Setting

We will perform a national prospective cohort study in the Netherlands. This study is embedded in the Princess Máxima Center, a national health care center that has been set up to treat all children diagnosed with cancer. Collaboration with the audiological department of Wilhelmina Children's Hospital in the Netherlands has been established to perform audiological testing of children of all ages. The selection, invitation, and inclusion of patients takes place in the Princess Máxima Center. The audiological assessment is age-adjusted, according to recently published guidelines [24]. It will be performed before the start of treatment, during cancer treatment according to treatment protocols, and within 3 months after the end of treatment (Table 1). Information about the screening outcome of the neonatal hearing screening is retrieved for all patients [25].

Table 1. Stratification and time point for audiological examination based on treatment.

Treatment	Stratum	Audiological assessment		
		Before start treatment	During treatment[a]	Within 3 months after treatment
Platinum agents (cisplatin, carboplatin, oxaliplatin)	1	✓[b]	✓	✓
CNS[c]/ENT[d] irradiation	1[e]	✓		✓
CNS/ENT surgery	1[e]	✓		✓
No platinum agents, CNS/ENT irradiation, or CNS/ENT treatment	2	✓		✓

[a]Time points for audiological assessments during treatment are based on recommendations in the childhood cancer treatment protocol.

[b]The checkmark indicates that the assessment was performed at this time point.

[c]CNS: central nervous system.

[d]ENT: ear-nose-throat.

[e]Patients are included in stratum 1 if audiological examinations are part of standard care; otherwise, they are included in stratum 2.

Study Population

Children aged 0 to 19 years who will be diagnosed with a CNS or solid tumor between January 2021 and January 2023 are eligible for participation in the study. They will be divided in two strata (Table 1). Stratum 1 consists of patients treated with platinum agents (cisplatin, carboplatin, or oxaliplatin), CNS/ear-nose-throat (ENT) irradiation, or CNS/ENT surgery, and audiological examinations are part of standard care. Stratum 2 consists of patients not treated with therapies described in stratum 1 or any patients in which audiological examinations are not part of standard care. The independent contribution of any comedication on ototoxicity development will be studied in stratum 2.

Recruitment and Informed Consent

Pediatric oncologists from the Princess Máxima Center will select patients for invitation. For patients in whom audiological examinations are not standard of care, written informed consent will be obtained from parents/guardians (patients) according to good clinical practice regulations. Withdrawal is possible at any time during the study without providing a reason.

Study Procedures

All patients will be examined by standard audiological examinations (Table 2), which always includes otoscopic inspection of the ears and tympanometry. Depending on the age of the child, (a combination of) brainstem-evoked response audiometry (BERA), distortion product otoacoustic emissions (DPOAEs), visual reinforcement audiometry (VRA), conditioned play audiometry, and extended high-frequency pure tone audiometry (PTA) will be applied. Anamnestic screening for tinnitus and vertigo will be performed during audiological examinations as a standard procedure for patients 8 years and older and 10 years and older, respectively [24,26,27]. We will schedule at least two visits during the study period, including a baseline visit before the start of cancer treatment to exclude pre-existent hearing loss and a follow-up visit within 3 months after the end of cancer treatment.

Otoscopy is used for inspection of the external auditory canal and tympanic membrane, which focuses on accumulation of cerumen, infections, and perforations of the tympanic membrane [28,29]. Tympanometry is routinely applied as an indicator of conductive hearing loss due to middle ear pathology. Static air pressure is varied systematically in the ear canal while an acoustic stimulus of 226 or 1000 Hz is delivered. This procedure measures the ability of the middle ear system to transfer low-frequency acoustic energy to the cochlea as a function of static air canal pressure [30]. Abnormal functioning of the middle ear due to a thickened tympanic membrane; presence of middle ear fluid, for example, caused by acute otitis media; or dysfunction of the Eustachian tube can be detected [31].

BERA will be performed for objectively measuring hearing thresholds to quantify the type and severity of hearing loss [32]. Electric activity of the VIII nerve and its central connections are evoked by a broadband click stimulus or frequency-specific stimulus through a headphone, insert phone, or bone conductor. The responses can be measured by electrodes placed on the scalp and is represented as a registration of measured electrical potentials as a function of time after stimulus presentation, characterized by reproducible peaks at specific time delays (latencies). No active cooperation is required, but a prerequisite is that the patient is asleep or lies in a relaxed position to avoid artifacts due to muscle activity.

Evoked otoacoustic emissions (OAEs) are sounds generated within the inner ear after presentation of a stimulus. OAEs are related to the nonlinear behavior of the cochlea, often referred to as the cochlear amplifier. A clear relationship exists between the presence of normal OAEs and functional outer hair cells, which implies that OAEs can only be evoked in ears with normal hearing thresholds or very mild hearing loss (<25 dB HL) [33,34]. Different types of OAEs exist, but often DPOAEs and transiently evoked OAEs (TEOAEs) are measured. TEOAEs are evoked by using a click stimulus and frequency range up to 4 kHz, in contrast to the DPOAEs that are evoked by using pairs of primary tones with particular intensity. The frequency range that can be monitored is much larger than with TEOAEs and ranges up to 10 kHz [31,33,34]. As ototoxicity will start in the high frequencies, measuring DPOAEs is preferred in addition to TEOAEs in our study.

Table 2. Audiological assessments per age category.[a]

Assessment	Age categories			
	0-6 months	6 months-3 years	3-5 years	5-18 years
Check eligibility	✓[b]	✓	✓	✓
Determine stratum	✓	✓	✓	✓
Check treatment plan	✓	✓	✓	✓
Demographic data	✓	✓	✓	✓
Audiological examination				
Anamnesis[c]/case history	✓	✓	✓	✓
Otoscopy	✓	✓	✓	✓
Tympanometry	✓	✓	✓	✓
Otoacoustic emissions	✓	✓		
Brainstem-evoked response audiometry	✓			
Visual reinforcement audiometry		✓		
Conditioned play audiometry			✓	
(Extended high-frequency) pure tone audiometry				✓
Anamnestic tinnitus questions				✓[d]
Anamnestic vertigo questions				✓[e]

[a]The listed audiological examination per age category provides an indication. Due to clinical circumstances or developmental status of the patients, another more appropriate test might be chosen.

[b]The checkmark indicates the assessment was given for these age groups.

[c]During anamnesis children/parents are asked for hearing loss in the past, results of the neonatal hearing screening, ear-nose-throat surgery in the past, and family members with (heredity) hearing loss.

[d]Tinnitus screening will be performed for children 8 years and older.

[e]Vertigo screening will be performed for children 10 years and older.

VRA and conditioned play audiometry are both subjective tests based on a conditioning procedure. For VRA, the child is conditioned to make a head turn and to look at a "reward," for example, a short movie or picture, every time a frequency-specific stimulus is presented [35,36]. For conditioned play audiometry, children are conditioned to perform a motivation enhancing task when an auditory stimulus is presented, for example, putting a block into a box [31,35]. Frequencies up to 8 kHz can be measured, but for ototoxicity monitoring, the range is preferably extended to the high frequencies up to 12 kHz, as in an early stage, ototoxicity may affect the high frequencies [37].

PTA is a subjective behavioral measurement of hearing thresholds. Conventional PTA measures the faintest tone a person can hear at selected frequencies. Hearing thresholds are obtained via air conduction (0.25-8 kHz) by using headphones and via bone conduction (0.5-4 kHz) by using a vibrating transducer. Additionally, extended high-frequency hearing thresholds may be determined up to 12 to 14 kHz, depending on the age of the child [31,34,38].

Anamnestic screening for tinnitus and vertigo will be performed during audiological assessments as a standardized procedure. Regarding tinnitus, children 8 years and older will be asked whether they hear noise in their ears. If the answer is yes, questions follow on the type of noise (ringing, buzzing, humming, whistling, sea noise, banging, blowing sound, like a machine, clicking, beep, like the wind, or like cars), the moment of onset (dates, after which chemotherapy course), laterality (left ear, right ear, or both), pitch (high vs low), perceived loudness (graded according to a Likert scale 0-5) at the peak moment, duration (intermittent, most, some of the time, or continuous), annoyance degree (always annoyed, seldom annoyed, very annoyed, little annoyed), and severity with regard to causing worry (not at all, slightly, sometimes, more severely) [26]. Regarding vertigo, children 10 years and older will be asked whether they ever get dizzy. If the answer is yes, questions follow on the moment of onset (dates, after which chemotherapy course), presence of light-headedness (yes/no), tendency to fall (yes/no), experiencing spinning or turning objects (yes/no), sensation of turning or spinning (yes/no), loss of balance when walking or running (yes/no), duration (intermittent, most/some of the time, or continuous), and severity (graded according to a Likert scale 0-5) [27].

Speech Audiometry

In case of hearing loss at the end of cancer treatment, speech audiometry is recommended to test the ability to hear and understand speech. Several lists of words are offered to the child through headphones or a free field loudspeaker. The child is asked to repeat the words. The number of correctly repeated phonemes or words are recorded. The results are registered in

a speech audiogram. The test reveals the amount of speech discrimination at various stimulus intensities and provides an indication on the influence of hearing loss on communication. Different test procedures are available, including determination of the ear's ability to discriminate speech in silence or in different types of noise. Speech audiometry in children is often used as a diagnostic test. In addition, the test can be useful to evaluate the outcome of an intervention with hearing aids [31,34,39].

Sample Size

A power analysis based on two-sided CIs for one proportion has been performed. The Clopper-Pearson exact formula for computing binomial CIs was used. The method is based on the cumulative probabilities of the binomial distribution rather than an approximation [40,41]. A sample size of 367 patients produces a two-sided 95% CI with a width (distance between lower and the upper limit for the CI) equal to 1% when the sample size proportion is 35%. PASS software (NCSS, LLC) has been used for computing the sample size.

Outcomes

Baseline Characteristics

Baseline variables will be collected including age; gender; weight; height; medical and audiological history; solid/CNS tumor type; presence of neurofibromatosis (yes/no); hydrocephalus (yes/no); which national or international cancer treatment protocol will be applied; and whether a patient receives treatment with CNS/ENT surgery, CNS/ENT irradiation, or platinum agents.

Primary Outcome Measures

The primary outcome is the prevalence of hearing loss at the end of cancer treatment in a prospective cohort of children with CNS and solid tumors. Hearing loss is classified according to the Muenster classification [42]. The definition of sensorineural hearing loss at the end of treatment will be >40 dB at 4 kHz (corresponding to Muenster grade 2b) [42] measured by BERA, VRA, conditioned play audiometry, or PTA. The SIOP Boston criteria will be applied as a second grading for a reliable determination of hearing loss [43].

Secondary Outcome Measures

Secondary outcomes include the prevalence of tinnitus and vertigo, and the treatment components that may be associated to hearing loss, tinnitus, and/or vertigo development. Tinnitus and vertigo will be measured by the aforementioned study procedures. The definition of tinnitus at the end of treatment will be "a sensation of a noise in the ear or head when no apparent source for the noise is evident" [26]. The definition of vertigo is "an abnormal sensation of motion," which can occur in the absence of motion or when a motion is sensed inaccurately [27]. Treatment components of included patients that will be collected include total cumulative dose of cisplatin, carboplatin, and oxaliplatin; irradiation type (photon or proton) and total dose in Gray (especially on inner ear structures); type of CNS/ENT surgery, cerebral shunt, or Ommaya reservoir; aminoglycoside type, levels, and total cumulative dose; glycopeptide type, levels, and total cumulative dose; and diuretic

type and cumulative dose. Liver and kidney function will be measured during treatment. These results will be collected and considered, as platinum agents, antibiotics, and diuretics are (partially) excreted by liver and kidneys.

Secondary outcomes also include the feasibility of standard care audiological testing of all patients with solid and CNS tumors treated with platinum, CNS/ENT irradiation, or CNS/ENT surgery before and after childhood cancer therapy by using standardized diagnostic tests, timing, and frequency of audiological evaluations in this population (stratum 1).

Statistical Analysis

Continuous variables will be reported with medians and ranges while categorical variables with percentages. To assess differences between patients with and without hearing loss, tinnitus, or vertigo, chi-square and Student t tests will be used for categorical and continuous variables, respectively. In case of violation of normality, Mann-Whitney U tests will be used.

A logistic regression model will be estimated to investigate the effect of risk factors such as platinum use and cumulative dose, type of CNS/ENT surgery, type of CNS/ENT irradiation and dose, type of comedication and its dose and levels, age at diagnosis, and gender on ototoxicity at the end of treatment. To quantify the effect of prognostic factors on the risk of ototoxicity at the end of treatment, odds ratios along with 95% CIs will be estimated. Statistical analysis will be performed with SPSS, version 26.0.0.1. (IBM Corp) [44].

In the presence of missing data, imputing techniques are used [45].

Ethics Approval

The study protocol has been approved by the Clinical Research Committee of the Princess Máxima Center and by the Medical Research Ethics Committee Utrecht (Identifier 20-417/M), and has been registered in the Netherlands Trial Register (NL8881).

Results

Inclusion started on January 4, 2021. Participant recruitment and data collection are still ongoing. Patient inclusion will be finished on January 1, 2023.

Discussion

Study Rationale

Ototoxicity is a serious adverse event of childhood cancer treatment. However, the prevalence of hearing loss, tinnitus, and vertigo during and shortly after treatment has never been studied in large prospective pediatric oncology patient cohorts. To date, the association of clinical characteristics and treatment components on the development of ototoxicity is not fully understood. Therefore, we will investigate the feasibility of testing all patients with a potential risk on ototoxicity with standardized audiological examinations. The prevalence and determinants of hearing loss, tinnitus, and vertigo will be investigated in a prospective cohort of childhood cancer patients. Accurate audiological testing and timely detection of ototoxicity will identify novel compounds at risk for ototoxicity and create

awareness, which may lead to improved patient care and improved quality of life. Furthermore, we aim to collect high-quality data on the relation between disease status, type of treatment, and audiological functioning in children with solid and CNS tumors before and shortly after treatment. In the future, these data could be used to identify children who are at risk and might benefit from otoprotective agents that are currently under development.

Limitations

First, it is important to realize that pediatric oncology patients can be critically ill at the time of presentation at the hospital. In that case, it may not be feasible to perform baseline audiological examination. For these selected children, we decided to use audiological anamnesis to exclude any type of pre-existent hearing loss. Second, it is possible that patients will receive medication (eg, antibiotics and diuretics) in shared care centers, which are not reported and may lead to underreporting comedication.

Data Availability

Data sharing is not applicable, as no data set is currently available for analysis in this study protocol. A data transfer agreement between the Wilhelmina Children's Hospital/University Medical Center Utrecht and the Princess Máxima Center is available to transfer audiological data.

Authors' Contributions

MvdHE, MvG, FAD, and AJMM contributed by receiving ethical approval for the Study on Prevalence and Determinants of Ototoxicity During Treatment of Childhood Cancer (SOUND). FAD and AJMM were major contributors in writing the manuscript. MvdHE, MvG, SLAP, AEH, GOJ, RJS, AJMM, and FAD all contributed to the study design and critically revised the manuscript. AEH revised the audiological part of the Methods section. MF wrote the statistical analysis section of the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BERA: brainstem-evoked response audiometry
CNS: central nervous system
DPOAE: distortion product otoacoustic emission
ENT: ear-nose-throat
OAE: otoacoustic emission
PTA: pure tone audiometry
ROS: reactive oxygen species
SOUND: Study on Prevalence and Determinants of Ototoxicity During Treatment of Childhood Cancer
TEOAE: transiently evoked otoacoustic emission
VRA: visual reinforcement audiometry

<u>Original Paper</u>

Buccal Mucosal Grafts as a Novel Treatment for the Repair of Rectovaginal Fistulas: Protocol for an Upcoming Prospective Single-Surgeon Case Series

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Abstract

Background: Rectovaginal fistulas (RVFs) are abnormal communications between the rectum/anus and the vagina. They are most frequently formed a result of obstetric injury and have deleterious effects on patients' quality of life. Despite several treatment modalities, RVFs remain difficult problems to manage, and many patients fail multiple attempts at surgical repair. Buccal mucosal grafts (BMGs) may be a solution to this problem. A BMG is an oral mucosal tissue harvested from the inner cheek. There are 2 case reports that describe the successful use of BMGs in the repair of RVFs.

Objective: Our objective is to validate these findings with a prospective case series while also addressing the key issues of indication, technical details, procedure safety, and short-term outcomes.

Methods: A prospective single-surgeon case series will be undertaken at a university-affiliated academic tertiary care hospital in Calgary, Alberta (Canada). The estimated recruitment is between 3 and 5 patients. Patients will undergo surgical repair of their RVFs with an autologous BMG. Data on patient characteristics, fistula characteristics, and surgical variables will be collected and analyzed prospectively. The primary outcome is fistula closure. This study has been approved by the Conjoint Health Research Ethics Board at the University of Calgary (REB20-1123).

Results: Two previous case reports have described the successful use of BMGs in the repair of RVFs. We have received ethics approval to attempt to validate these findings through a prospective case series.

Conclusions: RVFs cause significant patient morbidity and are difficult problems to manage. Bolstered by the successful use of BMGs in urologic surgery and the previously published case reports demonstrating success in RVFs, we believe that BMGs may be a solution to RVFs.

International Registered Report Identifier (IRRID): PRR1-10.2196/31003

Introduction

Rectovaginal Fistulas

Rectovaginal fistulas (RVFs) and anovaginal fistulas are abnormal communications between the rectum/anus and the vagina. They are most often secondary to obstetric injury, occurring in approximately 0.1% of vaginal births [1]. Other causes include infections, inflammatory and neoplastic conditions, and iatrogenic injuries. Despite their rarity, RVFs are an important problem, resulting in significant morbidity with demonstrable negative impacts on patients' quality of life [1,2]. Despite numerous treatment modalities that have evolved over time, RVFs remain difficult problems to manage, and many patients fail several attempts at repair [1]. The procedure of choice for a simple RVF is an endorectal advancement flap,

with reported success rates in the range of 41%-78% [2]. Recurrent and complex RVFs may require other surgical techniques, including fecal diversion, sphincteroplasty, muscle flaps, or even rectal resections (Multimedia Appendix 1) [3]. The variety of different techniques utilized in the surgical management of RVFs illustrates the complexity of this problem.

Buccal Mucosal Grafts

A buccal mucosal graft (BMG) is an oral mucosal tissue harvested from the inner cheek or lower lip. It is frequently used for the repair of urethral defects, including rectourethral and vesicovaginal fistulae [4-8]. This technique was popularized after 1992 and is the first-choice graft tissue for urethroplasty in the repair of male urethral strictures [4,9] The use of oral mucosa is favored by urologists because of its similarities and compatibility with the mucosa of the urethral tract. The buccal mucosa is a nonkeratinized tissue, and its thick epithelium with vascular lamina propria gives it strength and adaptability to withstand the shearing forces in the mouth as well as defend against the microbial environment of the oral cavity [10]. Complications from BMGs are rare. A systematic review found a 4% complication rate occurring at the buccal donor site—most commonly scarring and contracture. Bleeding and hematoma formation occurred in <1% of cases. Patients can expect to have mild pain and discomfort for up to 4 weeks postoperatively. Patients may have limited range of jaw opening, but most return to preoperative range within 4 weeks [10].

BMGs for RVFs

A systematic review of the literature was undertaken to identify whether BMGs have previously been used in the repair of RVFs. The electronic databases of Ovid MEDLINE, Embase, Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials), and CINAHL (all years) were systematically searched for studies reporting on BMGs used for RVFs. The following medical subject heading terms were used: rectovaginal fistula, rectovaginal fistul* or recto-vaginal fistul* or anorectal vaginal fistul* or rectoneovaginal fistul* or recto-neovaginal fistul* or RVF or ARVF or AVF. All studies reporting on the use of BMGs for RVFs were considered eligible, and no restrictions were applied. Two case reports were identified:

1. In 2014, Grimsby et al [11] published the use of an autologous BMG in the repair of a recurrent iatrogenic RVF in a 4-year-old female. This patient's RVF was a complication of a Soave procedure for Hirschsprung disease and failed 1 repair attempt prior to the use of the BMG.
2. In 2019, Elmer-DeWitt et al [12] described the use of an autologous BMG to repair an iatrogenic RVF in a 64-year-old transgender woman. This patient had previously undergone a penile skin inversion neovaginoplasty, which was complicated by intraoperative rectal injury.

These 2 reports demonstrated the successful use of buccal mucosa as a graft repair for an RVF. To our knowledge, these are the only such published accounts. Additional details from these case reports can be found in Table S2 of Multimedia Appendix 2.

Idea, Development, Exploration, Assessment, Long-term Follow-up Framework for Surgical Innovation

This protocol is modelled from the IDEAL (Idea, Development, Exploration, Assessment, Long-term follow-up) framework for surgical innovation, which describes the stages of optimal surgical innovation: idea, development, exploration, assessment, and long-term follow-up [13]. The goal of this framework is to improve the quality of research in surgical and interventional procedures.

Hypothesis and Objective

We hypothesize that an autologous BMG can successfully repair an RVF. Our objective is to validate the findings of the aforementioned case reports while also reporting on the safety, short-term outcomes, and technical details of the procedure (in keeping with the IDEAL framework for surgical innovation [13]).

Methods

Study Design

This study is a prospective single-surgeon case series.

Ethics Approval

This study has been approved by the Conjoint Health Research Ethics Board at the University of Calgary (REB20-1123).

Study Population and Recruitment

Patients will be recruited by a colorectal surgeon from a university-affiliated academic tertiary care hospital in Calgary, Alberta (Canada). Given the rarity of RVFs, the estimated recruitment is between 3 and 5 patients. The inclusion criteria are as follows: (1) female patients with a clinical or imaging diagnosis of a rectovaginal or anovaginal fistula; (2) fistula resulting from obstetrical injury, infection, inflammatory bowel disease, or radiation; (3) any number of recurrent fistulas; (4) fistula ≤2.5 cm diameter; and (5) adults ≥18 years of age. The exclusion criteria are as follows: (1) fistula resulting from neoplasia and (2) fistula >2.5 cm. Patients who meet the inclusion criteria and none of the exclusion criteria will be offered the opportunity to participate in this study. They will be provided with all the relevant information for informed consent verbally and in writing. If they decide to participate, they will be asked to sign informed consent.

Surgical Technique

Donor Site Harvest

Buccal mucosa harvested from the inner cheek (vs lower lip) is recommended by the American Urological Association 2016 guidelines [4]. A local urologist experienced in BMGs will perform the buccal mucosal harvesting. Multimedia Appendix 3 describes our planned technique.

Fistula Repair

The technique for fistula closure/graft implantation is developed from standard techniques and practices for advancement flap closures of RVFs in addition to the work from the original 2014

case report [11]. The technique described in the 2019 case report [12] is less applicable, given the neovagina anatomy. Multimedia Appendix 4 describes our planned technique.

Variables for Data Collection and Analysis

The variables for data collection and analysis are described in Textbox 1.

Textbox 1. Variables in this study.

Patient characteristics

- Age

- BMI

- Number of vaginal deliveries and history of obstetrical injuries

- History of vaginal surgery

- History of anorectal surgery

- History of pelvic radiation

- Sphincter function (based on clinical examination and Cleveland Clinic Florida Fecal Incontinence Score [14])

Fistula characteristics

- Etiology of fistula (eg, obstetrical, infectious, inflammatory, radiation, iatrogenic)

- Location (distance from anal verge)

- Size

- Previous attempts at repair

Surgical variables

- Size of buccal mucosal graft

- Operative time

- Variations in surgical technique (sequential reporting, with nature and timing of modifications reported)

Outcome variables

- Primary outcome:

  - Fistula closure at 2, 6, 12 weeks, and 1 year after the operation

- Secondary outcomes:

  - Postoperative complications, including donor site morbidity (Clavien-Dindo classification, Multimedia Appendix 5).

  - Postoperative sphincter function (based on clinical examination and Cleveland Clinic Florida Fecal Incontinence Score [14])

Results

Two previous case reports have described the successful use of BMGs in the repair of RVFs. We have received ethics approval (Multimedia Appendix 6) to attempt to validate these findings through a prospective case series. This study has been approved by the University of Calgary Conjoint Research Ethics Board (REB20-1123). Plans for dissemination include publication of our results upon completion.

Discussion

RVFs cause significant patient morbidity and are difficult problems to manage, with frequent recurrences from failed attempts at surgical repair [1]. Bolstered by the successful use of BMGs in urologic surgery and the previously published case reports demonstrating success in RVFs, we believe that BMGs may be a solution to RVFs. Historically, surgical innovation has been largely unstructured and variable, without adequate and timely evaluation [15]. This has been noted by some to have resulted in "persistent difficulties in obtaining high-quality evidence for surgical innovations" [13]. In response, recommendations for the development and assessment of new interventions have been created in the form of the IDEAL framework [15]. The 2014 and 2019 case reports describing BMG utilization in the repair of an RVF are IDEAL stage 1 (innovation) studies. Our planned case series will take on the form of an IDEAL stage 2a (development) study. As such, we plan to follow the IDEAL recommendations, which are to address the key issues of procedure safety, short-term outcomes, indications, and technical details with potential modifications.

Authors' Contributions

CC was responsible for concept generation, drafting, and revision of protocol. She will assist in patient recruitment, surgical intervention, data collection and analysis, and ultimate manuscript drafting. NK drafted and revised the protocol. She will assist in patient recruitment, surgical intervention, data collection and analysis, and ultimate manuscript drafting. JH is the Principal Investigator and a colorectal surgeon. Patients will be recruited through JH's clinical practice. JH will be the primary operating surgeon in this upcoming case series.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Table outlining rectovaginal fistula treatment options.
[DOCX File , 15 KB - resprot_v11i4e31003_app1.docx]

Multimedia Appendix 2
Table comparing known case reports using buccal mucosal graft as treatment for rectovaginal fistulas.
[DOCX File , 17 KB - resprot_v11i4e31003_app2.docx]

Multimedia Appendix 3
Buccal mucosal graft harvest information.
[DOCX File , 15 KB - resprot_v11i4e31003_app3.docx]

Multimedia Appendix 4
Buccal mucosal graft repair of rectovaginal fistula information.
[DOCX File , 14 KB - resprot_v11i4e31003_app4.docx]

Multimedia Appendix 5
Clavien-Dindo classification system.
[DOCX File , 232 KB - resprot_v11i4e31003_app5.docx]

Multimedia Appendix 6
Ethics approval.
[DOCX File , 449 KB - resprot_v11i4e31003_app6.docx]

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Abbreviations

BMG: buccal mucosal graft
IDEAL: Idea, Development, Exploration, Assessment, Long-term follow-up
RVF: rectovaginal fistula

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Corrigenda and Addenda

Correction: Comparing Online and On-Site Cognitive Behavior Therapy in Major Depressive Disorder: Protocol for a Noninferiority Randomized Controlled Trial

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Related Article:

Correction of: https://www.researchprotocols.org/2022/4/e29726

In "Comparing Online and On-Site Cognitive Behavior Therapy in Major Depressive Disorder: Protocol for a Noninferiority Randomized Controlled Trial" (JMIR Res Protoc 2022;11(4):e29726), the following change was made:

In the originally published article, the Conflicts of Interest section inadvertently appeared as follows:

> *None declared.*

In the corrected version, the Conflicts of Interest section has been corrected as follows:

> *NW is an employee of NexJ Health and holds stock in the company. NexJ Health provides in-kind subscriptions for the digital health platform of NexJ Connected Wellness, which enables the delivery of the CBT-M program and provides health coaching to the participants in the CBT-M intervention group. PR receives in-kind software support from NexJ Health for this investigator-initiated study, funded by the Canadian Institutes of Health Research (CIHR). He also receives research support from NexJ Health through the Digital Health Research Fund administered by the Faculty of Health at York University. ZD has received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc and Magventure Inc. He is also on the scientific advisory board for Brainsway Inc. His work has been supported by the National Institutes of Mental Health (NIMH), Canadian Institutes of Health Research (CIHR), Brain Canada, and Temerty Family Foundation, and Grant Family Foundation.*

The correction will appear in the online version of the paper on the JMIR Publications website on April 21, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Protocol

Adaptive Text Messaging for Postpartum Risky Drinking: Conceptual Model and Protocol for an Ecological Momentary Assessment Study

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Abstract

Background: Risky drinking is prevalent among women of childbearing age. Although many women reduce their drinking during pregnancy, more than half return to prepregnancy levels during the early postpartum period. Risky drinking in new mothers may be associated with negative child and maternal health outcomes; however, new mothers are unlikely to seek treatment for risky drinking because of stigma and fear of child protective service involvement. SMS text messaging is a promising approach for reaching non–treatment-seeking new mothers at risk because of risky drinking. SMS text messaging interventions (TMIs) are empirically supported for alcohol use, but a tailored intervention for new mothers does not exist. This study aims to fill this gap by developing a just-in-time adaptive TMI for postpartum risky drinking.

Objective: The objectives of this paper are to present a preliminary conceptual model of postpartum risky drinking and describe the protocol for conducting an ecological momentary assessment (EMA) study with new mothers to inform the refinement of the conceptual model and development of the TMI.

Methods: This paper presents a preliminary conceptual model of postpartum risky drinking based on the motivational model of alcohol use, social cognitive theory, and temporal self-regulation theory. The model proposes three primary intervention targets: motivation, self-efficacy, and self-regulation. Theoretical and empirical literature in support of the conceptual model is described. The paper also describes procedures for a study that will collect EMA data from 30 participants recruited via social media and the perinatal Central Intake system of New Jersey. Following the baseline assessment, EMA surveys will be sent 5 times per day for 14 days. The assessment instruments and data analysis procedures are described.

Results: Recruitment is scheduled to begin in January 2022 and is anticipated to conclude in March 2022. Study results are estimated to be published in July 2022.

Conclusions: The study findings will enhance our understanding of daily and momentary fluctuations in risk and protective factors for risky drinking during the early postpartum period. The findings will be used to refine the conceptual model and inform the development of the TMI. The next steps for this work include the development of intervention components via an iterative participatory design process and testing of the resulting intervention in a pilot microrandomized trial.

International Registered Report Identifier (IRRID): PRR1-10.2196/36849

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Introduction

Background and Rationale

Risky drinking, defined as the consumption of ≥4 drinks in a day or ≥8 drinks in a week [1-3], is prevalent among women of childbearing age. A 2019 national survey found that, among women aged 18-25 years, 55% reported past-month alcohol use, 34% reported past-month binge drinking (defined as drinking ≥4 drinks at once), and 7% reported past-month heavy alcohol use (defined as drinking ≥4 drinks at once at least 5 days in the previous month). Among women aged 26-44 years, 59% reported past-month alcohol use, 30% reported past-month binge drinking, and 6% reported past-month heavy alcohol use [4]. Although many women reduce their drinking during pregnancy, more than half return to prepregnancy levels by 3 months after delivery [5,6]. Patterns of postpartum drinking vary widely, with 8%-12% of women showing patterns of escalating risky drinking in the early postpartum period [7-9]. Depending on severity, postpartum alcohol use can lead to impaired parenting and an increased risk of child maltreatment [10], which can have devastating impacts on brain development, leading to long-term impairment [11,12]. Given the increase in drinking and the potential for severe consequences to the child [13-15], the postpartum period is a critical time for intervention to address risky drinking. However, most adults who engage in risky drinking do not seek treatment [16]. New mothers may be particularly unlikely to seek treatment because of stigma and fear of child protective service involvement [17]. Thus, there is a critical need for innovative approaches to reach non–treatment-seeking new mothers at high risk for negative consequences associated with risky drinking. The goal of this study is to meet this need by developing an SMS text messaging intervention (TMI) to address postpartum risky drinking. In this paper, we describe two critical first steps toward this goal: (1) development of a preliminary conceptual model of postpartum risky drinking and (2) presentation of a protocol for data collection via ecological momentary assessment (EMA) to refine the conceptual model and inform TMI development.

SMS text messaging is a promising approach for reaching non–treatment-seeking risky drinkers and may be particularly suitable for addressing postpartum risky drinking. With 97% of Americans owning a cell phone as of 2021, access to SMS text messaging is widespread [18]. Studies suggest that 99% of received SMS text messages are opened, and 90% are read within 3 minutes of receipt [19]. TMIs are highly acceptable to people with drug and alcohol dependence [20] and have high scalability potential at a relatively low cost. Of particular importance for new mothers, TMIs provide a way of delivering interventions anonymously, potentially overcoming the stigma and fear of consequences that often prevent mothers from accessing more traditional forms of treatment [17,21-24]. In a recent survey, low-income new mothers with histories of risky drinking reported high levels of mobile phone ownership and use of SMS text messaging as well as favorable reactions to receiving SMS text messages to address alcohol use [25].

A growing body of literature demonstrates support for TMIs in reducing risky drinking in non–treatment-seeking adults [20,26-30]. In a recent review of mobile health interventions for unhealthy alcohol use, over half of the TMIs reviewed were effective in reducing alcohol use or increasing readiness to change [31]. However, the existing literature on TMIs for alcohol use has several limitations, including a lack of theoretical behavior change models guiding intervention design, small samples, and lack of long-term follow-up [20,21,32]. In addition, most existing studies have compared whole TMIs to attention- or assessment-only controls and were not able to disentangle the impacts of individual intervention components. Generalizability is also limited as most studies have focused on college drinkers, adults with alcohol use disorder, or patients in the emergency department. There are currently no TMIs for alcohol use that are tailored to the unique characteristics of the postpartum period.

TMIs that tailor content to specific participant characteristics or clinical needs show larger effects on clinical outcomes and lower rates of attrition than programs that deliver generic messages [20,26,33]. Interventions that are dynamically tailored in response to reports of changing needs or other variables assessed regularly throughout intervention delivery are referred to as *just-in-time adaptive interventions* (JITAIs). JITAIs aim to provide interventions at times when individuals are particularly vulnerable and when opportunity for positive change is greatest [34], making this approach a good fit for the postpartum period. The postpartum period is inherently a time of high vulnerability, as demonstrated by higher rates of depression and perceived stress among new mothers [35], which are known risk factors for alcohol use [36-38]. New mothers experience unique transient influences on vulnerability, including daily stress associated with caring for a new baby that can be exacerbated by factors such as lack of sleep and baby irritability [39-41]. The postpartum period is also a time of opportunity for positive change. Pregnant and postpartum people generally report high levels of motivation to change behaviors that may negatively affect their baby, making this time of life a *teachable moment* with maximum potential for effecting positive behavior change [42].

This study will apply the multiphase optimization strategy (MOST) framework [43] to develop and pilot-test the first theory-driven just-in-time adaptive TMI for postpartum risky drinking. The MOST is an engineering-inspired framework that allows for the identification of the optimal package of intervention components and is recommended for building efficient, scalable mobile health interventions [44]. The MOST proceeds in 3 phases. The preparation phase, which is the focus of this study, is aimed at (1) developing a conceptual model that specifies the relationships between intervention components, intervention targets, and outcomes; (2) developing content and delivery strategies for each intervention component; and (3) pilot-testing the developed intervention components. In the optimization phase, the intervention components are further tested in an efficient experimental design with the goal of identifying the best combination of components [45]. Finally, the evaluation phase consists of a traditional randomized controlled trial comparing the full intervention package with a suitable control group.

Following the MOST framework, the first step in developing a theory-driven JITAI for postpartum risky drinking is to specify the theoretical pathways from the postpartum risk factors that are the primary intervention targets to the ultimate desired outcome of reduced risky drinking. Our proposed conceptual model (described in the *Methods* section) is based on three theoretical frameworks that have been widely used to explain alcohol and substance use: the motivational model of alcohol use [46], social cognitive theory [47], and temporal self-regulation theory [48]. These theories have been used previously in the development of TMIs for alcohol use [49-52] but have never been applied to risky drinking in the postpartum period. On the basis of these theories, we have identified three core intervention targets: motivation, defined as commitment to avoid drinking [53]; self-efficacy, including self-efficacy to avoid drinking and self-efficacy in the maternal role; and self-regulation, defined by the use of a range of adaptive coping strategies. All 3 intervention targets correspond to behavior change techniques that have demonstrated efficacy in the context of brief interventions for alcohol use [54-56]. All 3 theoretical frameworks describe internal and external contextual variables operating as risk and protective factors for the intervention targets that ultimately affect drinking behavior. On the basis of the theoretical frameworks as well as the limited empirical literature on the postpartum period, we have selected the following internal and external factors for inclusion: mood, stress, and fatigue (internal factors), and baby fussiness, social support, and drinking cues (external factors). Empirical literature supporting the conceptual model and the selection of contextual variables is described in the *Methods* section.

As JITAIs aim to intervene at the momentary level, a comprehensive understanding of the daily and momentary fluctuations in risks and protective factors for postpartum risky drinking is needed to inform the design of a tailored JITAI for this population. EMAs collect data in real time over the course of a day and are designed to capture momentary fluctuations in feelings and behaviors as participants go about their daily lives [57]. EMAs are particularly suitable for tracking changes in state-level characteristics, which are thought to change significantly within short periods. This method has been widely used in research on substance use and other health behaviors [57-59]. In total, 2 EMA studies with new mothers [60,61] offer preliminary support for the feasibility of this approach with this population. However, almost nothing is known about the in-the-moment predictors of daily drinking in the postpartum period, information that is crucial for the design of effective interventions for this population.

Objectives

The objectives of this paper are to (1) present a preliminary conceptual model of postpartum risky drinking and (2) describe the protocol for conducting an EMA study with new mothers to inform the refinement of the conceptual model and the development of a just-in-time adaptive TMI to address postpartum risky drinking.

The purpose of the EMA study is to assess and refine the conceptual model and test the feasibility of EMA data collection procedures in a sample of new mothers. The primary research questions of the EMA study are as follows: (1) How do momentary and daily fluctuations in internal and external contextual factors affect motivation, self-efficacy, and self-regulation? (2) Which internal and external factors are most salient at particular times of the day? (3) What is the relationship between maternal self-efficacy and drinking self-efficacy and how does this relationship fluctuate throughout the day? (4) What is the relationship between momentary and daily changes in motivation, self-efficacy, and self-regulation and daily drinking? (5) To what extent are the study methods (eg, number and length of surveys and item wording) acceptable and feasible for the target population of new mothers within the early postpartum period?

Methods

Project Overview

This EMA study is part of a 3-year effort to develop a JITAI for postpartum risky drinking that comprises the preparation phase of the MOST framework (Figure 1). EMA data collection represents the first stage of this work, aimed at refining a conceptual model of postpartum risky drinking and informing JITAI development. This paper presents our preliminary conceptual model of postpartum risky drinking and our protocol for EMA data collection. Following completion of the EMA, components of the JITAI will be developed via an iterative participatory design process with focus groups of new mothers. Finally, the resulting JITAI will be tested in a pilot microrandomized trial.

Figure 1. Study timeline. EMA: ecological momentary assessment; JITAI: just-in-time adaptive intervention; MRT: microrandomized trial.

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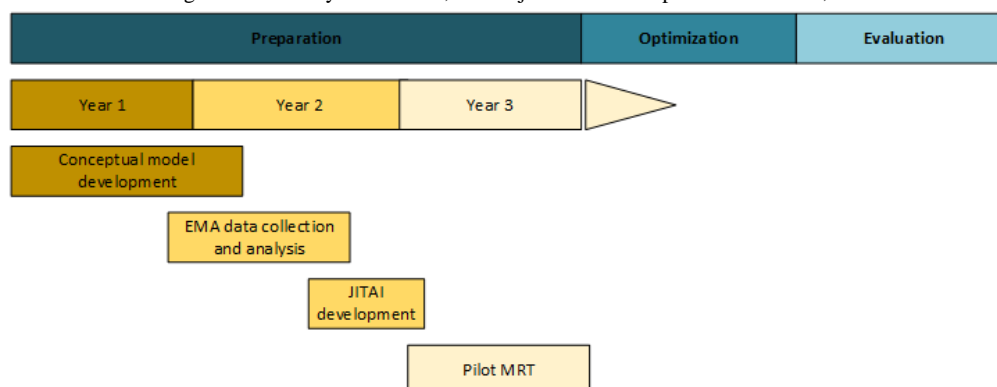
Ethics Approval

The study was approved by the Solutions Institutional Review Board in October 2020 (#2020/06/15) and registered at ClinicalTrials.gov. All study participants will provide informed consent to take part.

Conceptual Model

Overview

Our preliminary conceptual model was developed via a review of relevant theoretical and empirical literature combined with a series of brainstorming conversations among the study team.

Figure 2 depicts the proposed conceptual model of postpartum risky drinking that guided the development of our EMA data collection protocol. This model is preliminary and subject to adjustment based on the findings of the EMA study. Drawing from the motivational model of alcohol use [46], social cognitive theory [47], and temporal self-regulation theory [48], this model identifies three core intervention targets (motivation, self-efficacy, and self-regulation) that have been reliably assessed at the momentary or daily level in EMA studies. This section describes the empirical literature that supports our conceptual model organized according to the intervention target.

Figure 2. Preliminary conceptual model of postpartum risky drinking. SE: self-efficacy.
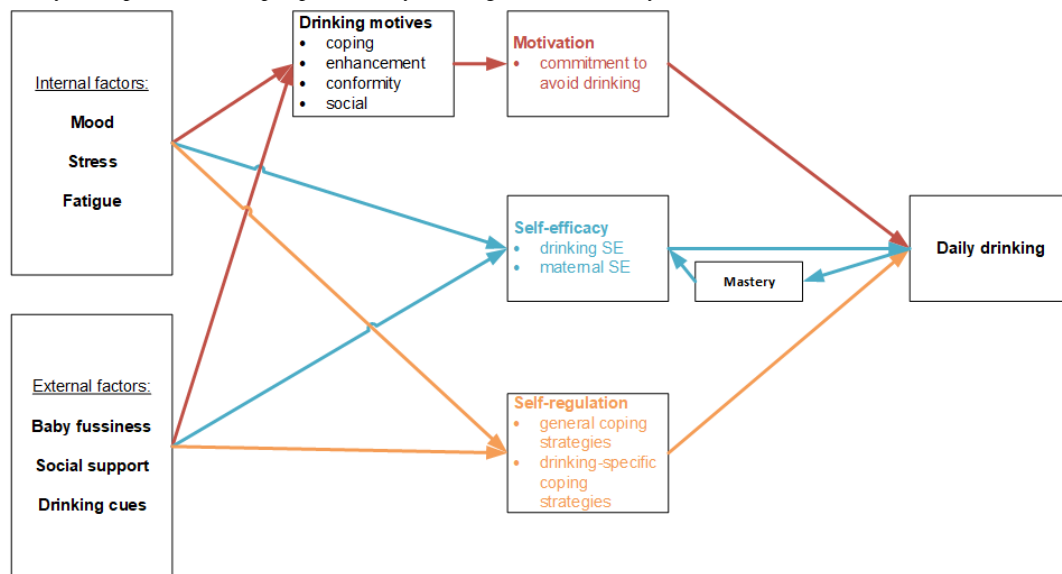
Motivation

According to the motivational model of alcohol use, motivation to drink is the most proximal predictor of drinking behavior [46]. Our conceptual model operationalizes motivation as commitment to avoid drinking, consistent with other studies examining within-day fluctuations in motivation as a key mechanism of change in substance use treatment [53,62,63]. Measured in this way, motivation has been found to fluctuate within a single day, and these changes were associated with drinking the following day [53].

The motivational model proposes four types of drinking motives that may affect within-day fluctuations in motivation to drink: coping (aimed at reducing negative emotions), enhancement (aimed at increasing positive emotions), conformity (aimed at avoiding social rejection), and social (aimed at increasing positive social experiences), with varying antecedents and consequences of each [64]. Findings from EMA studies of alcohol motivations demonstrate that motives vary within persons and across time and situations in response to internal and external contextual factors [65]. Previous EMA studies suggest that higher positive affect is associated with greater enhancement motives [66-68] and higher negative affect is associated with greater coping motives at the daily level [69,70]. Studies examining links between drinking motives and outcomes have shown that daily enhancement motives are generally associated with poorer daily drinking outcomes [68,71,72].

Findings for coping motives are less consistent, with some studies finding that coping motives are associated with increased quantity and severity of alcohol use [71,72] and others finding no relationship [67,68,73]. Most existing research has been conducted with college student samples, and there may be different patterns among new mothers, which we will begin to elucidate in this study.

Self-efficacy

Consistent with social cognitive theory, the conceptual model suggests that two types of self-efficacy—drinking self-efficacy and maternal self-efficacy—may contribute to drinking behavior. Drinking self-efficacy, defined as a person's belief in their ability to avoid drinking, is well-supported as a significant predictor of drinking behavior. Higher drinking self-efficacy has been shown to predict less drinking and improved long-term outcomes in the context of treatment for alcohol use disorder [74-78]. Studies with individuals who engage in problematic drinking and are treatment-seeking have found that daily within-person change in self-efficacy to avoid drinking is associated with intensity of drinking the next day [53,62].

In addition to drinking self-efficacy, our conceptual model includes self-efficacy specific to the maternal role, defined as a mother's belief in her ability to successfully care for her baby. There is currently no research examining associations between maternal self-efficacy and alcohol use. In addition, no study to date has examined daily or momentary changes in maternal

self-efficacy during the postpartum period despite evidence that self-efficacy in other domains changes over brief periods [59,79,80]. This study will explore the associations between maternal self-efficacy and drinking at the daily and momentary levels to inform whether maternal self-efficacy may be an important intervention target for new mothers who engage in risky drinking.

Both drinking self-efficacy and maternal self-efficacy are influenced by internal and external contextual factors, as reflected in the conceptual model. Variations in mood, stress, and fatigue have been shown to affect both drinking self-efficacy [62,81,82] and maternal self-efficacy [83-85]. In addition, maternal self-efficacy is affected by difficult infant behavior [39,40,86,87] and a lack of social support [88-90]. The model also includes a feedback loop between self-efficacy, daily drinking, and mastery such that mastery experiences can increase self-efficacy, thereby reducing the likelihood of next-day drinking. For example, a successful attempt to avoid drinking is likely to increase an individual's belief in their own capacity to avoid drinking in the future, and this heightened self-efficacy makes them more likely to succeed in future attempts to avoid drinking. Empirical studies on the mastery feedback loop are limited, but there is some support for the reciprocal relationship between mastery and self-efficacy in a sample of adults who smoke [91].

Self-regulation

According to temporal self-regulation theory, self-regulation, or the ability to monitor and adapt cognitions, emotions, and behaviors in response to internal or external contextual factors in a goal-directed manner, is a key factor affecting risky behaviors, including alcohol use [92,93]. Internal and external factors can act as triggers for substance use, and adaptive self-regulation strategies must be applied to avoid drinking alcohol in the presence of these triggers [94]. In addition, internal and external factors can predict the likelihood that a person will apply self-regulation strategies in a particular situation [93,95]. Self-regulation is a core theoretical mechanism of behavior change in cognitive behavioral treatments for addiction [96,97], although findings related to the effectiveness of specific self-regulatory strategies for alcohol use have been mixed [95].

A small number of studies have examined daily within-person changes in self-regulation strategies in the context of alcohol use [94]. Studies typically define self-regulation as the use of adaptive coping strategies [69,98,99] or protective drinking strategies [100,101]. Daily engagement in coping strategies has been associated with drinking behavior, with some studies finding differences based on the specific strategy used [69,98] and others not [102]. Given that nearly all studies have used college student samples and there is no research to guide the selection of specific strategies for new mothers, our study includes a broad range of self-regulation strategies with the aim of determining those most salient for our target population.

Target Population, Eligibility Criteria, and Sample Size

The study target population is adults aged 18-45 years who live in New Jersey and gave birth to a live infant within the previous 2 weeks who is currently in their care. This study is being conducted in New Jersey to leverage existing partnerships between the study team and the New Jersey state system of care for perinatal women. Additional eligibility criteria include speaking English and access to a smartphone with internet. Participants must also report one of the following: (1) a score of ≥2 on the Tolerance, Annoyance, Cut Down, Eye-Opener (T-ACE) alcohol risk screener, (2) having ≥8 standard drinks in 1 week in the 12 months before becoming pregnant, or (3) having ≥4 drinks at one time once a month or more often in the 12 months before becoming pregnant. We aim to recruit 30 participants who meet the eligibility criteria. Similar sample sizes have been used in other EMA studies of individuals who engage in substance use [103-105] and new mothers [106].

Recruitment, Eligibility Screening, and Informed Consent Procedures

This study will use two primary recruitment strategies: (1) recruitment via social media advertisements on Facebook and Instagram and (2) referrals from providers in the New Jersey perinatal Central Intake (CI) system.

Social Media Recruitment

Advertisements for the study will be placed on Facebook and Instagram and will be geographically targeted to New Jersey. Additional advertisement targeting will include interests related to birth, pregnancy, motherhood, infant care, and drinking alcohol. Individuals who click on an advertisement will be directed to the study website. Social media recruitment via Facebook and Instagram is widely used in research study recruitment and has been used successfully with both new mothers [107-109] and individuals who are using substances [110,111]. Individuals who access the study website via a social media advertisement will have the option to complete eligibility screening and informed consent on the web or to connect directly with the study coordinator and complete the process via phone.

CI Recruitment

New Jersey operates a state-wide CI system that provides a single point of entry into services for pregnant and postpartum people to promote improved care coordination and access to needed services. For this study, we will partner with one of the CI sites that serves a large, demographically diverse county in the state. CI workers will introduce the study to their clients using a script provided by the study team. If a client is interested in learning more about the study, the CI worker will provide their contact information to the study coordinator, who will contact the client within 2 weeks of her due date to complete eligibility screening. For clients who are interested in the study but prefer not to share their contact information, the CI worker will direct them to the study website, where they can complete eligibility screening and informed consent on the web.

Baseline Survey and EMA Training

Eligible participants who complete the informed consent process will be invited to complete the baseline survey. Baseline survey data will be used to describe the study sample and understand the impact of baseline characteristics on momentary changes in the variables of interest. The baseline survey can be completed either on the web via Qualtrics (Qualtrics International Inc) or via phone with the study coordinator, depending on the participant's preference. The baseline survey will take approximately 30 minutes to complete, and participants will receive a US $25 gift card upon completion. The baseline survey will assess demographic characteristics, maternal self-efficacy, mental health, stress and coping, motivation, alcohol use, and other substance use. See Table 1 for a complete list of the baseline measures. Following completion of the baseline survey, participants will complete a one-on-one 30-minute EMA training session with the study coordinator via Zoom. During the training, the study coordinator will instruct the participants in the installation and use of the MetricWire (MetricWire Inc) data collection app as well as in best practices for maintaining privacy throughout the study. Participants will be considered enrolled in the study after they complete both the baseline survey and EMA training.

Table 1. Baseline measures.

Construct	Description	Measure (reference)
Demographics	Age, gender, marital status, race, ethnicity, living arrangements, childbirth history, education, employment, income, and substance use treatment history	__[a]
Drinking self-efficacy	Perceived ability to handle various drinking situations	Drinking Refusal Self-efficacy Questionnaire–Revised [112]
Alcohol and drug use history	Use of alcohol, marijuana, and illegal drugs before pregnancy, during pregnancy, and since giving birth	Adapted from the NIDA[b]-modified ASSIST[c] [113]; NIAAA[d] drinking questions [114]
Motivation	Readiness to change alcohol use	Maternal Motivation Scale [115]
Postpartum depression	Symptoms of depression since giving birth	Beck Depression Scale [116]
Maternal self-efficacy	Confidence in carrying out various baby care tasks	Karitane Parenting Confidence Scale [117]
Trauma history	Experiences of trauma during childhood	Adverse Childhood Experiences Questionnaire [118]
Pandemic stress	Stress related to the COVID-19 pandemic	Adapted from the Pandemic Stress Index [119]
Attachment to infant	Mother experience of bonding and attachment to baby	Infant Bonding Scale [120]
Fatigue	Experiences of emotional and physical fatigue	Fatigue Assessment Scale [121]
Stress	Perceptions of stress related to general life experiences	Perceived Stress Scale–4 [122]
Drinking motives	Motivation to consume alcohol	Drinking Motives Questionnaire–Revised [64]
Coping self-efficacy	Perceived ability to cope with challenging life events	Coping Self-efficacy Scale [123]
Social support	Perceptions of social support	Interpersonal Support Evaluation List–12 [124]
Digital literacy	Comfort using technology to complete tasks, such as SMS text messaging, using a smartphone, and accessing health information on the web	Media and Technology Usage and Attitudes Scale [125]; the eHealth Literacy Scale [126]

[a]There is no specific citation for the demographic items.

[b]NIDA: National Institute on Drug Abuse.

[c]ASSIST: Alcohol, Smoking, and Substance Involvement Screening Test.

[d]NIAAA: National Institute on Alcohol Abuse and Alcoholism.

EMA Data Collection Procedures

All EMA data will be collected via the MetricWire app. The MetricWire app is available for free download from the Apple App Store and Google Play Store and has been used in other EMA research studies [127,128]. The participants will use their own smartphones to complete the EMA surveys 5 times daily for 14 days. The five surveys will include a *morning survey*, which is a daily diary asking about the previous day, and 4 shorter *hourly surveys*, which ask questions about the period since the previous survey. The selection of 5 daily surveys is based on the need to balance desire to assess fluctuations in risk factors with considerations of participant burden [129], and 3-4 surveys a day has been found to be acceptable to young mothers [130].

Figure 3 displays a sample daily schedule of EMA prompts. Upon enrollment in the study, the participants will be asked to select a morning start time for receiving messages each day. Each day, the morning survey will be sent within 1 hour after the selected start time and will ask questions about the previous day. The morning survey should take approximately 2-3 minutes to complete and will remain available for 10 hours before expiring.

Figure 3. Sample schedule of daily survey prompts.

Sample day in the BabySteps study

- **9 AM** • Participant receives the morning survey
- **9:30 AM** • Participant receives first hourly survey
- **11 AM** • Participant receives second hourly survey
- **2 PM** • Participant receives third hourly survey
- **5 PM** • Participant receives fourth hourly survey
- **1 AM** • Participant decides to complete **optional** nighttime survey while they are awake with their baby

- Please note that participants will never receive notifications after 9 PM. The nighttime survey is available after 10 PM, but will not send a notification. This is an optional survey.
- These are sample survey times, participants' survey times will differ based upon their chosen start time.

The remainder of the day will be divided into 4 equal segments, and hourly surveys will be sent randomly within each segment. No surveys will be sent later than 9 PM. After each survey prompt, the survey will be available for up to 60 minutes, with 2 reminder prompts sent at 20 and 40 minutes. Surveys that are not completed within the 60-minute window will expire. Completion of each hourly survey will take 1-2 minutes.

Between the last survey in the evening and the first survey in the morning, an optional EMA survey will be available for the participants to complete. The reason for this optional survey is to enable data collection during the night, when the participants may be awake with their baby. Nights may be times of high stress and high risk of drinking for new mothers. This survey will allow us to capture data on these middle-of-the-night times without disturbing the participants by sending prompts. The participants who complete the night survey will receive an automatic response SMS text message with contact information for a 24-hour support hotline.

Participant Remuneration

Study participants will be remunerated for taking part in the study in the form of gift cards to Amazon or Target. The participants will be paid US $25 for completion of the baseline survey. During EMA data collection, the participants will be paid US $2 for each EMA survey completed, with a bonus of US $20 for completing >50% of the EMA surveys and US $30 for completing >80% of the EMA surveys. Bonus incentives are used routinely in EMA studies to boost compliance and have been used in EMA studies with postpartum women [131]. The participants will be able to view their progress toward earning bonus incentives within the MetricWire app.

Participant Support

To ensure that the participants are adequately supported during the study, we will engage in the following: (1) check in briefly by phone with all participants after 3 days of EMA to obtain initial feedback on the questions and address any technical difficulties, (2) provide information on how to obtain immediate support via hotlines, and (3) provide all participants with a list of local mental health and substance use treatment and support resources at the outset of the study. Information about how to obtain immediate support will be available within the MetricWire app at all times for the participants to access as needed.

EMA Measures

The study team reviewed the existing literature and selected EMA measures that align with each construct in the conceptual model (Figure 1). As EMA measures must be brief, we prioritized measures that have been used in other EMA studies, particularly those used with a similar population. For measures that have not been used in previous EMA studies, we reviewed factor analyses of full-length scales and selected the highest-loading items to represent the constructs of interest. For some items, we adapted the wording to fit the momentary nature of the EMA. The final list of items included in the morning and hourly EMA surveys is shown in Table 2 organized according to the constructs in the conceptual model. At the beginning of each survey, the participant is asked to indicate how much time they spent with their baby the previous day (morning survey), whether they were with their baby since the previous survey, and whether they will be with their baby in the next hour (hourly survey). Responses determine which survey questions are asked based on skip patterns. For example, participants who report that they were not with their baby since the previous survey will not be asked how many times their baby fussed or cried since the last survey. The morning survey includes a total of 23 items, and the hourly surveys include a total of 14 items.

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Table 2. Morning and hourly ecological momentary assessment (EMA) survey items and response options.

Construct, subcategories, and measure (reference)	Item (response options)	Morning	Hourly
Internal factors			
Mood			
Adapted from the studies by Nguyen et al [58], Godell et al [111], and Thrul et al [132]	• What is your overall feeling right now? (1=very unpleasant to 7=very pleasant) • What is your overall energy level right now? (1=very low to 7=very high) • What is your anxiety level right now? (1=very low to 7=very high)		✓
Stress			
Adapted from the Perceived Stress Scale [122]; single item used in previous EMA studies [58,61]	• What is your overall stress level right now? (1=very low to 7=very high)		✓
Fatigue			
Adapted from the Fatigue Assessment Scale [121]	• How physically exhausted are you right now? (1=not at all to 7=extremely) • How mentally exhausted are you right now? (1=not at all to 7=extremely)		✓
Adapted from the studies by Dennis and Ross [40] and Mendez et al [61]	• How well did your baby sleep last night? (1=poor to 7=excellent) • How well did you sleep last night? (1=poor to 7=excellent)	✓	
External factors			
Baby fussiness			
Selected items from the Infant Characteristics Questionnaire [133]	• Yesterday, how easy or difficult was it for you to calm or soothe your baby when they were upset? (1=very easy to 7=very difficult) • Yesterday, how much did your baby cry and fuss in general? (1=very little to 7=a lot)	✓	
Adapted from the study by Adams et al [134]	• Since the last survey, how many times did your baby fuss, cry, or seem upset? (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more times) • How many of these times were you able to successfully soothe your baby? (All of them; most of them; some of them; a few of them; none of them)		✓
Social support			
Item from the Maternal Social Support Index [135]	• How often was support available to you when you needed it yesterday? (None of the time; little of the time; some of the time; most of the time)	✓	
Drinking cues			
Adapted from the study by McQuoid et al [103]	• Was alcohol available to you yesterday? (Yes or no) • Were other people in your household drinking alcohol yesterday? (Yes or no)	✓	
Motivation			
Drinking motives			
Selected items from the Drinking Motives Questionnaire [64]	• If you drank alcohol yesterday, why did you drink? (Because it makes social gatherings more fun; to forget about your problems; because it gives you a pleasant feeling; to be liked)	✓	
Commitment to avoid drinking			
Adapted from the study by Kuerbis et al [53]	• How committed are you to not drink alcohol in the next hour (for hourly survey) or today (for morning survey)? (1=not at all to 7=extremely)	✓	✓

Construct, subcategories, and measure (reference)	Item (response options)	Morning	Hourly
Self-efficacy			
Maternal self-efficacy			
Developed for this study	• How confident are you that you will be able to meet your baby's physical needs (such as needs to be fed or changed) over the next hour (for hourly survey) or today (for morning survey)? (1=not at all confident to 7=extremely confident) • How confident are you that you will be able to meet your baby's emotional needs (such as needs to be soothed or entertained) over the next hour (for hourly survey) or today (for morning survey)? (1=not at all confident to 7=extremely confident)	✓	✓
Drinking self-efficacy			
Adapted from the study by Kuerbis et al [53]	• How confident are you that you can avoid drinking alcohol for the next hour (for hourly survey) or today (for morning survey)? (1=not at all confident to 7=extremely confident)	✓	✓
Self-regulation			
Adaptive coping—general			
Adapted from the studies by Roos et al [94] and Cambron et al [136]	• Did you use any strategies to cope with negative feelings or stress since the last survey (for hourly survey) or yesterday (for morning survey)? (I didn't experience negative feelings or stress; I drank alcohol; I changed my thinking; I changed my current situation; I found something else to do; I sought advice or support; I came up with a plan to cope; I set a goal or kept track of my current progress toward a goal; I directly communicated my needs to others; I tried to relax; I took medication; I pushed negative feelings or stress away; I used another strategy; I didn't use any strategies)	✓	✓
Adaptive coping—drinking			
Adapted from the studies by Roos et al [94] and Cambron et al [136]	• Did you use any strategies to manage the urge to drink alcohol since the last survey (for hourly survey) or yesterday (for morning survey)? (I didn't experience an urge to drink alcohol; I changed my thinking; I changed my current situation; I found something else to do; I sought advice or support; I came up with a plan to manage the urge to drink alcohol; I set a goal or kept track of my current progress toward a goal; I directly communicated my needs to others; I tried to relax; I made an effort to stay safe and avoid risks while drinking alcohol; I took medication; I tried to ignore the urge to drink alcohol; I used another strategy; I didn't use any strategies)		
Mastery			
Mastery—parenting			
Selected items from the Perceived Maternal Parenting Self-efficacy Tool [137]	• Yesterday, I was good at feeding my baby (1=strongly disagree, 2=disagree, 3=agree, 4=strongly agree) • Yesterday, I was good at soothing my baby when they became upset (1=strongly disagree, 2=disagree, 3=agree, 4=strongly agree) • Yesterday, I was good at reading my baby's cues (1=strongly disagree, 2=disagree, 3=agree, 4=strongly agree) • Yesterday, my baby responded well to me (1=strongly disagree, 2=disagree, 3=agree, 4=strongly agree)	✓	
Mastery—drinking			

Construct, subcategories, and measure (reference)	Item (response options)	Morning	Hourly
Developed for this study	• How strong was your urge to drink alcohol yesterday? (1=very low to 7=very high) • To what extent did you feel that you overcame your urge to drink alcohol yesterday? (1=not at all to 7=to a very great extent)	✓	
Daily drinking			
Drinking			
Adapted from the studies by O'Donnell et al [73] and Thrul et al [138]	• Did you consume any alcohol yesterday? (Yes or no) • If yes, how many alcoholic drinks did you consume? (Enter numeric value) • If yes, select all the time periods when you drank alcohol yesterday (Morning; lunchtime; afternoon; evening; during the night)	✓	

Acceptability and Feasibility

Drawing from other EMA feasibility studies [58,128,139-142], feasibility outcomes will include the percentage of EMA surveys completed each day, each week, and at the end of the 14-day period; the percentage of each EMA measure completed; and the percentage of respondents who completed 50% and 80% of the EMA surveys [58,139]. Acceptability measures will be collected via a short text-based survey at the end of the 14-day EMA period and will include an assessment of technical challenges, burden, emotional response, and overall satisfaction using Likert scale items from other EMA studies [128,140-142].

Compliance Monitoring Strategies

We will apply the following established methods to encourage and monitor compliance: (1) one-on-one training on EMA procedures before the start of data collection [128,131,140,143-146], (2) availability of technical support by phone throughout the EMA period [131,140,144], (3) daily SMS text message reminders to complete the EMA surveys [143,144], (4) bonus incentives for completing >50% and >80% of the EMA surveys [131,143,144], (5) keeping the participants informed of their progress toward earning bonus incentives [143,144], and (6) outreach to participants who did not complete any EMA surveys 3 days in a row [144,146]. If 3 days pass without any EMA responses, the participants will receive an automated SMS text message reminding them to complete the surveys. The reminder message will be sent once per day for 5 days. If there is still no response, the participant will be considered dropped from the study.

Data Analysis

As the primary purpose of the EMA is to inform the development of the JITAI, the analyses will be largely descriptive. To avoid issues of data quality stemming from noncompliance, we will exclude participants who complete <50% of the required EMA surveys [58]. On the basis of rates of EMA compliance in studies of young adults who drink alcohol [147,148] and of postpartum women [106,131], we expect that nearly all participants will complete ≥50% of the EMAs. We will use descriptive statistics to describe the baseline characteristics of the study sample as well as the feasibility outcomes. Patterns of missing data in the EMA surveys will be

studied using frequency distributions and graphs to discern whether there are certain times when participants are more or less responsive to prompts. We will also examine the average time to respond following each prompt. As in other EMA studies [131], the variation in response to each variable will be graphed using scatter plots with a Loess smoother and examined visually to detect patterns in fluctuations within and across days. To test associations among variables, we will apply generalized estimating equations following the procedures used by Nguyen et al [58] and Thrul et al [132], testing linear and quadratic effects. Generalized estimating equations account for the nesting of multiple observations within participants [149]. To inform the selection of decision rules for the JITAI, we will examine associations among predictors (internal and external factors), mediators (intervention targets), and outcomes (daily drinking) based on individual EMA surveys and averaged across each day. To inform the selection of tailoring variables, we will examine variability in internal and external factors across EMA surveys as well as variability in their relations to the primary intervention targets (motivation, self-efficacy, and self-regulation). For these analyses, the internal and external factors will be examined as time-varying predictors of intervention targets as recommended by Shiffman [150]. We will assess participant differences in EMA feasibility and acceptability measures using independent sample 2-tailed *t* tests and repeated-measures analyses of variance.

Results

Recruitment for this study is scheduled to begin in January 2022. We anticipate completing recruitment and enrollment by March 2022 and expect to have completed EMA data collection by April 1, 2022. Study results will be published in peer-reviewed scientific journals upon completion of data analysis, which is estimated to be in July 2022.

Discussion

Principal Findings

This paper presents a preliminary conceptual model of postpartum risky drinking as well as a protocol for an EMA data collection study aimed at refining the conceptual model and informing the development of the first JITAI for postpartum

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risky drinking. This study is the first to assess in-the-moment predictors of risky drinking in the postpartum period and will thus fill critical gaps in existing research. New mothers who engage in risky drinking and other substance use are understudied and underserved as much of the intervention research on perinatal substance use is focused on pregnancy despite high risks of increasing substance use in the early postpartum weeks [5].

The study findings will enhance our understanding of daily and momentary fluctuations in risk and protective factors for risky drinking during the early postpartum period, a time when risk for alcohol use is high and access to treatment is often low [5]. Although there is substantial theoretical and empirical literature on the risk and protective factors for risky drinking in the general adult population [53,151,152], this study will be the first to examine whether established models apply to the unique population of new mothers. In addition, the study findings will elucidate the role of maternal-specific factors such as baby fussiness and maternal self-efficacy in postpartum risky drinking. Very little is currently known about alcohol use risk during the early postpartum weeks, and data gleaned from this study will provide the information needed to develop tailored interventions for this underserved and high-risk population.

Strengths and Limitations

A primary strength of this study is the reliance on theory to guide EMA data collection and JITAI development. A recent systematic review of JITAIs for substance use found that most existing studies did not apply state-of-the-art methods such as the MOST framework and did not sufficiently incorporate theory into intervention development [153]. The base of empirical studies on brief interventions for postpartum risky drinking is extremely small, and those studies that do exist have not adequately incorporated theoretically driven behavior change techniques [154]. Thus, the JITAI to ultimately be developed in this study stands to significantly improve upon existing interventions by including specific behavior change techniques that are clearly mapped onto theory. Studies show that TMIs that integrate behavior change principles and are adaptively tailored generate larger effects on clinical outcomes [20,33].

The inclusion of variables that are especially salient in the postpartum period, such as maternal self-efficacy, baby irritability, and sleep, is an additional strength of this study. Studies of mothers in substance use treatment demonstrate a complex relationship between motherhood and substance use treatment and recovery. Although motherhood and caring for children are often described as a critical motivating factor for seeking treatment and reducing substance use [42,155], mothers are also more likely to conceal their substance use and avoid seeking help because of fears of losing their children [156,157]. Loss of child custody may also lead to relapse in mothers because of the stress and trauma of child removal [158,159]. Given these complex relationships, assessing variables related to the mother's role, such as maternal self-efficacy, is critical for the appropriate tailoring of interventions.

Study limitations include the requirement to speak and read English and own a smartphone with internet access, limiting generalizability. In addition, the study is focused on alcohol use only, which may leave needs related to the use of other substances unaddressed. Many pregnant and postpartum people who engage in risky drinking also use other substances [160,161]. Finally, participant noncompliance and attrition is often a limitation of EMA studies [57]. Although the few previous EMA studies that have been conducted with new mothers report compliance rates of 75%-80% [106,131], one of the goals of this study is to assess the feasibility of the EMA protocol in this understudied population to inform future research.

Conclusions and Future Directions

The need for tailored digital supportive interventions for the postpartum period is greater than ever given the increasing rates of perinatal stress, depression, and substance use during the COVID-19 pandemic [162]. A growing number of studies have shown increases in postpartum anxiety and depression, perinatal stress, and difficulties with bonding and breastfeeding since the beginning of the pandemic [163,164], all of which significantly increase the risk for risky drinking. This increased risk is combined with the fact that women who use substances are less likely to receive postpartum care [165] and are more likely to report poor relationships with their health care providers and negative experiences seeking care [166]. Digital interventions are generally acceptable to new mothers as a way of receiving support for risky drinking and other behavioral health concerns [25,167] and have the potential to fill a significant gap in services that is currently being exacerbated by the pandemic.

Despite the limitations, this study has the potential to significantly contribute to the existing literature by improving our understanding of the antecedents of postpartum risky drinking and informing the development of a tailored JITAI to address it. If feasibility is supported, the EMA protocol can also serve as a model for future studies that aim to collect real-time data from new mothers. This study represents a first step in a larger program of research aimed at using technology to reach underserved new mothers with interventions for perinatal substance use that are evidence-based and tailored to their identities as mothers and aim to empower mothers to seek help while reducing stigma and fear. The methods and findings of this study will be applied to future efforts to ultimately expand the JITAI to include other substances beyond alcohol as well as to create culturally tailored versions. Significant racial and ethnic disparities exist in access to support and treatment for substance use, with Black and Latinx mothers experiencing higher levels of stigma and greater access barriers to obtaining needed support [168,169]. An important future direction for our research program is to partner with Black and Latinx communities to develop theory-driven, tailored, and technology-based interventions to better meet the needs of Black and Latinx new mothers.

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Abbreviations

CI: Central Intake
EMA: ecological momentary assessment
JITAI: just-in-time adaptive intervention
MOST: multiphase optimization strategy
TMI: text messaging intervention

Protocol

Home Delivery of Water for Caries Prevention in Latinx Children ("Sediento por una Sonrisa," Thirsty for a Smile): Protocol for a Single-Arm Feasibility Study

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Abstract

Background: Dental caries has significant public health implications afflicting young children. In addition to low social economic status, the most prominent risk factor for early childhood caries is sugar in the diet, particularly sugar-sweetened beverages. Dental treatment for caries in young children is commonly performed under general anesthesia and a significant proportion of children require repeated treatment. Interventions to reduce sugar-sweetened beverage consumption could lead to reduced rates of retreatment for dental caries in young children.

Objective: This protocol describes the rationale, design, and methods of the "Thirsty for a Smile" feasibility study. The aim of the study is to assess the feasibility, acceptability, and appropriateness of a dietary intervention promoting water consumption in lieu of sugar-sweetened beverages among young patients, mostly from Latino heritage.

Methods: This protocol describes a single-arm feasibility study. Twenty-one dyads of children and their caregivers will be recruited. Children between 2 and 9 years old who recently had treatment under general anesthesia for early childhood dental caries will be eligible to participate. The intervention has two components: (1) environmental, in which bottled water is delivered to participants' homes; and (2) behavioral, in which caregivers will receive patient-centered counseling to increase children's water intake and reduce sugar-sweetened beverages consumption. Dental caries and anthropometric data will be collected at examination during baseline and final visits. The primary outcome is feasibility and secondary outcomes are acceptability and appropriateness of the intervention.

Results: Funding has been obtained from the National Institute of Dental and Craniofacial Research and the University of Washington approved the study. The feasibility study was conducted from March to November 2019.

Conclusions: This feasibility study will test the study processes prior to a two-arm randomized controlled trial to determine feasibility and acceptability of the intervention and study procedures. This study may provide useful information for other researchers attempting to test similar interventions.

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Introduction

Early childhood caries (ECC) is a condition with significant public health implications for young children (0-3 years), especially in lower socioeconomic groups [1-5]. In one systematic review, the most prominent risk factor for dental caries was sugar in the diet, in addition to low socioeconomic status (SES) [6]. There is overwhelming evidence that sugar-sweetened beverages (SSBs) are associated with dental caries in young children [7-14]. SSBs—defined as beverages with energy-containing sweeteners such as fruit juice concentrates, sucrose, or high-fructose corn syrup—are the primary source of sugars in the American diet [15]. These drinks represent approximately half of all added sugar consumption of children [16] and children in low SES groups drink more SSBs than those from high-income families [17]. The typical daily consumption of added sugar in 2001 was 12 teaspoons for children 1-3 years old and was 21 teaspoons for children 4-8 years old [18]. For reference, a 12-ounce can of cola contains 8 teaspoons of sugar [19].

The standard of care for dental caries involves surgical removal or restoration of the teeth, application of a topical fluoride, and recommendations to minimize decay-promoting dietary habits such as the frequent consumption of SSBs [20]. Treatment of dental caries under general anesthesia is becoming more common and costly, which has a major impact on families. More importantly, the outcome of this treatment for ECC is poor: 37%-79% of treated children develop new carious lesions within 24 months [21-25] and 17% require surgical retreatment within 2 years [25]. An intervention focused on decreasing dental caries relapse postsurgery would avoid traumatic and expensive dental care.

A comprehensive approach that targets the main causes of the disease is necessary to improve the clinical outcomes for severe dental caries [26]. Unfortunately, the trials of one-on-one dietary counseling undertaken in dental settings have been neither promising nor rigorous [27]. Dietary management of other chronic diseases—specifically childhood obesity—has been successfully implemented in studies [28-30] and can be adapted to clinical settings. Evidence is mounting that interventions to reduce the consumption of SSBs [28,29,31-36], including interventions promoting water consumption to displace SSBs [30], can be effective. Many children with severe ECC (S-ECC) are treated in major academic health centers or hospitals with programs in pediatric dentistry. These centers have sufficient scale to implement new, more effective approaches to the secondary prevention of ECC. Moreover, the lessons learned from preventing recurrent disease can also be applied to primary prevention. Reducing the consumption of SSBs and promoting the consumption of water is an appropriate strategy to prevent dental caries and other chronic diseases.

The primary objective of the proposed study is to test the feasibility of an environmental dietary intervention designed to promote the consumption of water, in lieu of SSBs, on dental caries relapse among Latino and non-Latino children. A secondary objective is to investigate the acceptability of the environmental dietary intervention strategies and tools among families and patients. This short-term feasibility project will refine the study methods and data collection tools to effectively plan and perform a randomized controlled trial (RCT).

Methods

Design

This will be a single-arm feasibility study, named "Sediento por una Sonrisa" ("Thirsty for a Smile"). Using a mixed methods approach, we will evaluate the feasibility of the intervention and procedures intended for use in a phase II RCT. Children will be clinically examined at baseline and at a follow-up visit, and caregivers will answer a questionnaire and dietary intake interview.

Ethics and Confidentiality

The Institutional Review Board (IRB) of the University of Washington (UW) will serve as the IRB of oversight for this study. The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

A consent form describing the detailed study procedures and risks will be given to the potential participant. The investigator or designee will explain the research study to the potential participant and answer any questions that may arise. Study staff conducting the consent process will be bilingual (English and Spanish) to accommodate non-English speakers. All study forms and materials will be available in Spanish and English. Participants will elect their preferred language for all communications. The consent process will be documented in the clinical or research record.

Study participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover any study information relating to subjects. The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in the US Code of Federal Regulations Title 45: Public Welfare, part 46 and/or the International Council for Harmonisation's Guidelines for Good Clinical Practice E6.

This project does not meet the National Institutes of Health (NIH) definition of a clinical trial as it will not study the cause-and-effect relationship between an intervention and a

health outcome. Therefore, this study will not be registered in a public trials registry such as ClinicalTrials.gov.

Participants and Setting

Inclusion criteria for parents/caregivers and child dyads for enrollment include providing a signed and dated consent form, willingness to comply with all study procedures, availability for the duration of the study, a child aged 2 to less than 9 years, a diagnosis of S-ECC, previous treatment for ECC under general anesthesia, and a child in good general health based on parent self-report. The study clinical site treats approximately 700 pediatric patients with ECC per year; approximately 500 of these patients would be eligible to participate in the study with a goal of enrolling 21 participants. Exclusion criteria for parents/caregivers and child dyads include a parent/caregiver under 18 years of age or a child with American Society of Anesthesiologists Physical Status IV or higher.

Caregivers will be recruited by the onsite research coordinator during the initial examination visit at the dental clinical site once the child is determined to have S-ECC and to meet the other eligibility requirements. A promotional pamphlet or flyer will be distributed to caregivers of children scheduled to undergo surgical treatment for S-ECC by the research coordinator.

Study Intervention

Overview and Aims

The conceptual model of the study proposes that families have a high degree of control over children's environments, with parents being the most influential in the selection of diet [37] and the development of eating and drinking behaviors [38,39]. Family practices associated with beverage choices include the availability and accessibility of water and SSBs in the home environment [40-43], and role-modeling beverage choices [41,44-47] and habits such as drinking water between meals [48]. Lack of knowledge, beliefs, and skills such as self-efficacy, action planning, and motivation, along with social norms, support, and environmental opportunities are intra- and interpersonal barriers for healthy drinking and eating [49-51], which can in turn increase the risk of dental caries [52] and obesity [53,54] (Figure 1).

Figure 1. Conceptual framework using the Capabilities, Opportunities and Motivation-Behavior (COM-B) and Theoretical Domains frameworks. SSB: sugar-sweetened beverage.
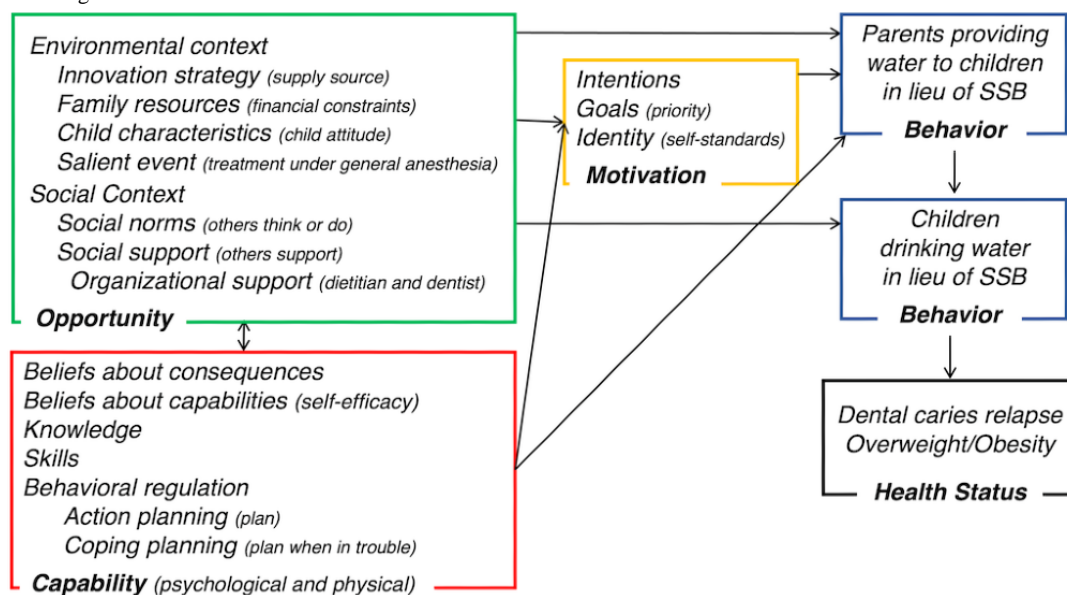
The intervention aims to provide parents with physical and social opportunities, motivation, and physical and psychological capabilities (knowledge and skills) to modify three key domains within the home environment. The first domain is the availability and accessibility of water: the intervention encourages parents to ensure that water is available and accessible in the home, and that it is prepared, presented, or maintained in a ready-to-use form that encourages consumption. The second is supportive family eating routines: the intervention will seek to improve parent knowledge and facilitate the acquisition of skills to support the children to drink water and milk at meals and water at all other times, establish and enforce family rules about drinking, and develop boundaries regarding when and how SSBs are offered to the children. The third domain involves parental role-modeling of water consumption: parents will be encouraged to increase the number of servings of water that they consume in front of their children and to express supportive attitudes toward the consumption of water to their children, such as by making positive and encouraging comments. The two components of the intervention are: (1) a dietary-environmental change, which involves home delivery of child-friendly bottles of fluoridated water to replace SSB choices; and (2) a behavioral counseling intervention intended to increase parents' knowledge of the adverse effects of SSB consumption on young children's oral health, along with the strategies and skills needed to reduce SSB consumption.

Product Description

The product is fluoridated water packaged in child-friendly, brightly colored, animal-shaped plastic bottles with resealable spouts. The product will be obtained from a specialty drink manufacturer in Mukilteo, Washington. Specifically, the water will be packaged in individually sealed 8-ounce food-grade plastic containers, and the boxes will be labeled with the study

name, contents, and information about how to contact the investigators. Bottles will be shipped by a commercial carrier from the manufacturer to the clinical site storage and then delivered to the enrolled subjects. Included are instructions to consume up to 3 bottles per day as the water contains approximately 0.7 parts per million fluoride.

Behavioral Intervention: In-Person Counseling

The behavioral component will provide a combination of in-person and telephone counseling by trained dietitians to help parents overcome barriers to decreasing their children's consumption of SSBs and increasing their consumption of water. By involving parents and children, the intervention has the potential to establish new family norms for beverage consumption.

The first in-person session will be approximately 30-45 minutes in duration. Following the first in-person session, parents will receive four telephone check-in visits. The calls will be weekly for 3 weeks after the first in-person visit and a fourth call will occur at the middle of the second month. Telephone interventions have become increasingly popular for health education and behavior change counseling, as they are convenient and cost-effective [55]. There will be one final in-person session of approximately 20 minutes duration at the final visit at 2 months. Sample scripts for the three types of counseling sessions will be provided to the dietitians.

Procedures for Training Interventionists and Monitoring Intervention Fidelity

Training of the dietitians delivering the counseling intervention occurs in person and will follow a manual written for this study. Interventionists will be trained to defined performance criteria and be "certified." During the training, interventionists will be asked to undertake role-playing exercises, which will be scored according to preestablished checklists of the essential elements necessary in each type of counseling session (eg, assessing motivation, goal-setting, and anticipating challenges). After the role-playing exercises, interventionists will evaluate their own performance and identify, along with the trainer and other participants, aspects that would benefit from additional practice or improvement. This additional work will be completed during the training days or by phone immediately following the training.

Fidelity monitoring will be guided by recommendations of the Treatment Fidelity Workgroup of the NIH Behavior Change Consortium [56]. To assess fidelity, we will audio-record approximately 25% of each type of session (first and final in-person visits, telephone check-ins) delivered by each interventionist and provide individualized feedback. The trainer will listen to the audio recordings and evaluate fidelity using the training checklists designed for each type of counseling session. Intervention fidelity ensures that the intervention was conducted as planned (ie, follows the study protocol).

The onsite research coordinator will oversee the activities of the clinical site and will report to the project principal investigators. Staff training for the research coordinator, clinic dietitians, and dental hygienists will occur onsite at the clinical site. Although the training varies depending on the staff

member's role in the project, at minimum, all staff will be trained in the topics of Human Subject Protection, Good Clinical Practice (GCP), and protocol training.

Procedures

Study Schedule

Screening, Recruitment, and Enrollment

Caregivers will be recruited during the initial examination visit at the dental clinic once the child is determined to meet eligibility requirements. The dental provider will introduce the study and a study coordinator will continue the recruitment and consent processes.

The process will include reviewing the written consent form with the potential participant; the study staff signs the consent form acknowledging that informed consent was reviewed and the caregiver signs acknowledging that consent was obtained. We will also obtain demographic and contact information as well as the record time for recruitment and consent.

Baseline and Final Visit

The examiner will conduct a dental caries exam, and measurements of height, weight, and waist circumference (anthropometrics) will be obtained from the child and their primary parent/caregiver. Time for each data collection element will be recorded. Caregiver/parent participants will complete the Child Oral Health Questionnaire where time to completion will be recorded. The caregiver/parent participants will then participate in an in-person counseling session with the clinic dietitian where time will be recorded.

Phone interviews will be conducted with caregiver/parent participants at baseline and at the final visit at 2 months to collect 24-hour dietary recall data. Interviews will last approximately 45 minutes and the time will be recorded.

Intermediate Phone Call Follow-ups

The clinic dietitian will call participants weekly for the first month and then once at the middle of the second month to check in about behavior change progress and address any questions or concerns regarding the topics covered during the in-person counseling sessions. The amount of time per check-in call will be recorded and the number of attempted phone calls will be tracked.

Data Collection

Data for this study will include: (1) dental examination data, (2) height and weight measurements, (3) study questionnaires to assess oral health–related quality of life and dietary behavior, and (4) dental claims data. Dental hygienists will be trained to collect the dental caries measurements using the International Caries Detection and Assessment System. Data for this study are captured using examinations, standardized forms, and questionnaires. The investigators will maintain adequate case histories of study subjects, including accurate case report forms and source documentation.

Data will be entered directly into the Research Electronic Data Capture (REDCap) system, including the results of the physical examinations, questionnaires, and intervention counseling notes;

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time and staff conducting the activities; and reasons for unsuccessful attempts and actions to overcome barriers.

Paper forms will be securely stored in a locked file cabinet when they are not in use. Completed paper forms will be transferred between sites via courier or another secure document service. Dietary recall data will be entered directly into the secure web-based system and data will be securely transferred to UW. Dental claims data will be securely transferred to UW.

Assessment of Safety

Safety parameters for this study include monitoring unanticipated problems, adverse events, serious adverse events, and time and frequency for event assessment and follow-up.

Incidents or events that meet the US Office for Human Research Protections (OHRP) criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline: unanticipated problems that are serious adverse events will be reported to the UW IRB and to the sponsor within 1 week of the investigator becoming aware of the event; any other unanticipated problem will be reported to the UW IRB and to the sponsor within 2 weeks of the investigator becoming aware of the problem. All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the OHRP within 1 month of the IRB's receipt of the report of the problem from the investigator. All unanticipated problems will be reported to the sponsor's centralized reporting system.

Quality Control

A sample of study staff telephone contacts (reminder calls for study and follow-up appointments) and of each type of the 3 counseling sessions (first in-person, last in-person, and telephone check-ins) will be audio-recorded in digital media and reviewed (approximately 25% of the study staff–caregiver intervention interactions). The study investigator will then review the telephone contacts to ensure fidelity of the calls and accuracy of data recording. The staff will be provided with feedback on their performance and conduct, including but not limited to these specific areas: adherence to the telephone script, adherence to the protocol/manual of procedures, and adherence to GCP. Clinic staff with a telephone contact indicative of less than acceptable quality will receive a private training session focused on problematic areas. The dietitians will have their audio recordings reviewed by a behavioral psychologist and will be provided with feedback.

Measures

Primary Objectives

To assess feasibility of the intervention, we will determine if study procedures and processes can be executed and the resources and time necessary for execution. We will track how much and what type of support are needed to deliver the intervention, such as home delivery of water bottles, and how much staff time and resources it took to implement the study. To assess execution of study procedures and processes, we will

collect the following information (goals in parentheses): the participation rate among eligible caregivers and children (≥50%), the follow-up rate at the end of the 2-month study period (≥90%), the number of water bottles delivered and on time (≥90%), compliance with the recommended water consumption based on the delivered water bottles, the number of completed behavioral intervention sessions (100% at baseline, ≥90% for weekly sessions, and ≥90% at the final follow-up), reasons for noncompletion of intervention sessions, intervention fidelity, the number of completed dietary recall assessments at baseline (100%) and at the final follow-up (≥90%), and the number of dental and physical exams completed at baseline (100%) and final follow-up (≥90%).

Secondary Objectives

We will assess the acceptability, appropriateness, and perceived feasibility for each of the intervention components and health assessments, and the willingness to participate in a longer trial (1-year intervention plus 1 additional year of follow-up) (≥80%).

The questions to assess the intervention components were developed by the investigators and participants will be asked to rate each component on a scale from 1 to 10. Acceptability of survey completion will be assessed using questions adapted from Wolpin et al [57], which have been used to assess acceptability of an electronic self-report program for cancer patients. The six Likert-scale items, measured from 1 ("not at all") to 5 ("very much"), ask about ease of use, satisfaction, helpfulness, and completion time.

Statistical Considerations

Power

The sample size is primarily based on what is feasible within the constraints of the funding mechanism with respect to cost and length of the grant period. The proposed sample size is 21 caregivers and children, which will provide estimates with sufficient precision for sample size determination for the secondary outcomes in the trial. Estimates for quantitative outcomes will have a precision of ±0.30 SD and estimates for subjective outcomes will have a precision of ±10%, based on an 80% CI. Estimates for the primary outcome (caries relapse after 2 years) will be obtained from other sources.

Statistical Analysis

The data analysis will be descriptive, using frequency and percent for categorical measures and mean (SD and range) for quantitative outcomes. No a priori hypotheses will be tested. The 80% CIs will be computed to describe the precision of the estimates for both aims and to guide sample size determination for the larger study.

The qualitative analysis will be based on data from a focus group comprised of caregivers of child participants involved in the study and interviews as needed for those who cannot attend the focus group. The interviews will be conducted and recorded in Spanish, transcribed, and translated into English and checked for accuracy. Coding will be completed by two researchers, first individually and then they will meet to discuss and agree upon codes. Researchers will utilize an inductive process to thematically analyze codes.

Results

Funding has been obtained from the National Institute of Dental and Craniofacial Research (NIDCR) and the UW IRB has approved the study. The feasibility study was conducted from March until November 2019. Data analysis is currently underway and the results are expected to be published by the end of 2022.

Discussion

Hypothesis and Significance

We hypothesize that a combined dietary environmental and counseling intervention—home delivery of bottled water and parental counseling regarding water consumption—will lengthen the time to onset of new dental caries relative to the current standard of care for pediatric patients with S-ECC. The intervention to be evaluated in this study is family-focused [58] and introduces new familial norms by making changes in the home environment (more attractive water choices, fewer SSBs, and parental role-modeling of a preference for water over SSBs). It is expected to strengthen caregiver self-efficacy for implementing change in the child's diet. Parents assume a leadership role in implementing the intervention and in negotiating buy-in from other adults and older children present in the home.

The main behavioral change techniques used will be physical environmental restructuring by adding an object to the environment (water bottles with fluoridated water delivered twice a month to the home environment for 2 months). Water bottles are being used because they are acceptable to the families and because many of the potential participating families—who have immigrated to the United States—distrust tap water safety [59-61].

The physical environmental restructuring will be supported by providing a service (behavioral counseling) to restructure the social environment of the child using self-regulatory techniques. Behavioral counseling to caregivers about healthy drinking for their children will change parental skills and self-efficacy on the child's healthy drinking. Consumer Information Processing Theory [62] posits that health information must be wanted, understood, and presented at a time the patient is most receptive. Thus, we will initiate the behavioral counseling at the child's first recall visit to the dental clinic following surgery, typically 14-21 days postdischarge, when parents and children are no longer preoccupied by the upcoming surgery but are in an early stage in their transition to reestablish home routines.

The in-person and telephone check-in sessions consist of motivational techniques [63] to increase the parents' self-efficacy [64] about their ability to increase their child's water drinking and decrease their SSB consumption. These sessions include volitional techniques to facilitate realistic goal-setting [65] and to translate intentions into routine practices (eg, action and plans) [66]. Throughout, parents are encouraged in "cope planning," to identify factors that support or hamper behavior change, and make plans to bring about the supportive factors and overcome the barriers [66]. The final in-person session focuses on plans to maintain behavior changes in the absence of the home water delivery and a discussion of relapse prevention.

Limitations

The sample size is relatively small and the length of time for the intervention is only 2 months. As noted, this is a feasibility study and larger studies will be needed to provide adequate power and assess the effectiveness of the intervention in decreasing S-ECC. Participation may be hindered by the nature of human behavior and the time constraints of families with multiple children with competing needs. Because our focus here is on ECC, we have a limited age range; however, children older than 8 years may also benefit from this dietary-environmental intervention. The feasibility and acceptance outcomes may not be generalizable and may be specific to the community and setting. However, the feasibility study will allow the investigators and the clinical site staff to test recruitment and retainment of participants, intervention delivery, and outcome assessments at the clinical site.

Conclusions

Expected outcomes of this study will provide a basis for a successful RCT. Results of this project will produce an intervention suited to the environment and people who will use it, and will indicate challenges and opportunities for refinement of the intervention and study procedures, including how much and what type of support are needed, and how much staff time and resources it will take to implement the study.

Authors' Contributions

All authors contributed to the concept and design of the study. JCC, LM, and MLR drafted the manuscript and all authors critically reviewed it. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
National Institute of Dental and Craniofacial Research (NIDCR) Peer Review Report.
[PDF File (Adobe PDF File), 150 KB - resprot_v11i4e37200_app1.pdf]

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Abbreviations

ECC: early childhood caries
GCP: Good Clinical Practice
IRB: Institutional Review Board
NIDCR: National Institute of Dental and Craniofacial Research
NIH: National Institutes of Health
OHRP: Office for Human Research Protections
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
S-ECC: severe early childhood caries
SES: socioeconomic status
SSB: sugar-sweetened beverage
UW: University of Washington

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Investigating Why and How Young Adults Use Protective Behavioral Strategies for Alcohol and Marijuana Use: Protocol for Developing a Randomized Controlled Trial

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Abstract

Background: Young adulthood is associated with increased alcohol and marijuana use compared with other developmental periods. Alcohol and marijuana use place individuals at high risk for acute and long-term negative consequences. Despite the relatively large cross-sectional and longitudinal literature on protective behavioral strategies (PBS; behaviors that individuals can use to limit consequences and reduce substance use), little is known about why young adults choose to use PBS on specific occasions or why they might use PBS differently across occasions (ie, quality and consistency). There is significant room for improvement in the conceptualization, application, and understanding of PBS.

Objective: This study aims to develop a novel, brief web-based and SMS text messaging intervention, with input from young adults who use alcohol and marijuana, which addresses the extent to which motivations for PBS use and nonuse (marijuana or alcohol) and the quality of PBS use (the degree of effectiveness or degree of implementation) differ when using alcohol alone versus concurrently or simultaneously with marijuana.

Methods: This research will be conducted in 2 phases. Phase 1 will involve web-based focus groups (N=100) and cognitive interviews (N=10) to determine why young adults (aged 18-24 years) use or do not use specific PBS related to alcohol and marijuana use and elicit feedback on how motivations and the quality of PBS could be incorporated into a web-based and SMS text messaging PBS intervention as well as elicit feedback on developed intervention material. In phase 2, young adults (N=200; aged 18-24 years), who typically use alcohol and marijuana for at least 2 days per week, will be randomized to either the intervention or waitlist control group. The intervention will be brief, web-based, focusing on self-selected alcohol and marijuana PBS messages and motives for using alcohol- and marijuana-related PBS, and including intervention content delivered via SMS text messages 3 days a week (random day, Friday, and Saturday) over 8 consecutive weeks. All participants will report on PBS use, motivations for PBS use (and nonuse), quality of PBS use, and alcohol and marijuana use in morning surveys timed to occur the day after the intervention SMS text messages for those in the intervention group.

Results: Recruitment and enrollment for phase 1 began in January 2022. Recruitment for phase 2 is anticipated to begin in January 2023. Upon completion of the phase 2 pilot, we will examine the feasibility, acceptability, and preliminary effect sizes of the newly developed brief web-based and SMS text messaging intervention.

Conclusions: This study will provide an in-depth understanding of young adults' PBS use and has the potential to develop a more efficacious intervention for co-occurring or simultaneous alcohol and marijuana behaviors.

Trial Registration: ClinicalTrials.gov NCT04978129; https://clinicaltrials.gov/ct2/show/NCT04978129

International Registered Report Identifier (IRRID): DERR1-10.2196/37106

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Introduction

Background

Young adulthood is associated with increased alcohol use compared with other developmental periods. Recent national US estimates show that 62.6% of young adults have consumed alcohol in the year before the data collection [1]. Acute alcohol-related negative consequences, including academic or occupational impairment, blackouts, injury, and death, occur in academic, interpersonal, social, and health domains [2-4]. Moreover, an estimated 29.2% of persons aged 18 to 29 years with past-year alcohol use have an alcohol use disorder [5]. Although a meta-analysis of 6 national surveys indicated that there had not been a significant increase in alcohol consumption among persons aged 18 to 29 years over the past decade [6], young adult alcohol use continues to be a public health concern in the United States because of the risk of acute and long-term negative consequences. The development of more efficacious interventions to reduce the proportion of young adults who engage in excessive alcohol use and experience negative consequences is a key priority of the National Institute on Alcohol Abuse and Alcoholism.

Unlike alcohol use, young adult marijuana use has increased in the past decade [1], whereas the perceived risk of regular marijuana use among adolescents and young adults continues to decrease [1,7]. Among young adults in the United States, the lifetime rate of marijuana use is 60.1%, with rates of past 30-day use at 24.1% and daily use at 8% [1]. Frequent and long-term marijuana use is linked to acute consequences, including decreased cognitive functioning [8], as well as longer-term consequences, including discontinuous college enrollment and unemployment [9,10].

Risks of Concurrent and Simultaneous Alcohol and Marijuana Use

Most people who use both alcohol and marijuana do so simultaneously [11,12]. Simultaneous alcohol and marijuana (SAM) use is defined as using alcohol and marijuana at the same time so that their effects overlap. Concurrent alcohol and marijuana (CAM) use is often defined in the literature by individuals retrospectively reporting both alcohol and marijuana use within the same period (eg, past month and past year), without reference to experiencing overlapping effects. Almost one-quarter of adolescents and young adults who report alcohol or marijuana use also report SAM use when asked about the past year or the last party attended [13,14]. SAM use, compared with marijuana use alone or CAM use, is associated with an increased risk of consequences [13,15-20]. In this study, all participants will be young adults who use alcohol and marijuana. Given our focus on substance use behavior across days, we will use a more precise definition of CAM use, such that CAM use occurs when individuals report the use of both alcohol and marijuana on the same day but not so that their effects overlap. It is increasingly important that interventions focus on both alcohol and marijuana use and evaluate whether they are effective at reducing CAM and SAM use.

Protective Behavioral Strategies

Alcohol Protective Behavioral Strategies

A way of preventing or reducing risk is promoting the use of protective behavioral strategies (PBS), which are behaviors that individuals can use to limit negative consequences and reduce alcohol use [21]. Several types of alcohol PBS have often been examined; three common types include (1) limiting or stopping drinking (eg, stopping drinking at a predetermined time), (2) manner of drinking (eg, drinking slowly rather than gulp or chug), and (3) serious harm reduction (eg, using a designated driver) [22]. Cross-sectional and longitudinal research demonstrate global associations between PBS and drinking behavior, such that greater overall use of PBS are negatively associated with the quantity and frequency of drinking and its consequences [23,24]. Emerging event-level research, such as our work, has demonstrated that the use of PBS varies across days, similar to the type of PBS used [23,25-29]. Specifically, although the manner of drinking PBS are negatively associated with alcohol use on a given day, event-level research shows that limiting or stopping PBS and the serious harm reduction of PBS are associated with more drinking on a given day. These findings for limiting or stopping PBS and serious harm reduction PBS contrast with research showing a negative global association, where individuals who tend to use more PBS also tend to report less alcohol use overall.

Marijuana PBS

As research on marijuana continues to address changing routes of administration, increasing concentration or potency (eg, tetrahydrocannabinol levels), and emerging products, research also acknowledges the challenges with reducing risks associated with marijuana use. Certainly, harm reduction approaches acknowledge that any steps toward reduced risk are steps in the right direction; however, although there are clear guidelines for *low-risk* drinking (eg, provided by the National Institute on Alcohol Abuse and Alcoholism), the same cannot be said of marijuana use. Very little research has been conducted on marijuana PBS. This developing area of research shows that the cross-sectional and longitudinal findings for marijuana PBS (eg, avoiding mixing marijuana with other drugs, avoiding high-frequency use, and using marijuana only among trusted peers) [30,31] are similar to those for alcohol [31-36]. Bravo et al [37] demonstrated that both alcohol and marijuana PBS help explain the association between known risk factors (ie, sex, age at substance use onset, substance use motives, and impulsivity-like traits) and associated consequences among those who report CAM use (used alcohol and marijuana for at least 1 day in the past month). Prince et al [36] examined PBS interventions to reduce young adult marijuana use and found that, regardless of intervention conditions, greater daily PBS use was associated with lower quantities of marijuana use that day, such that using PBS in a given episode was associated with lower marijuana use (ie, approximately half of a standard joint

less of marijuana or 0.25 g) compared with episodes when no PBS were used. As this study asked whether PBS were used for each event rather than asking about specific PBS, it was not possible to determine if certain PBS were associated with less use or consequences. Pearson et al [38] found that a marijuana PBS total score was associated with fewer marijuana sessions and a lower subjective high in participants from a daily diary study among college students. Overall, our findings suggest that marijuana PBS use at the daily level needs to be further defined and examined so that marijuana PBS can be effectively targeted in interventions. As the literature is limited, there is significant room for improvement in the conceptualization, application, and understanding of marijuana PBS. This research has the potential to add significantly to the literature as it will allow a fine-grained examination of the efficacy of marijuana PBS on alcohol use, marijuana use, and CAM or SAM use.

Event-Level Associations

Research has yet to examine how alcohol and marijuana PBS use on a given day relate to an individual's use of alcohol or marijuana alone in comparison with CAM or SAM use days. Knowledge in this area is necessary to inform PBS interventions or interventions with a PBS component, aiming to reduce alcohol and marijuana use. Given the concerning CAM and SAM use rates among young adults in the United States, alcohol interventions need to focus on marijuana use and examine whether these interventions can reduce CAM and SAM use, alcohol and marijuana use, and related consequences, as well as increase alcohol and marijuana PBS use. Specifically, an important research question that this study will answer is the extent to which the use of PBS (marijuana or alcohol) or the quality of PBS use differs if using alcohol alone versus concurrently or simultaneously with marijuana and how motivations to use or not use PBS affect these associations. Moreover, little is known regarding how alcohol or marijuana PBS differs on CAM or SAM use days compared with alcohol-only days. Thus, this study will collect event-level data to determine which alcohol or marijuana PBS are effective at reducing use and consequences when CAM or SAM use occurs compared with alcohol use alone.

Motivations for Use and Nonuse of PBS (Why Use PBS)

Event-level research that shows differences in PBS use across days suggests that young adults' motivations for using certain types of PBS may also differ across days [26-29,39]. However, motivations to use PBS for alcohol or marijuana across days have yet to be examined. For example, if a young adult wants to drink heavily but does not experience negative consequences, the individual might use fewer (if any) limiting or stopping PBS and use more serious harm reduction PBS. Very little is currently known about why young adults may or may not use various PBS when consuming alcohol. Given that many brief alcohol interventions for young adults introduce PBS [40], it is important to understand *why* (eliciting personally relevant reasons to make a change and decide to use PBS) young adults may elect to use or not use PBS on specific occasions or use it with more quality (ie, better implementation) across days. There are many reasons why an individual may not use any PBS or a specific PBS (eg, unaware of strategy, embarrassed, do not want to use strategy

as they want to drink more and drink longer), and understanding why and when certain strategies are preferred or disregarded could lead to critical refinements for the manner in which PBS are incorporated into alcohol interventions. For example, if an individual is not motivated to use any PBS, the common protocol of increasing the awareness of strategies and providing skills training regarding how to implement PBS may be insufficient to encourage or enable the individual to use PBS [41,42]. Furthermore, it is important to understand the motivations behind *not* using PBS, as these motivations may be barriers to change (ie, implementing PBS and reducing consequences). Research shows that friends can influence PBS use [27], such that greater friends' use of serious harm reduction PBS was associated with greater serious harm reduction PBS use by the participants. Friends' use of limiting or stopping and manner of drinking strategies were not associated with participants' drinking habits, consequences, or PBS. It may be that friends have high a use of or encourage the use of serious harm reduction strategies as a means of drinking more heavily, which suggests that friends' PBS use may be a barrier to using serious harm reduction PBS to reduce one's own use or consequences.

Recent research by Bravo et al [43] identified themes for reasons of using PBS (prevention of specific alcohol-related consequences and general safety) and themes for reasons of not using PBS (goal conflict, ineffectiveness, difficulty of implementation, and negative peer or social repercussions). The limitations of this research are that it focused on reasons for use and nonuse of PBS overall rather than for each specific strategy, and participants responded to survey items rather than being involved in focus groups or cognitive interviews, which allowed for a more in-depth examination of motivations, especially at this early stage of creating a foundational scientific knowledge base. The study by Bravo et al [43] also did not examine potential gender differences in PBS use and nonuse. Despite these limitations, the findings suggest that greater specificity is needed regarding why and when PBS are or are not used, so that intervention content can be tailored to include motivations for choosing to use or not use PBS, which has the potential to improve PBS-based interventions. Given that research based on the Health Belief Model has shown that real or perceived barriers prevent individuals from engaging in health-protective behaviors [44-46], it is important to better understand the motivations behind the nonuse of PBS. Interventions may need to focus on reducing perceived barriers or reasons for nonuse of PBS so that young adults can become more aware of how and when they can effectively implement these strategies. Thus, this research will inform our understanding of why PBS use among young adults is low by examining reasons for not using PBS, as well as barriers to implementing PBS, which can ultimately inform refinements to intervention content.

Regarding marijuana-related PBS, Prince et al [35] conducted focus groups with a community sample of young adults and found themes surrounding the reasons for regulating marijuana use (eg, health or legal problems and interpersonal), as well as strategies to moderate marijuana use or reduce the risk of consequences (eg, distraction and existential or spiritual strategies). There is even less literature examining the reasons for use and nonuse of marijuana PBS compared with alcohol

PBS, thus highlighting the pressing need for additional research to inform how to best incorporate marijuana PBS into interventions. Research, such as the work described herein, is needed to determine when and why young adults may or may not decide to use strategies to reduce harm when using either alcohol and marijuana alone as well as PBS on days with CAM or SAM use. Thus, this research will allow for potentially more effective interventions and, ultimately, a greater public health impact by incorporating the reasons *why* PBS might be used rather than only listing options for *how* to use PBS.

Quality of PBS Use

In addition to the need to examine the reasons for PBS use or nonuse, there is a need to determine how well (ie, the quality with which) young adults implement PBS. For example, 2 young adults may indicate that they both watch their drinks to avoid harm; 1 carries their drink and keeps it with them at all times, and the other periodically looks at their drink on a table in a crowded room. Furthermore, it may be true that the same person engages in PBS with different qualities on different days (eg, on Friday, a person watches their drink while hanging out with a few close friends at dinner in a restaurant, and the same individual on Saturday watches their drink more sporadically while with a larger group of friends in a bar). These examples relate to the quality of alcohol in PBS and can be extended to marijuana PBS. Thus, the quality of implementing both alcohol and marijuana PBS likely varies across individuals and across occasions. The manner in which PBS are currently included in brief interventions (ie, skills training) does not address the varying quality with which PBS may be implemented, which likely results in differing levels of PBS effectiveness. Furthermore, many feedback-based interventions present the number of PBS used by the participant (ie, quantity) with nothing about the actual impact, usefulness, consistency, or effectiveness (ie, quality of implementation). Specifically, it is possible that someone may report using a certain PBS in a manner that is not actually protective against risk (ie, poor-quality PBS use). Therefore, it is important to elucidate the ways in which people use PBS, as well as the extent to which the manner of use is effective and protective, which can then inform brief interventions.

Gender Differences in PBS Use

Research is beginning to investigate the motivations for PBS use; however, research has yet to examine the possibility that the motivations and the quality of PBS use may differ by gender (eg, male, female, or nonbinary). For example, female college students may opt to bring their own alcohol to parties (eg, bring your own bottle) to know what is in their drink. However, research suggests that bringing alcohol to parties does not prevent sexual victimization in college [47]. Gender differences such as this are important as interventions may need to highlight or discuss varying motivations for alcohol and marijuana PBS use. Moreover, these findings demonstrate the need to evaluate gender-specific motivations for PBS use across a range of risk behaviors, as alcohol or marijuana PBS could be used to avoid consequences not directly related to substance use.

Current Intervention Approaches

PBS are often incorporated into multicomponent brief interventions [48,49] or SMS text message interventions [50,51] in the form of skills training for reducing both alcohol and marijuana use. The PBS are consistent with the harm reduction model, with the idea that any steps toward reduced risk are steps in the right direction [52,53]. Many personalized feedback interventions (PFIs) aim to identify a *hook*, or personally relevant reason to change, by using motivational interviewing principles and strategies that support building young adults' motivation to change their drinking or marijuana use behavior. Brief interventions that use motivational interviewing emphasize the importance of meeting people where they are in terms of their readiness to change and suggest that if personally relevant reasons for change can be elicited, contemplation of change or commitment to change can result. Interventions that target PBS provide *action stage* suggestions; however, if people are in precontemplation, contemplation, or preparation, there is a disconnect between these action stage suggestions and where they might actually be in terms of their readiness to change their substance use or even their PBS use. Furthermore, the PBS component of PFIs generally occurs at the end of the intervention or when of interest to the participant so that moderation tips and strategies (typically *action stage* strategies) can be provided after reviewing the intervention content (eg, norm comparisons or goals) that is likely to prompt the contemplation of change and increase the individual's motivation to reduce harm.

Collectively, most intervention components focus on *why* to change alcohol or marijuana use, whereas the PBS component focuses on *how* to change substance use. The investigation of what might be gained by avoiding, restricting, or limiting CAM or SAM use, in particular, has the potential to highlight any unique motivations for concerns or challenges associated with *why* someone would want to make changes in PBS use or CAM or SAM use. For interventions to be the most efficacious, content that can adequately result in the contemplation of change (ie, *why* changes might occur) is necessary to set the stage for PBS implementation (ie, *how* to make those changes). Prevention efforts have the potential to improve if the *why* is also a focus for PBS (why use certain PBS over other PBS in a given context), as examined in this project. By examining how interventions can better elicit personally relevant reasons to make a change in one's behavior and engage in quality PBS use for alcohol or marijuana use, we have the potential to optimize current intervention approaches.

Despite theoretical support for the inclusion of PBS content in PFIs (65% of interventions do so) [54], findings have been inconclusive regarding whether PBS use mediates college student alcohol intervention efficacy, with only some studies showing evidence supporting mediation [40] and others showing support for only certain types of individuals. For example, Riggs et al [49] found that a web-based PFI, which included marijuana PBS, reduced marijuana use among a sample of college students who used it heavily. However, PBS use increased only among women who received PFI. The study described here has great potential to increase the efficacy of an important component of PFIs, as PBS skill training is one of the few components that

reflect strategies for reducing use or consequences. Prince et al [36] examined an app used to collect event-level reports on marijuana use and PBS and found that event-level reductions in marijuana use were associated with greater PBS use. As this study used a single PBS item to assess the occurrence of any PBS use, it was not able to determine whether certain types of PBS were associated with less use or consequences. Thus, an essential step in determining the usefulness of alcohol and marijuana PBS on alcohol, marijuana, and CAM or SAM use is to conduct a rigorous pilot study of a PBS-focused intervention.

Methods

Study Design

This study will use an iterative process of focus groups and cognitive interviews (phase 1) to develop a novel web-based SMS text messaging intervention to be evaluated in a pilot randomized clinical trial (phase 2) to evaluate feasibility, acceptability, and preliminary effect sizes. In both phases, young adults from Texas, United States, aged 18 to 24 years, who typically use alcohol and marijuana at least twice per week, will be recruited.

Ethics Approval

This study was reviewed and approved by the North Texas Regional Institutional Review Board (1679036-1). All study procedures were approved by the single institutional review board of record. All participants will sign an approved consent form in accordance with the ethical standards of Helsinki.

Focus Groups and Cognitive Interviews (Phase 1)

Phase 1 will focus on examining motivations for alcohol and marijuana PBS use (and nonuse of PBS), as well as the quality of PBS use among young adults (aged 18-24 years) who use both alcohol and marijuana. We will conduct web-based focus groups (10 groups; N=10 per group) and cognitive interviews (N=10) to determine why young adults use or do not use specific PBS related to alcohol and marijuana use. Focus groups and cognitive interviews will discuss the level of the quality in which PBS are used and the various contexts in which PBS may or may not be used. All discussions will consider the use of either of the substances alone on a given day, as well as SAM or CAM use on a given day, and will address ways in which the motivations and quality of PBS could be incorporated into a web-based and SMS text messaging PBS intervention, as well as elicit feedback on drafted intervention material. The results of phase 1 will inform the development and delivery of the intervention to be tested in a pilot study (phase 2).

Pilot Study (Phase 2)

Overview

In phase 2, we will conduct a pilot study—informed from phase 1 findings—of web-based, and SMS text messaging intervention with young adults (N=200; aged 18-24 years), who typically use alcohol and marijuana for at least 2 days per week to determine the feasibility, acceptability, and preliminary effect sizes. Participants will be randomized to either the intervention or waitlist control group. All participants will complete screening, baseline and daily morning surveys, and a 2-month follow-up. Participants in the intervention condition will receive a brief, web-based intervention focusing on self-selected alcohol and marijuana PBS messages and motives for using alcohol- and marijuana-related PBS. The intervention content will also be delivered via SMS text messages 3 days a week (random day, Friday, and Saturday) for 8 consecutive weeks. Participants in both conditions will report on PBS use, motivations for PBS use (and nonuse), quality of PBS use, and alcohol and marijuana use in morning surveys timed to occur the day after the intervention SMS text messages for those in the intervention group (morning after random day, Saturday, and Sunday).

The hypotheses for the phase 2 pilot randomized controlled trial are detailed in the following sections.

Hypothesis 1

We hypothesize that the intervention will be feasible (achieving the recruitment goal and doing so within an acceptable time frame; high study retention) and acceptable (enrolling a high proportion of eligible participants; obtaining favorable participants' ratings of intervention components and ratings of accessibility, usability, convenience, and relevance, as measured after the web-based intervention and after SMS text message assessments).

Hypothesis 2

We expect that receiving the intervention will be associated with short-term (2-month) increases in PBS use, motivations for PBS use, and quality of PBS use, as well as decreases in motivations for PBS nonuse and reductions in past 2-month alcohol use, CAM and SAM use, and related consequences.

Hypothesis 3

Using event-level data, we expect that on days when individuals' motivations to use PBS are elevated (ie, higher than their average level) or the quality of their PBS use is elevated (ie, higher than their average level), they will report lower alcohol use, be less likely to report CAM or SAM use, and report fewer negative consequences. These effects will be stronger in the intervention group than in the waitlist control group.

Hypothesis 4

Using event-level data, we will examine whether days when young adults use alcohol alone, compared with both CAM and SAM use days, are associated with greater use of alcohol PBS, greater motivation to use alcohol PBS, and higher quality of alcohol PBS use. Similarly, we will examine event-level associations between PBS use and consequences (alcohol and marijuana use) to determine whether PBS are as effective at reducing consequences when CAM or SAM use occurs.

General Recruitment

For both phases, we will use a multimethod approach to reach a wide cross-section of young adults (aged 18-24 years) living in Texas, United States, who use alcohol and marijuana, such as in-person recruitment, flyers in businesses and community centers, web-based and newspaper advertisements, bus advertisements, and social media. Social media outreach will comprise a web-based Facebook fan page, which will provide

a brief description of the study and links to the study website. We will use a combination of paid Facebook, Twitter, and Instagram advertisements and promote boosts on our study page to increase our web-based presence. Social media will be our main recruitment strategy; however, other strategies such as newspaper advertisements, Craigslist advertisements, Google advertisements, and flyers will be used to ensure that we reach participants who may not participate in social networking sites. Moreover, we will collaborate with local community organizations that have community outreach, such as local Young Men's Christian Associations and substance use prevention organizations. All advertisements will provide a

website address (URL) for more information and eligibility screening.

The initial screening will be conducted on the web to determine eligibility (Textbox 1). Eligibility questions will be embedded in demographic and behavioral questions to avoid making the criteria obvious. We aim to recruit an equal number of young adults at each age (eg, 18, 19, and 20) and sample based on the demographics of Texas. Our prior studies have successfully used similar procedures to recruit demographically diverse samples [55,56]. We have developed and programmed a system database for recruitment and tracking in our studies, which we will adapt for this research.

Textbox 1. Eligibility criteria for phase 1 and phase 2.

Inclusion criteria

- Aged 18 to 24 years

- Live in Texas, United States

- Have a valid email address

- Own a cell phone number with SMS text messaging capabilities

- Okay with receiving SMS text messages

- Typically drink at least 2 days a week

- Typically use marijuana at least 2 days a week

- Report having at least one alcohol-related and one marijuana-related consequence in the past month

- Report being in contemplation or action stage based on readiness to change scale for alcohol or marijuana (ie, not in precontemplation stage)

- If female, not pregnant or trying to become pregnant

- Not currently in treatment for alcohol or substance use

- Willing to participate in a web-based focus group or cognitive interview via Zoom videoconferencing (criterion for phase 1 only)

- Device must meet the system requirements to participate in the web-based focus group or cognitive interview (eg, have iOS 8.0 or later and Android 4.0x or later or have another video-enabled device; criterion for phase 1 only)

- Willing to participate in a pilot study with daily morning surveys (criterion for phase 2 only)

Phase 1: Focus Groups and Cognitive Interview Procedures

Overview

An iterative process of focus groups and cognitive interviews will inform the development and delivery of the intervention to be tested in the pilot study (aim 2). Focus groups and cognitive interviews will allow us to better elicit personally relevant reasons to make a change in one's behavior and decide to engage in PBS for alcohol use or marijuana use so that we can optimize our SMS text messaging intervention. Results from the phase 1 focus groups will inform phase 2 by providing guidance on the specific motives behind PBS use or nonuse most commonly reported, informing the definitions and descriptions of the quality of PBS use to be presented to participants in phase 2, and making any additional changes to the proposed intervention materials or delivery based on participant feedback. The primary goal of the focus groups and cognitive interviews is to obtain participant feedback to help us develop an intervention that is clear, understandable, relevant, usable, and acceptable to the target population.

Focus Groups and Cognitive Interviews

A total of 10 focus groups will be run with approximately 10 people in each group, for a total of up to 100 individuals. For individuals who self-report as gender nonbinary, we will present two options from which the participant can select one: (1) their preferred gender focus group or (2) an individual cognitive interview. All focus groups and cognitive interviews will have a phenomenological focus, allowing for a free-flowing discussion among participants, with the flexibility to probe participants' responses by the moderator. Focus groups and cognitive interviews will consider the use of alcohol or marijuana alone on a given day; CAM and SAM use on a given day; and how CAM and SAM use may affect motivation to use PBS, the type of PBS used (alcohol or marijuana), and the quality of PBS use. Focus groups and cognitive interviews will focus on the *why* behind using PBS as participants will be asked to discuss various ways in which the motivations for and quality of PBS use could be incorporated into a web-based and SMS text messaging PBS intervention, such as eliciting feedback on the use of drafted intervention material. Participants will be asked to provide reasons why they may choose not to use a certain PBS and what might motivate them to consider using

the same strategy. Participants will be asked to discuss why some PBS are used more or less often and why they are used with lower or higher quality. These questions will provide the necessary information related to the motivations and reasons for using PBS, which will ultimately be targeted in the subsequent pilot study. The moderator will explore experiences of and reactions to the drafted intervention materials and will probe to see whether young adults, in general, would want to learn about opportunities to participate in an intervention study and gauge the interest for involvement in an intervention outside of a paid research study. Focus groups and cognitive interviews (60 minutes) will be conducted on the internet via Zoom videoconferencing software, and participants will receive US $50 compensation. Focus groups and cognitive interviews will be audiotaped using the Zoom recording feature. Audiotapes will also be transcribed using transcription software and checked by the team for any errors. Focus groups and cognitive interviews will be conducted in an iterative process, whereby, after the initial sessions, investigators will meet to decide what changes, if any, should be made before conducting the remaining focus groups and cognitive interviews.

Phase 2: Pilot Randomized Controlled Trial Procedures

Phase 2 will involve a pilot study with 200 young adults (aged 18-24 years) from Texas, United States, who typically drink alcohol and use marijuana for at least 2 days per week to

determine the feasibility, acceptability, and preliminary effect sizes (Figure 1). Participants will be randomized to the web-based and SMS text messaging intervention (N=100) or waitlist control (N=100) groups. All participants will complete a screening survey, baseline assessment, a 2-month follow-up, as well 24 daily morning surveys over 8 weeks. All surveys will be administered on the web. Informed by the content and process details generated through focus groups and cognitive interviews in aim 1, participants in the intervention condition will receive a brief, web-based intervention that is self-administered and focuses on self-selected alcohol and marijuana PBS messages [57] and motives for using alcohol- and marijuana-related PBS. Participants will be prompted to choose 12 alcohol PBS and 12 marijuana PBS that they are motivated to use (from a list of possible PBS for alcohol and marijuana) and will identify whether they prefer to receive the PBS content during the week (random weekday) and on the weekend. For example, a participant could indicate that they are less likely to drink on a random weekday but more likely to use marijuana and, thus, would like the marijuana content during the week and the alcohol content on the weekend. Alternatively, a participant could indicate that they are likely to co-use alcohol and marijuana on weekends and, thus, would receive both types of PBS each weekend day. For each self-selected PBS, the web-based intervention will prompt them to provide information about why they selected that particular PBS.

Figure 1. Randomized controlled trial workflow diagram. PBS: protective behavioral strategies.
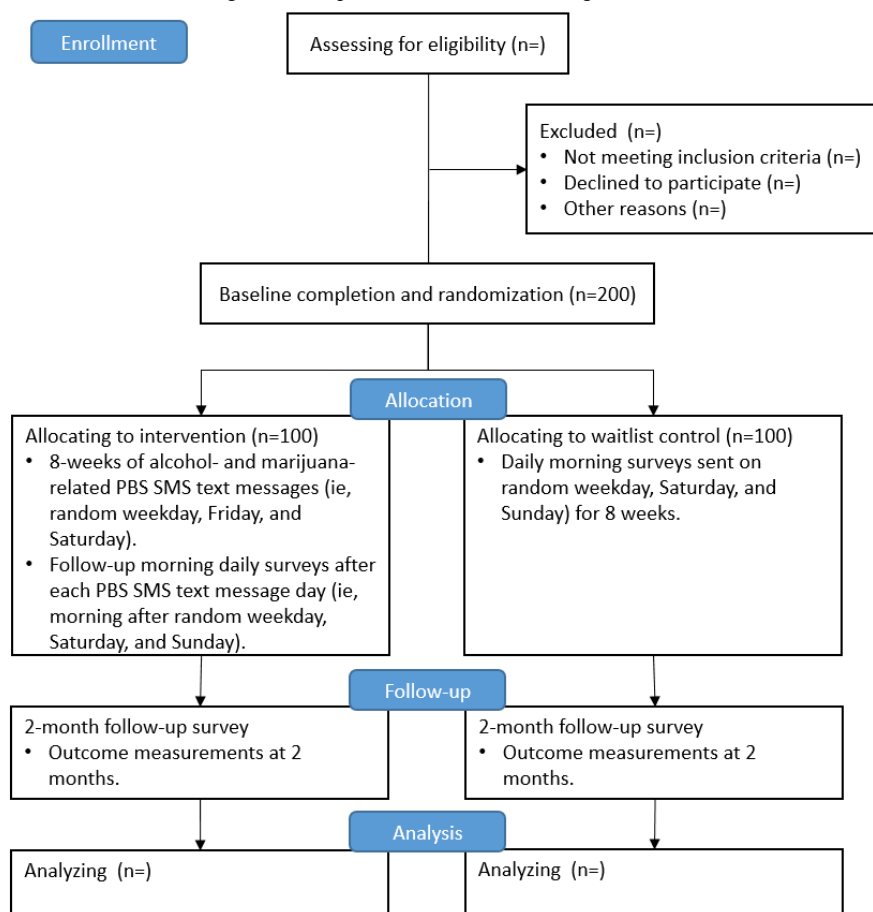
The web-based intervention will also include examples related to how to use PBS in a high-quality manner to ensure that not only are PBS being used but that when they are used, the PBS are being used in an effective manner to affect substance use outcomes. For example, for the alcohol PBS specifying to *determine not to exceed a set number of drinks*, participants will navigate web-based content related to the process of deciding what is a safe limit to set based on personalized estimated blood alcohol concentration calculations. For the PBS to *use a designated driver,* the intervention content will emphasize the importance of ensuring that the designated driver has not had anything to drink or used any marijuana and that even one drink is too much. When participants select the marijuana PBS to *use a little and then wait to see how you feel before using more*, participants will be guided through deciding how much a *little* is and how long they should wait to see which effects they experience before using more marijuana. When they select *take periodic breaks if it feels like you are using marijuana too frequently,* they will be prompted by the web-based intervention to decide how they would know if they are using it too frequently and what kind of break would be ideal to actually reduce harm (eg, a few days, weeks, or months). The expected length of time to complete the self-administered web-based intervention is 20 minutes.

After completion of the web-based intervention, participants assigned to the intervention condition will receive a brief postintervention survey to assess the acceptability of the intervention content they received. Next, the intervention content will be delivered via SMS text messages 3 days a week (random day, Friday, and Saturday) over 8 consecutive weeks. On the days that participants will be receiving SMS text messaging intervention content, their day will start with 4 SMS text messages requesting a numerical reply consistent with other protocols assessing readiness and goal setting [58]. The first series of 2 SMS text messages will ask them to complete a readiness ruler assessing the importance of making a change in their alcohol use and, separately, marijuana use. Although the stem with the ruler during screening is *in general*, for these day-of-intervention SMS text messages, it will be *at this moment* (eg, "at this moment, on a scale of 0 [not important] to 10 [extremely important], how important is it for you to change your current drinking if you decided to?"). Then, the second series of 2 SMS text messages request a response to a modified readiness ruler assessing thoughts about openness to changing their behavior separately for alcohol and for marijuana (eg, "at this moment, on a scale of 0 [not at all] to 10 [extremely willing], how willing are you to try a new strategy around your alcohol use today?"). Later that day, the PBS content they receive will be personalized and matched to their importance or willingness ratings, such that SMS text messaging content is stage appropriate. For participants who rate a 0 to 3, typically precontemplation, they will receive a statement with a serious harm reduction PBS suggestion aiming to prompt contemplation of change with no action stage suggestion that they could or should do so (eg, "Eating before or during drinking slows absorption of alcohol & people find they can avoid unwanted consequences. Consider how this might work for you, if at all."). Participants who rate a 4 to 6, which reflects ambivalence and contemplation, will receive an SMS text message with a small

step, manner of drinking PBS suggestion (eg, "Drinking slowly can keep degree of intoxication from sneaking up on you. What might you be willing to try to slow down rate (if anything)? (a) pacing sips, (b) alternating sips/drinks with water, (c) something else, (d) I'm not sure this would work for me."). Finally, participants who rate 7 to 10 will receive an action stage PBS reflecting stopping or limiting strategies (eg, "Determining not to exceed a set number of standard drinks can reduce unwanted effects. You said you're ready to try something new and make a change in your drinking. What limit do you want to set for yourself tonight? Please text back the number of drinks you have in mind.").

Participants in both conditions will report on PBS use and nonuse, including motivations for and quality of PBS use and alcohol and marijuana use in a morning survey that is timed to occur the day after the intervention messages (the morning after random day, Saturday, and Sunday). The waitlist control condition will not receive any intervention content during the 8-week period of data collection to support testing of the primary aims but will complete baseline, 2-month, and daily surveys according to the same schedule as the intervention group to assess event-level PBS use, PBS nonuse, alcohol and marijuana use, CAM and SAM use*,* and related consequences for up to 24 days over 8 weeks. All waitlist control participants will receive the intervention and postintervention survey at the end of the 2-month survey.

Participants will be compensated US $25 for the baseline survey, US $10 for postintervention assessment, up to US $58 for completion of all 24 daily surveys (US $2 per completed daily survey, with an additional US $10 bonus incentive for completing at least 90% of the surveys), and US $25 for a 2-month follow-up survey, for a total of up to US $118 across the study period.

Phase 2 Measures

Baseline and 2-Month Measures

Demographics

Demographics will include, but are not limited to, sex assigned at birth, gender, age, height, weight, and living situation.

Alcohol Measures

Lifetime, past year, and past month alcohol use measures will include items from the Monitoring the Future (MTF) study [59]. Drinking will be assessed using the Daily Drinking Questionnaire (Cronbach α=.73) [60] and the Alcohol Use Disorders Identification Test (Cronbach α=.85) [61]. Negative consequences will be assessed using the Young Adult Alcohol Consequences Questionnaire (Cronbach α=.79) [62]. Alcohol PBS will be assessed using the Protective Behavioral Strategies Survey-20 (Cronbach α=.63-.81) [63]. Motivations for alcohol PBS use and nonuse will be assessed (Cronbach α=.80) [43,64]. The Readiness to Change Questionnaire (Treatment Version Revised) will be used to assess the readiness to change drinking habits [65,66].

Marijuana and Other Substance Use Measures

Marijuana use will be measured using MTF items such as lifetime, past year, and past month [59]. The Daily Marijuana

Questionnaire will be used to assess marijuana use based on the typical number of hours spent high per day (Cronbach α=.97) [67]. The Marijuana Consequences Questionnaire [68] will measure a broad range of negative marijuana consequences (Cronbach α=.89). We will also administer the Marijuana Problem Scale (Cronbach α=.85) [69]. To assess risk for substance use disorder, we will use the Cannabis Use Disorders Identification Test-Revised (Cronbach α=.80) [70]. Marijuana PBS will be assessed using the PBS for Marijuana-36 (Cronbach α=.93) scale [34]. Other substance use will be assessed for lifetime and past month frequency using the Customary Drinking and Drug Use Record (Cronbach α=.70-.94) [71,72]. Motivations for marijuana PBS use and nonuse will be assessed using items parallel to the alcohol PBS motivation measure [43,64]. The Readiness to Change Questionnaire (Treatment Version Revised) will be adapted to assess readiness to change marijuana use [65,66].

Questions regarding SAM use will be adapted from MTF [73]: "On how many occasions (if any) during the last 30 days have you used alcohol and marijuana at the same time–that is, so that their effects overlapped?" CAM use will be determined from alcohol and marijuana measures (ie, endorsement of both alcohol and marijuana use within the same time frame) [67].

Acceptability Measures

A modified System Usability Scale [74-76] and Website Analysis and Measurement Inventory (WAMMI) [77] will assess the perceived usability of the web-based intervention and SMS text messages, perceived favorability of the web-based design, ease of navigation and use, convenience, relevance, and usefulness. The perceived engagement and appeal of the intervention and SMS text messages will also be assessed [78,79]. Participants will complete items to evaluate the web-based portion's content (thought provoking, easy to understand, relevant, useful, motivation to change self or others, and open-ended questions on the most useful and engaging portion of the web-based feedback session) and format (attention grabbing, interesting, and enjoyable).

Daily Measures

Our strategy is to collect daily reports each morning after the intervention participants receive the SMS text messaging content. Each intervention participant will be yoked to a participant in the waitlist control group.

Yesterday's Alcohol or Marijuana Use

Participants will report the number of standard drinks consumed on the previous day, the number of hours they spent drinking, whether they used marijuana, the number of sessions that they used marijuana, and how long they were high. SAM use will be assessed by asking, "Yesterday, did you use alcohol and marijuana at the same time–that is, so that their effects overlapped?" [14]. CAM use will be identified by the endorsement of alcohol and marijuana use the previous day but responding *no* to the SAM use item.

Substance-Related Consequences

The consequences experienced the previous day will be assessed using items from the alcohol and marijuana consequences scales.

For alcohol, we will administer items used in our previous daily diary study on alcohol use [55]. A modified Marijuana Problem Scale [80] and Rutgers Marijuana Problem Index [81] will assess marijuana consequences, selecting acute items appropriate for daily-level measurements [82].

PBS Use and Quality

PBS use and quality on the previous day will be assessed by having participants report which, if any, alcohol and marijuana PBS they used the previous day and, for those they report using, how well they implemented the PBS (ie, quality) and how helpful they perceived the strategy to be.

Motivations to Use PBS

Motivations for each alcohol and marijuana PBS use will be assessed by asking open-ended questions on why they selected to use those strategies that day.

Readiness to Change

Participants' readiness to change [66,83] will be assessed with "At this moment, on a scale of 0 to 10, how important is it for you to change your current drinking/marijuana use if you decided to?"

Feasibility and Acceptability

We will assess feasibility and acceptability (ie, participant responses after reading SMS text messaging content and whether alcohol or marijuana was being used when participants read the SMS text messages). SMS text messages will comprise a 2-way dialog to assess whether the participants read the message. Adherence will be calculated as the percentage of SMS text messages that prompted participants' response [57]. Participants will respond by indicating helpfulness, likeability, thought provoking, and clarity (eg, 1=*not at all* to 5=*very*). We will track message timing and content to determine factors that may affect intervention efficacy and alcohol or marijuana use. We will examine the response rates to intervention SMS text messages on days of alcohol and marijuana use.

Statistical Analysis

Before inferential statistics, univariate and bivariate descriptive statistics will be used to examine the distributions and simple associations among the variables. Preliminary analyses will include the nature of missing data and the identification of extreme values. The baseline equivalence of PBS, alcohol, and marijuana measures and demographic representation across conditions in phase 2 will be examined. Feasibility and acceptability will be the primary outcomes of phase 2. Behavioral alcohol and marijuana outcomes (PBS use, PBS motivation, PBS quality, alcohol use, alcohol consequences, marijuana use, marijuana consequences, CAM use, and SAM use) will provide estimates of the base rates and variance in the outcomes.

The feasibility and acceptability (*hypothesis 1*) of the intervention will be tested in several ways. First, feasibility will be established by (1) achieving the recruitment goal (N=200); (2) achieving the recruitment goal within 6 months; and (3) the rate of study retention being ≥90%, including the proportion of young adults who complete the intervention, the proportion of daily surveys completed, and the 2-month follow-up retention.

The acceptability of the intervention will be determined by (1) the proportion of eligible young adults enrolled (80% of eligible young adults agreeing to participate); (2) ratings of individual intervention components, including both web and SMS text messaging content (rating content as favorable overall); (3) ratings of accessibility (acceptable length of intervention and acceptable timing of intervention delivery), usability (ease of viewing and navigating web-based intervention and SMS text messages), convenience (mode of intervention delivery), and relevance of intervention content (engaging and helpful content); and (4) the proportion of young adults who would recommend the program (outside of a paid research study). Acceptability will be achieved if 80% of the responses in each domain are rated ≥4 (out of 5). For the System Usability Scale, scores <4.0 on the 5-point items indicate a need to re-examine intervention features, and scores of ≥68 on the 100-point total support overall usability. In the case that intervention areas do not meet these criteria, the investigative team will revise the intervention components before conducting a future large-scale randomized trial. The WAMMI comprises 20 validated statements used to evaluate websites and intervention programs. We will use this measure to assess the acceptability of our web-based and SMS text messaging intervention. Each statement is rated on a 5-point scale from strongly agree to disagree, and scores will be calculated for attractiveness, controllability, efficiency, helpfulness, and learnability, as well as the overall global usability score. All scores will be automatically calculated by the WAMMI website and compared with a large international database of scores for other projects. A global usability score of ≥50 indicates that a given website or intervention program is above average (50), according to a large international database maintained by the creators of the WAMMI.

For *hypothesis 2,* given the repeated measures design, generalized linear mixed models (GLMMs) [84,85] will be used. GLMMs (ie, hierarchical generalized linear models) allow for nonnormal outcomes (eg, count outcomes such as the number of days high or the number of negative consequences) and missing data, handle varying time points, and accommodate time-varying and time-invariant covariates. The models include two repeated measures (baseline and 2 months), yielding up to 400 observations (level 1: repeated measures) across 200 individuals (level 2: people; n=100 per condition). To test the intervention effects, the intervention condition will be a dummy variable that compares the intervention condition to the waitlist control condition (reference category). Of particular interest are the parameters that reflect the interaction between the intervention conditions and time. For count outcomes (eg, alcohol use and consequences), the outcome is connected to covariates through a log link function, which is the standard link function for Poisson GLMMs. Covariates can be exponentiated to yield rate ratios that describe the proportional change in the count outcome associated with a 1-unit increase in the covariate. If data show overdispersion when the variance exceeds the mean, the model will be extended to include a scale parameter to fit an overdispersed Poisson, or we will consider zero-altered models to ensure accurate inferences [86]. Sex assigned at birth, age, and baseline readiness to change will be included as covariates in all the analyses.

Both *hypothesis 3* and *hypothesis 4* use event-level data and can be tested with GLMMs, which are also used for *hypothesis 2*. The 2-level model accounts for the clustering of observations, whereby morning surveys (level 1: day-level) are nested within individuals (level 2: person-level). GLMMs can accommodate unequal observations per person. We will use an appropriate modeling distribution for all outcomes (eg, a zero-inflated Poisson distribution for count outcomes such as consequences and normal distribution for PBS motivation). We will evaluate whether the model assumptions are met (eg, normality of error terms) so that the data are modeled appropriately [86]. Centering of predictors and controlling for the associated higher-level effects will be performed based on standard practice and current recommendations. Sex assigned at birth and age will be person-level covariates in all analyses, and daily-level covariates will be alcohol use, marijuana use, weekends, and readiness to change in all analyses. Owing to the large number of models, *P* values will be adjusted [87].

Event-level designs using daily surveys produce rich and complex data sets that permit the examination of different types of associations among constructs, and these complex associations can be tested using GLMMs. For instance, *hypothesis 3* specifies that on days when individuals' motivations to use PBS are elevated (ie, higher than their average level), they will report lower alcohol use. Here, PBS motivation is the predictor (person-centered), and the number of drinks consumed that day is the outcome. A cross-level interaction between the predictor (level 1) and condition (level 2) can be tested to determine whether this effect is stronger among those in the intervention condition than in the waitlist control condition. GLMM specifications can easily be modified for event-level data to test all the hypotheses specified by *hypothesis 3* and *hypothesis 4*. For instance, in *hypothesis 4*, each day will be coded as neither alcohol nor marijuana, alcohol alone, marijuana alone, CAM, or SAM. Then, dummy codes will be created to make specific comparisons (eg, alcohol alone days vs SAM use days).

Results

This research was funded in May 2021 and approved by institutional review board in March 2021. Recruitment and enrollment for phase 1 began in January 2022. The findings of phase 1 will inform the development of novel web-based and SMS text messaging interventions that will be tested in phase 2. Phase 2 is anticipated to begin in January 2023. The findings will be published in peer-reviewed journals and presented at international, national, or regional professional meetings and conferences.

Discussion

Principal Findings

The most successful young adult alcohol or marijuana interventions involve the provision of accurate, nonjudgmental, and personalized feedback [88]; however, notably, the inclusion and effectiveness of PBS content are inconsistent [54]. Moreover, the active components of brief interventions are not well understood [89], and findings have been inconclusive

regarding whether PBS mediates the intervention efficacy of college student PFIs, with only some studies showing evidence of mediation [40]. A possible reason for these findings is that we often do not know young adults' motivations for using (or not using) PBS or the quality of PBS use across individuals or across drinking occasions. This study will provide an in-depth examination of which PBS young adults are motivated to use (including implementation quality) and the reasons that young adults may or may not use PBS. Understanding why young adults choose not to use PBS on specific occasions or do not engage in effective or high-quality PBS use on certain occasions has significant clinical implications, whereby interventions may need to spend more time increasing motivations to use PBS in an effective manner or work on reducing the perceived barriers (ie, reasons individuals are not using PBS). Clinicians may then be better able to work with young adults in various settings (eg, campus counseling and health centers, residence halls, health and wellness services, and community mental health clinics) to reduce or prevent excessive alcohol and marijuana use and related negative consequences. This study has great potential for making a substantial impact in the field and public health (particularly as more states permit legal access to marijuana for those aged ≥21 years) as it will address the problem of high importance (young adult alcohol and marijuana use) by being the first to develop and refine a PBS intervention that specifically focuses on the motivations for alcohol and marijuana PBS use and nonuse, as well as the quality of use, which is an overlooked aspect of current PBS-related intervention approaches.

Limitations

Although this study will use a strict application of the scientific method to achieve robust, unbiased, and replicable results via several design features, including explicit inclusion and exclusion criteria, study design (randomization and inclusion of a waitlist control), and data analytic plans, there are several potential limitations that need to be acknowledged. First, the use of incentives in research may lead to selection effects that could have an impact on external validity. A meta-analysis found small effects of incentives to increase recruitment for web-based research [90]. However, selection effects are typically not a problem for randomized trials, as random assignment ensures relatively similar characteristics across study conditions [91]. However, we will include questions in the focus groups to assess what would make participants willing to participate in a similar study without monetary incentives. A second potential limitation of this research is that we will collect data in a single state that does not currently have legalized marijuana. Thus, we will not be able to directly test how legalization influences alcohol and marijuana use and related PBS in young adult populations. Furthermore, as this is a small-scale pilot study, it was not designed to be fully powered; however, the results of this study will provide preliminary effect sizes to calculate power for a subsequent full-scale randomized controlled trial.

Conclusions

This study will fill critical gaps in the literature by identifying the extent to which motivations for PBS use and nonuse (marijuana or alcohol) and the quality of PBS use (degree of effectiveness or degree of implementation) differ when using alcohol alone versus concurrently or simultaneously with marijuana. The overall goal of this study is to inform a pilot study of a newly developed alcohol and marijuana PBS intervention. This research will (1) collect pilot data to establish the feasibility and acceptability and test the web-based and SMS text messaging PBS intervention (baseline and 2 months) and (2) collect event-level data to examine daily-level associations among PBS motivation and quality, PBS use and nonuse, alcohol and marijuana use, and negative consequences, with a focus on how PBS may differ on CAM or SAM use days compared with alcohol-only days. This study will provide an in-depth understanding of young adults' PBS use and has the potential to develop a more efficacious intervention for these co-occurring or SAM behaviors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report form the Epidemiology, Prevention and Behavior Research Review Subcommittee, National Institute on Alcohol Abuse and Alcoholism Initial Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 359 KB - resprot_v11i4e37106_app1.pdf]

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Abbreviations

CAM: concurrent alcohol and marijuana
GLMM: generalized linear mixed model
MTF: Monitoring the Future
NIAAA: National Institute on Alcohol Abuse and Alcoholism
PBS: protective behavioral strategies
PFI: personalized feedback intervention
SAM: simultaneous alcohol and marijuana
WAMMI: Website Analysis and Measurement Inventory

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<u>Corrigenda and Addenda</u>

Correction: Survivorship of Patients After Long Intensive Care Stay With Exploration and Experience in a New Zealand Cohort (SPLIT ENZ): Protocol for a Mixed Methods Study

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Related Article:

Correction of: https://www.researchprotocols.org/2022/3/e35936/

In "Survivorship of Patients After Long Intensive Care Stay With Exploration and Experience in a New Zealand Cohort (SPLIT ENZ): Protocol for a Mixed Methods Study" (JMIR Res Protoc 2022;11(3):e35936) the authors noted one error.

In Textbox 1, one of the exclusion criteria was reported as follows:

- *>18 years*

This has been corrected as follows:

- *<18 years*

The correction will appear in the online version of the paper on the JMIR Publications website on April 4, 2022 together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Corrigenda and Addenda

Correction: mHealth Intervention to Improve Treatment Outcomes Among People With HIV Who Use Cocaine: Protocol for a Pilot Randomized Controlled Trial

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Related Article:

Correction of: https://www.researchprotocols.org/2022/3/e28332

In "mHealth Intervention to Improve Treatment Outcomes Among People With HIV Who Use Cocaine: Protocol for a Pilot Randomized Controlled Trial" (JMIR Res Protoc 2022;11(3):e28332) the authors noted two errors.

First, in the originally published article the affiliation for author Archana Krishnan appeared as follows:

Department of Social Scienes, University at Albany, State University of New York, Albany, NY, United States

This has been corrected as follows:

Department of Communication, University at Albany, State University of New York, NY, United States

Second, in the originally published article a footnote appeared below the affiliations as follows:

*all authors contributed equally

This was deleted in the correction, as it is not applicable.

The correction will appear in the online version of the paper on the JMIR Publications website on April 7, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Protocol

Student, Staff, and Faculty Perspectives on Intimate Partner and Sexual Violence on 3 Public University Campuses: Protocol for the UC Speaks Up Study and Preliminary Results

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Abstract

Background: Intimate partner and sexual violence are pervasive public health issues on college and university campuses in the United States. Research is recommended for creating and maintaining effective, relevant, and acceptable prevention programs and response services for student survivors.

Objective: The University of California (UC) Speaks Up study aims to examine factors contributing to intimate partner and sexual violence on 3 UC campuses and use the findings to develop and test interventions and policies to prevent violence, promote health, and lay the groundwork for subsequent large-scale quantitative research.

Methods: A mixed methods study was conducted at UC Los Angeles, UC San Diego, and UC Santa Barbara. Phase I (2017-2020) involved a resource audit; cultural consensus modeling of students' perceptions of sexual consent; in-depth interviews (IDIs) and focus group discussions with students to understand perceptions of campus environment related to experiences as well as prevention of and responses to violence; and IDIs with faculty, staff, and community stakeholders to investigate institutional and community arrangements influencing students' lives and experiences. Phase II (2020-ongoing) involves IDIs with student survivors to assess the use and perceptions of campus and community services. Qualitative content analysis is used to generate substantive codes and subthemes that emerge, using a thematic analysis approach.

Results: In January 2019, we conducted 149 free-listing interviews and 214 web-based surveys with undergraduate and graduate and professional students for the cultural consensus modeling. Between February 2019 and June 2019, 179 IDIs were conducted with 86 (48%) undergraduate students, 21 (11.7%) graduate and professional students, 34 (19%) staff members, 27 (15.1%) faculty members, and 11 (6.1%) community stakeholders, and 35 focus group discussions (27/35, 77% with undergraduate students and 8/35, 23% with graduate and professional students) were conducted with 201 participants. Since September 2020, 50% (15/30) of the planned student survivor interviews have been conducted. This segment of data collection was disrupted by the COVID-19 pandemic. Recruitment is ongoing.

Conclusions: Data analysis and phase II data collection are ongoing. The findings will be used to develop and test interventions for preventing violence, promoting health and well-being, and ensuring that survivor services are relevant and acceptable to and

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meet the needs of all individuals in the campus community, including those who are typically understudied. The findings will also be used to prepare for rigorous, UC–system-wide public health prevention research.

KEYWORDS

Introduction

The Public Health Problem of Intimate Partner and Sexual Violence on College Campuses

Intimate partner violence (IPV) and sexual violence are pervasive public health issues on college and university campuses in the United States [1,2]. IPV is defined by the US Centers for Disease Control and Prevention as "physical violence, sexual violence, stalking, and psychological aggression (including coercive tactics) by a current or former intimate partner (i.e., spouse, boyfriend or girlfriend, dating partner, or ongoing sexual partner)" [3]. It is estimated that one-third of all college students in the United States have experienced some form of IPV [4], and 20% of female and 6% of male students [1] have experienced sexual violence while in college [1,2]. Sexual violence, defined by the Centers for Disease Control and Prevention as "a sexual act that is committed or attempted by another person without freely given consent of the victim or against someone who is unable to consent or refuse," includes sexual assault, rape, and sexual coercion [5]. Although most commonly perpetrated by individuals known to the victim or survivor, including and oftentimes an intimate partner, sexual violence also includes unwanted acts used by persons who are not intimate partners and by persons not known to the victim or survivor [5].

IPV and sexual violence have been associated with increased risk of anxiety and depression, suicidal ideation, migraines, unprotected sex, unintended pregnancy, reduced access to reproductive health services, alcohol and substance use, and HIV and other sexually transmitted infections [2,6]. Compared with students unexposed to violence, college survivors of sexual assault are significantly more likely to have reduced grade point averages and slower time to completion of their degree and have an increased likelihood of leaving college or university altogether [7].

Data from 71,421 undergraduates found higher odds of sexual assault among cisgender women (vs cisgender men), transgender people (vs cisgender men), gay (vs heterosexual) men, and bisexual (vs heterosexual) students [8]. A study at a Hispanic-serving institution found that sexual and gender minority undergraduate students who experienced past-year violence were more than twice as likely to report some type of interference with their academic lives (eg, obtaining poor grades and missing class or work) compared with heterosexual, cisgender students who experienced past-year violence [9]. Studies have consistently found that violence is perpetrated at higher rates against students with (vs without) disabilities both

during [10-12] and before enrolling in college or university [12]. This body of research highlights the need for culturally, racially, socially, and gender-relevant services for survivors of sexual and relationship violence.

White House Task Force to Protect Students From Sexual Assault

In January 2014, President Barack Obama established the *White House Task Force to Protect Students from Sexual Assault* (hereinafter referred to as the *White House Task Force*) to strengthen federal enforcement efforts and provide recommendations and tools that colleges and universities could use to address sexual assault on their campuses [13]. Since its establishment, US institutions of higher education have increasingly adopted approaches to address campus-based violence. Many schools have received funding through the Office on Violence Against Women *Campus Program* of the US Department of Justice, created by Congress to provide grants to develop and strengthen trauma-informed victim services and strategies to prevent, investigate, and respond to sexual assault, sexual harassment, domestic violence, dating violence, and stalking [14]. Other schools have used institutional funding to establish and support violence prevention programs, including the University of California (UC), a public university system of 10 campuses that identifies preventing and responding to sexual violence and sexual harassment (SVSH) as top priorities.

UC Sexual Assault Prevention and Response

In June 2014, in response to the *White House Task Force*, UC President Janet Napolitano formed the *President's Task Force on Preventing and Responding to Sexual Violence and Sexual Assault* to improve current UC sexual violence prevention processes and develop recommendations for implementing strategies to improve prevention, response, and reporting procedures [15].

Between June 2014 and January 2016, UC implemented 7 components of an intended *comprehensive* system-wide model for addressing campus SVSH. These included (1) creation of a system-wide website for access to campus resources and important information; (2) mandatory education and training on sexual violence issues and prevention; (3) establishing a *Campus Assault Resources and Education (CARE): Advocate Office for Sexual and Gender-Based Violence and Sexual Misconduct* on each campus; (4) designating individuals on each campus to help respondents (ie, perpetrators) understand their rights and the investigation and adjudication processes of UC; (5) strengthening UC policy against sexual and domestic violence, stalking, and harassment as part of ongoing compliance with the federal Violence Against Women Act; (6) following

a standardized 2-team response model at each campus (including 1 team for case management to review sexual misconduct reports and a second team focused on policies, community relations, prevention, and intervention using a campus collaborative approach); and (7) system-wide procedures for investigating, adjudicating, and imposing sanctions in student cases of SVSH [15].

Although the multicomponent approach of UC to address SVSH has established a strong foundation for cultivating a system-wide culture of respect and safety, it is not *comprehensive* per the definition used by the *White House Task Force*. Their recommended model for comprehensively assessing and responding to campus violence includes four action steps: (1) identifying the prevalence and determinants of sexual assault on campus through climate surveys, (2) developing evidence-based prevention strategies for sexual assault, (3) establishing investigation and adjudication procedures to respond to reports of sexual violence, and (4) improving federal enforcement efforts [13]. Missing from the approach of UC is the implementation of a campus climate survey and the development of evidence-based prevention strategies.

Campus climate surveys have been recommended for assessing the scope and context of violence on campuses to create and maintain effective, relevant violence prevention and response programs that are acceptable to the students and meet the needs of student survivors [13,16]. To date, UC Berkeley is the only UC campus that has conducted a climate survey focused on sexual violence and other forms of sexual, dating, and relationship harm. Thus, we lack evidence on the scope and nature of SVSH across the UC system, precluding our ability to tailor programs to meet the needs of each campus population.

Objectives

This paper describes the protocol for phase 1 (2017-2021) and phase 2 (2020-ongoing) of a mixed methods research study conducted on 3 UC campuses. The goal of this research is to prepare for future implementation of a quantitative climate survey or an alternative research design that will allow for systematic, in-depth assessment of the prevalence, determinants, and nature of campus-based violence. Textbox 1 shows the 6 research aims of this study.

The design of this project was informed by guidelines from the comprehensive campus sexual assault climate assessment model developed by the Center on Violence Against Women and Children (VAWC) of Rutgers University [17,18] and from the implementation overview and lessons learned report of the MyVoice Working Group [19].

Textbox 1. Research aims of this study.

Research aims

- Aim 1: assess students' perceptions of sexual consent

- Aim 2: understand students' perceptions of the campus environment related to sexual assault, sexual harassment, and dating violence

- Aim 3: investigate institutional and community arrangements influencing students' lives and experiences

- Aim 4: examine how campus prevention, education, and response efforts can be tailored to meet the unique needs of diverse individuals and communities

- Aim 5: learn about student survivors' use and perceptions of campus- and community-based violence and mental health services

- Aim 6: lay the groundwork for subsequent quantitative research and effective prevention programs coupled with healing-centered comprehensive response services at each campus

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Methods

Study Setting and Timeline

There are 10 campuses in the UC system, and this project was conducted on three in Southern California: UC Los Angeles (UCLA), UC San Diego (UCSD), and UC Santa Barbara (UCSB; Figure 1). The project began during the 2017-2018 academic year (AY). The main phase of data collection was conducted in AY 2018-2019, during which time student enrollment by campus was as follows: 30,873 undergraduate and 14,074 graduate students at UCLA; 30,285 undergraduate and 8513 graduate students at UCSD; and 23,070 undergraduate and 2906 graduate students at UCSB [20-22]. The full project timeline is shown in Figure 2.

Figure 1. Map of California showing the 10 University of California campuses and highlighting the 3 campuses involved in this study.

Figure 2. Timeline and steps of planning and implementing the project from academic year (AY) 2017-2018 to AY 2020-2021. CCM: cultural consensus modeling; FGD: focus group discussion; IDI: in-depth interview; UC: University of California; UCOP: University of California Office of the President.
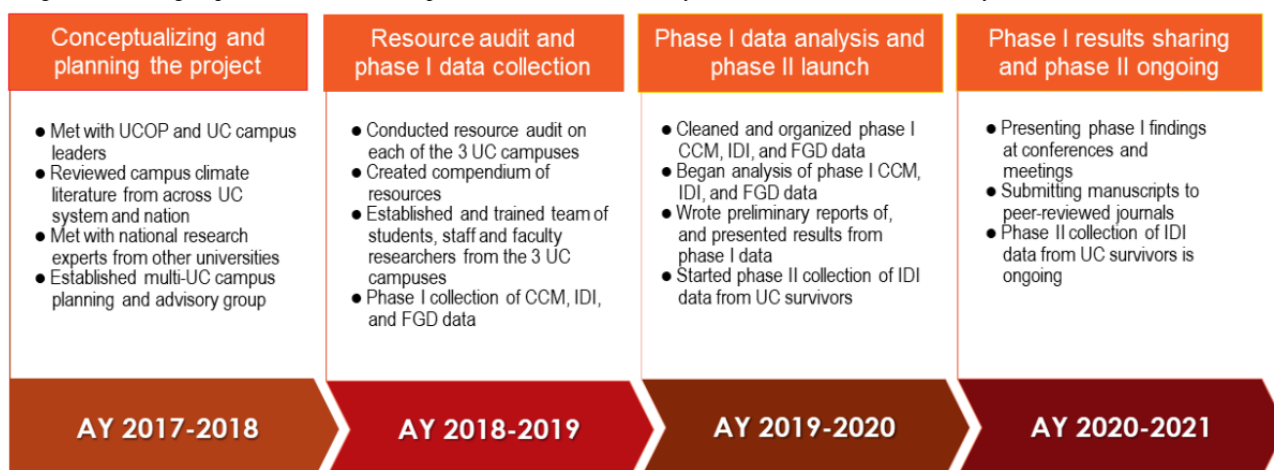
Conceptualizing and Planning the Project (AY 2017-2018)

Project conceptualization began with a visioning and prioritization workshop at a meeting of faculty, staff, and students involved with the Women's Health, Gender, and Empowerment Center of Expertise (WHGE-COE) of the UC Global Health Institute. WHGE-COE participants from all 10 UC campuses identified prevention of campus-based sexual violence as a high priority for system-wide mobilization and collaboration. Official project planning began by reviewing the literature on campus-based violence prevention research from UC and other US colleges and universities. Concurrently, we began iteratively reaching out to, meeting with, and gathering input from leaders and key stakeholders. All planning and advisory group participants and stakeholders are listed in Textbox 2.

To learn from experts in campus-based violence prevention research, we invited leaders from 4 experienced teams to consult with our group. A total of 2 half-day learning sessions were led by the Center on VAWC of Rutgers University (drawing on experiences with the #iSPEAK Campus Climate Survey) and the PATH to Care Center at UC Berkeley (drawing on experiences with the MyVoice Survey). In total, 2 full-day consultations were led by researchers from Columbia University (drawing on experiences from the Sexual Health Initiative to Foster Transformation study) [18] and from the Division of Student Life of the University of Oregon (drawing on their Crisis Intervention and Sexual Violence Support Services). Participants included the faculty leads from each campus; the WHGE-COE Directors; the UCSD Center on Gender Equity and Health staff research associate; the UC Office of the President team; and the CARE Directors from the UC Irvine, and UCSD Advocate Offices for Sexual and Gender-Based Violence and Sexual Misconduct.

Textbox 2. Project conceptualization, planning, and advisory group members.

Campus, office, or center and position

University of California (UC), Berkeley

- Violence prevention counselors and advocates from the PATH to Care Center at UC Berkeley
- MyVoice survey research team members

UC Irvine

- Director of UC Irvine Campus Assault Resources and Education office

UC Los Angeles

- Associate Professor of Psychiatry and Biobehavioral Sciences, and Epidemiology (these 2 positions are held by the same person)
- Doctoral student of Community Health Sciences

UC San Diego (UCSD)

- Assistant Professor of Medicine
- Graduate student ambassador to Women's Health, Gender, and Empowerment Center of Expertise (WHGE-COE)
- Director of UCSD Campus Assault Resources and Education office

UC Santa Barbara

- Professor and Chair of Feminist Studies
- Undergraduate student ambassador to WHGE-COE

UC Office of the President

- Vice President of Student Affairs
- System-wide Title IX director
- System-wide Title IX coordinator

WHGE-COE

- Codirector from UC Berkeley
- Codirector and UC Los Angeles Associate Professor (these 2 positions are held by the same person)
- Deputy Director of Research from UC San Francisco
- Deputy Director of Education from UC Santa Barbara
- Deputy Director of Violence Prevention Research and UCSD Assistant Professor (these 2 positions are held by the same person)

UCSD Center on Gender Equity and Health

- Codirector and Professor of Medicine
- Staff research associate
- Doctoral fellow

Resource Audit and Phase I Data Collection (AY 2018-2019)

Resource Audit

We conducted a resource audit on each campus to examine available information on responding to and preventing IPV and sexual violence, gather input from key informants and stakeholders, and develop relationships with campus community members. This process was informed by the guidelines of the Center on VAWC of Rutgers University [23]. The assessment was coordinated by the study's faculty investigators at UCLA, UCSD, and UCSB, who led all activities with assistance from

their teams and from undergraduate and graduate WHGE-COE student ambassadors on each campus. The resource audit involved 3 main steps.

First, we gathered information through web-based searches, phone calls, and in-person office visits. This was done to explore UC-wide and campus-specific SVSH policies, investigative and adjudicative protocols, campus- and community-based support services for student sexual assault survivors, and on-campus prevention programs to reduce sexual and relationship violence.

Second, we engaged key stakeholders. At each campus, we spoke with the CARE Director or an advocate from the CARE

office, the Title IX coordinator or a Title IX officer, a residential housing administrator, providers from student health services and Counseling and Psychological Services, the Director of Student Affairs, a director or administrator from athletics, and representatives from the Office of Equity, Diversity, and Inclusion; campus police or security; the campus Panhellenic Council; the International Student Center; the LGBT Resource Center; the Undocumented Student Center; and the Black and African American Student Center. Each stakeholder was invited to review and provide feedback on the list of resources gathered, suggest others we should talk with, and make recommendations for the study.

Third, information gathered during steps 1 and 2 was used to compile a compendium of resources for each campus. The findings were also used to tailor study design, decide on research methods, and inform the development of research questions. Contacts made during the audit contributed to long-term partnerships and introduced us to people who became members of the research team.

Establishing and Training the Research Team and Branding the Project (November-December 2018)

The full research team was established in November 2019 and included 6 faculty investigators, 3 staff coordinators, and 16 student investigators (10/16, 63% undergraduate and 6/16, 38% graduate students) divided evenly across the 3 UC campuses. In December 2019, all team members participated in a 3-day, in-person training at the UCSD School of Medicine campus. Training focused on (1) research ethics and how to conduct safe and trauma-informed research on SVSH; (2) how to provide short-term mechanisms of support to any participant triggered or distressed by the topics addressed in the study; (3) how to practice *self-care* given the potentially traumatic nature of the research; and (4) where to refer participants for additional, comprehensive services on each UC campus. Through participatory discussion, we named our study the UC Speaks Up Project and decided on the following guiding values: student-centered, evidence-based, health-centered, intersectional, inclusive, trauma-informed, and ethical.

Data Collection Procedures by Method and Phase

UC Speaks Up uses three research methodologies: cultural consensus modeling (CCM), qualitative in-depth interviews (IDIs), and focus group discussions (FGDs). The first and main phase of data collection was conducted between January 2019 and June 2019. All 3 methodologies were used, and data were gathered from students, staff, and faculty from the 3 UC campuses and local stakeholders from communities surrounding each campus. Phase II of data collection, a smaller subinvestigation with sexual violence survivors, began in September 2020 and is ongoing. The methods are described in detail below by phase.

CCM With Students (Phase I: January 2019)

Overview

CCM is a technique for estimating the extent to which people share common beliefs and understandings about a topic. Individuals who answer questions about their culture in a similar

pattern are assumed to be giving the most culturally salient or correct answer [24,25]. We used CCM to understand (1) if there was a culture of sexual consent on campus (in other words, if students had a common frame of reference for consent that they could reasonably expect their partners to share), (2) if that culture of consent varied by gender or other demographics, and (3) what knowledge (rules) constituted the culture of consent. CCM allowed us to identify *answer keys* of the culturally correct meaning of sexual consent by identifying clusters of similar informant responses. It also allowed us to identify cultural experts; that is, individuals who provided a large number of *culturally salient or correct* answers (according to the identified answer key) and were presumed to likely have a large amount of expertise on the topic. The CCM process was performed in 3 steps using 2 types of data collection (free-listing interviews and a web-based survey).

CCM Step 1: Free-Listing CCM Interviews

The CCM process began with the use of free listing, a technique for gathering data about a specific cognitive domain by asking people to list all the items they can think of that fall into that category. At each campus, student researchers approached fellow students in public spaces, such as the quad or the library, introduced themselves, explained the purpose of the study, and invited them to participate. Interested students were asked to disclose their age, gender identity, and student status (undergraduate, graduate, or professional student). Eligibility criteria included self-reporting as a current student of the UC campus where data collection was being conducted, being between the ages of 18 and 26 years, and providing verbal consent. After obtaining verbal consent, student participants were asked the following three questions: (1) *How do students in your campus community know their partner is signaling sexual consent?* (2) *How do students in your campus community signal their own sexual consent?* (3) *What words would students in your campus community use to describe a sexual encounter that feels good?* Up to 10 responses for each question were recorded by the researcher. Drinks and candy bars were provided to all the participants.

CCM Step 2: CCM Survey Development

We analyzed the free-listing responses to the 3 CCM questions using Microsoft Excel and the software package *AnthroTools* (R Foundation for Statistical Computing) [26] to create the web-based survey. We reviewed all responses to each question, then tallied the number of *unique responses* to each question (ie, if 3 students provided the same response for 1 question, 1 item reflecting that response was included in the list of possible items). Item salience was calculated using Smith S scores to rank averages across all samples separately by gender. Items were weighted by the order in which they were provided. The average Smith S score was ranked to determine the top 20-30 items by gender. The Smith S score determines the item's salience based on both the frequency with which participants mention a free-list item as well as the order in which an item is mentioned. If a free-list item is the first or second response given by a large number of participants, it is considered to be highly salient. The Smith S is calculated as follows:

$$S = ((\textstyle\sum(L - R_j + 1))/L/N)$$

where *L* is the number of items on the list (length), *R* is the order in which item *j* is mentioned (rank), and *N* is the number of items on the list [27].

We then created a web-based survey in REDCap (Vanderbilt University) by including items with high Smith *S* scores as well as some items of interest (based on our literature review and resource audit) with lower salience, such as *sober* and *not resisting*.

CCM Step 3: Web-Based Survey

Survey participants were recruited using a convenience sample approach across all 3 campuses. The study was advertised via email and social media. We printed paper flyers that were displayed in public spaces on campus. All recruitment materials provided information about the study, details of participation, contact information for the investigators, and a link to follow to be screened for eligibility. Eligibility criteria included being a current student at UCLA, UCSD, or UCSB; being aged 18-26 years; and providing electronic informed consent. Although these criteria likely excluded some re-entry, graduate, and professional students, the age range eligibility was restricted as individuals aged >26 years were more likely to have different generational life-course understandings of consent than participants aged 18-26 years. A 2-step recruitment and enrollment process was used. First, to ensure enrollment at UCLA, UCSD, or UCSB, students were required to enter their campus email address. Second, students with authentic UCLA, UCSD, and UCSB email addresses were sent a unique link to access the web-based survey. Clicking the link brought the participant to a page with a complete consent form and contact information for the principal investigator and research contact person. After reading the form, the participants were prompted to provide their digital signature if they consented to participate, which would enable them to proceed to the survey. Participants were enrolled until the target sample size of 250 was achieved. This sample size was a conservative target, based on recommendations to assume a low level of agreement (such as 50%) and require high validity (such as 0.95%) when beginning a new study [24]. Drawing on Weller's [24] sample size and validity estimates for different levels of agreement, we assumed a sample size of 250 would allow us to detect a significant consensus model with 99% validity, even with a low-average level cultural competency score of 0.40, which is equivalent to an average 0.16 Pearson correlation coefficient between respondents, based on Weller's [24] estimates.

All participants were given a US $5 electronic gift card as compensation for their time.

The web-based instrument collected demographic information—campus, age, gender identity, sexual orientation, level in school, field or discipline or major, residency and housing status, and group membership (eg, part of sports or athletics or student government)—and asked the participants to rate the importance of items identified during the free-listing phase. For each domain (*How do students in your campus community know their partner is signaling sexual consent?How do students in your campus community signal their own sexual consent?What words would students in your campus community use to describe a sexual encounter that feels good?*), the

participants were presented with approximately 20 items derived from the free-listing phase and asked to rate the items from 1 to 7 to describe how important that item was as a strategy to recognize consent or signal consent or as a way of describing a positive sexual encounter. The participants were prompted to rank the level of importance of 24 options for question 1, 28 options for question 2, and 21 options for question 3. The complete survey is provided in Multimedia Appendix 1.

IDI and FGD Methodology

Recruitment of IDI and FGD Participants

Related to phase I participant recruitment, additional eligibility criteria for students included self-reported enrollment in an undergraduate, graduate, or professional program at UCLA, UCSD, or UCSB. UC faculty and staff were only eligible if they were currently employed by the UC and had been in that position for at least 6 months. Additional eligibility criteria for community stakeholders were currently working at a sexual violence–related, sexual harassment–related, or domestic violence–related service agency; having been in that position for at least 6 months; and having experience in helping students seeking violence-related services or support within the Los Angeles, San Diego, or Santa Barbara region. A subset of eligible UC students, staff, and faculty participants was selected based on key demographics (eg, gender identity, sexual orientation, race and ethnicity, year in program, type of program, and academic department) to attempt to achieve representation at the group (ie, student, staff, and faculty) and campus level. Related to phase II participant recruitment, additional eligibility criteria for student survivors included being currently enrolled at one of the 3 UC campuses or having graduated within the last 3 years and self-reporting experience of sexual assault, sexual harassment, stalking, or dating violence while enrolled as a UC student. Participants selected for inclusion were connected with a trained UC Speaks Up student, staff, or faculty researcher to schedule an IDI or FGD.

Structure of IDIs and FGDs and Compensation of Participants

IDI and FGD data were gathered using semistructured guides with open-ended questions that allowed for conversational inquiry on the research topics described above. Probes were used to elicit additional information or clarify responses. Phase I data collection occurred on campus in accessible and convenient locations where privacy could be ensured. In-person IDIs and FGDs during phase I were audio-recorded, and the participants received a US $25 Visa gift card in compensation for their time. Remote interviews with survivors during phase II have been conducted via the Zoom platform on a day and at a time agreed upon by both the researcher and participant. Participants in remote interviews are invited to use both audio and video features during the interviews but are assured that the video is voluntary. Remote IDI participants receive a US $50 electronic gift card in compensation for their time. Compensation is higher in phase II than in phase I as we estimated that (1) the interviews might last longer and (2) the interviews may be more taxing owing to the highly sensitive nature of sexual violence and the potential for increased risk of participants feeling distressed or triggered by discussing past

experiences. All IDI and FGD participants throughout the study are provided with a resource sheet unique to their campus with comprehensive details of on-campus and community-based services (based on information collected during the resource audit).

Phase I (February 2019-June 2019) IDIs With Students, Staff, Faculty, and Community Stakeholders

IDIs were conducted with students, staff, faculty, and community stakeholders. IDIs with students aimed to explore their attitudes about relationships and sex; their definitions of sexual violence, sexual harassment, and healthy relationships; and their awareness of available services, prevention programs, and policies addressing sexual violence at the university. We sought students' opinions on how they can become more involved in making the campus an environment that does not tolerate sexual or gender-based violence. IDIs with faculty, staff members, and university administrators examined how they perceive their role and their office's role in prevention, education, and response services addressing sexual violence. The IDIs also aimed to learn about the process they and their office take when a student discloses. IDIs with community stakeholders were structured to explore their relationship with their university counterparts and assess the services and programs they offer to UC students and the larger community. The interviews lasted, on average, between 60 and 90 minutes (SD 15 minutes).

Phase I (April 2019-June 2019) FGDs With Students

FGDs were conducted with students and aimed to understand group norms surrounding the campus environment and how students felt about campus safety, healthy socializing, and acceptance and rejection of relationship violence. We explored students' definitions of healthy versus unhealthy relationships and sex as well as sexual assault and sexual harassment. Each discussion was facilitated by a trained moderator and note-taker. FGDs allowed for discussion of general themes, including awareness of services and education activities, challenges in accessing care and services, and ideas for prevention messaging that resonated with them. FGDs lasted, on average, 90 (SD 30) minutes.

Phase I Data Analysis and Phase II Launch (AY 2019-2020)

Analysis

Overview

In September 2019, we started analyzing the phase I data. This process, together with data interpretation, report, and manuscript development and results dissemination (through workshops, meetings, and conferences), is ongoing. Analysis of phase II data with survivors has not yet started. Descriptive analyses have been or will be conducted for demographic variables gathered for all the participants. Simple frequency distribution statistics (eg, mean and proportion) will be conducted using Stata (version 15.1; StataCorp).

Aim 1: Assess Students' Perceptions of Sexual Consent

Aim 1 involved the analysis of CCM survey data, which has been completed. Interview and focus group discussion data analysis is also part of aim 1, some of which has been completed and the rest is ongoing.

CCM survey data were entered into R software (R Foundation for Statistical Computing) [28] and analyzed by gender, age, and housing status using AnthroTools to determine (1) whether there were clusters of similar item ratings (ie, cultural consensus models) either across the full group of students or by gender, age, or housing status and, if so, (2) what the culturally *correct* rating or importance of each item was. Consistent with the methods by Weller [24], we considered a cluster of similar answer ratings to represent a distinct cultural consensus model if the group's eigenvalue was >3.0.

All qualitative IDI and FGD data have been or will be analyzed using Dedoose (SocioCultural Research Consultants, LLC [29]), a mixed methods web-based analysis platform. Qualitative content analysis is used to generate substantive codes and subthemes that emerged from the data for all domains we are examining. Primary domains are predetermined based on the semistructured interview and focus group guides, and subtheme code identification was or will be informed using a thematic analysis approach. A coding tree was or will be developed by the team for each aim after iterative rounds of discussion around substantive codes that evolved into tangible themes. The codes produced were or will be organized into broad conceptual codes (ie, parent codes) and more refined subcodes (ie, child codes). Discrepancies in codes are resolved through group discussion. At least 2 reviewers coded each transcript to ensure interrater reliability.

Aim 2: Understand Students' Perceptions of the Campus Environment Related to Sexual Assault, Sexual Harassment, and Dating Violence

We analyze IDI and FGD data from student participants, starting with an exploration of students' definitions of healthy versus unhealthy relationships, sexual assault, sexual harassment, stalking, and dating violence, to achieve this aim. FGD data are examined to understand group norms surrounding the campus environment for safety, opportunities for healthy socializing, and sexual and relationship violence. All data are analyzed to assess perceptions of whether violence is a problem on campus, how students think the university handles and responds to violence, and what are the levels of awareness about sexual violence services and programs. Data from IDIs and FGDs with graduate students further examine how power relations with faculty and trust or distrust of university processes contribute to graduate students' decisions about seeking services. The data capture graduate students' recommendations for improving campus climate and SVSH resources to meet graduate students' needs.

Aim 3: Investigate Institutional and Community Arrangements Influencing Students' Lives and Experiences

To achieve this aim, we analyze IDI data from staff, faculty, and community stakeholders to gain a full picture of the services, protocols, and policies related to violence that are available on

the campuses and surrounding communities. We will assess how faculty and key university administrators perceive their roles in supporting survivors who disclose abuse, harassment, or discrimination or who want to report an incident to a professional, such as a Title IX coordinator or law enforcement officer. We aim to learn how UC faculty and staff perceive their preparedness to contribute to both prevention and response efforts and where they feel gaps remain so recommendations can be made on where additional training and support is required. Another key component of this aim is the analysis of data from community stakeholders to assess relationships between local violence prevention advocates and the UC and explore how these relationships can be strengthened to improve prevention of sexual violence in and around each campus.

Aim 4: Examine How Campus Prevention, Education, and Response Efforts Can Be Tailored to Meet the Unique Needs of Diverse Individuals and Communities

In response to the literature suggesting that students from racial, ethnic, gender, and sexual minority populations as well as students with disabilities are disproportionately burdened by SVSH [8-12], we will analyze IDI and FGD data from students, staff, and faculty to discern the needs and preferences regarding SVSH prevention and response among both the general population and historically marginalized groups. We explore unique cultural and contextual configurations that emerge in conversations about SVSH in these populations. We also assess potential SVSH-related stressors associated with unique identities and barriers to accessing or continuing the use of physical and mental health, psychosocial, and other SVSH services. These findings will facilitate the development of tailored programs for subgroups.

Aim 5: Learn About Student Survivors' Use and Perceptions of Campus- and Community-Based Violence and Mental Health Services

In-progress interviews with survivors will be transcribed, coded (as described above), and analyzed to explore survivors' experiences of SVSH while enrolled as UC students. Codes will be developed to assess the number, frequency, and types of and overlap between different forms of harm and to examine what impact these experiences had on survivors' lives. We will examine what actions survivors took after the incident or incidents, including disclosure, use of services, legal actions, and pursuit of criminal justice, and what their perceptions were of these experiences and interactions. Recommendations provided by survivors will be recorded and distributed to service providers and administrators. The findings will be assessed overall, by campus, and by specific subgroups (race, ethnicity, gender orientation and sexual identity).

Aim 6: Lay the Groundwork for Subsequent Quantitative Research and Effective Prevention Programs Coupled With Healing-Centered Comprehensive Response Services at Each Campus

Building on the findings from the first phase of UC Speaks Up, we launched the *Listening to UC Survivors Study*, which aims to interview student survivors of SVSH to create recommendations on how the UC response and prevention systems can be improved to create a safer learning environment.

In addition, 3 student-led qualitative research projects have been launched or are under development. *Double Jeopardy: Asian International Students' Experiences of Sexual Violence and Xenophobia during COVID-19* explores Asian international students' experiences of SVSH during their time in the United States both before and during the COVID-19 pandemic. This study has received institutional review board (IRB) approval and is in the data collection phase. A second study (under development) aims to address lesbian, gay, bisexual, transgender, and queer students' unique needs in relation to SVSH. A third study (also under development) addresses perceptions of how the COVID-19 pandemic has affected SVSH within the Greek community (fraternities and sororities) at UCLA. These 3 student-led studies will be described in detail elsewhere (ie, not in this paper).

Launch of Phase II: IDIs With Student Survivors (September 2020-Ongoing)

We are conducting IDIs with current and recently graduated (ie, within the past 3 years) students who experienced sexual assault, sexual harassment, or dating violence while enrolled at UCLA, UCSD, or UCSB. We plan to conduct approximately 30 IDIs with 10 survivors from each campus. These interviews aim to learn what services and programs student survivors use on their UC campus or in the surrounding community; hear their perspectives on what was most or least helpful when dealing with experiences of violence; and seek recommendations for how the UC system can improve in terms of both preventing and responding to violence, harassment, and discrimination.

Phase I Results Sharing and Phase II Ongoing (2020-Ongoing)

Phase I Results Sharing

The findings from phase I have been and continue to be presented at professional and academic conferences across the globe. Student-led subanalyses of phase I data include barriers to access to care, SVSH among historically marginalized communities, student-generated recommendations to improve universities' responses to SVSH, student athletes' perceptions of SVSH, and the relationship between alcohol consumption and SVSH. To date, 5 academic papers exploring results from UC Speaks Up have been either published or accepted for publication [30-34].

Phase II Ongoing

To date, 15 interviews have been completed with student survivors of SVSH. Recruitment will continue throughout the 2021-2022 AY. We planned to begin these interviews in March 2020 after completing the analysis of phase I data. However, owing to the COVID-19 pandemic, we did not start until September 2020 because of the need to revise our research protocol—from in-person to remote IDIs—and receive IRB clearance. We took a 6-month break from data collection between March and August 2021 owing to hardship related to the ongoing COVID-19 pandemic and resumed interviews in September 2021. All the phase II survivor interviews are being conducted via the web-based teleconferencing software Zoom using a secure link and password-protected meeting space.

Data Management and Quality Assurance

All interviews and FGDs were or will be transcribed verbatim from audio recordings either directly into a Word document or using the transcription platform, Trint [35]. Transcripts were or will be redacted to remove personal identifying information and stored in a shared, encrypted file. All data files were or will be reviewed and cleaned (as needed) by a data manager to ensure they are properly labeled and complete. If details were or are missing from a file (eg, a participant's demographics), the data manager tried or will try to locate this information to complete the file.

Although the study procedures are minimally invasive and present low risks to the participants, we established numerous safeguards and followed several precautions to protect participants and ensure data confidentiality. The participants are assigned a numeric personal ID number that is used as a reference to the participant instead of their name on all study data. This number delinks personal identifying information from the study databases. The names of the participants are kept in separate secure files. All paper data collection tools are stored in secure, locked facilities at UCLA, and only a small number of designated staff members have access to these records. All electronic data are stored in encrypted, password-protected files that are only accessible to the study's principal investigators.

Safe and Ethical Conduct of Human Subjects Research Approval

The study protocol for phase I was approved by the UCSD Human Research Protection Program (HRPP) (Approval number: 181722). Agreements to rely on the UCSD HRPP were approved by the IRBs at UCLA (Approval number: 18-001885) and UCSB (Approval number: 128-19OA-1). In July 2019, the UC Speaks Up principal investigator (the first author) relocated from UCSD to UCLA and the study protocol for phase II was submitted to and approved by the UCLA HRPP (Approval number: 20-000445). Since all interviews for phase II are being done remotely by UCLA researchers, the IRBs at UCSD and UCSB indicated reliance agreements were not required. Before working with the UC Speaks Up study, all research staff received training on the safe and ethical conduct of research on violence against women based on recommendations developed for the World Health Organization Multi-Country Study on Women's Health and Domestic Violence [36]. Staff also received training on the ethical conduct of human subject research, compliance, and data management via a collaborative institutional training initiative for biomedical research. Students who took part in the CCM free-listing provided verbal consent before participating. CCM survey participants consented on the web before starting the questionnaire. Phase I IDI and FGD participants provided written consent to take part in the data collection and have the session audio-recorded. Phase II IDI participants provided oral consent to take part in the data collection and have the session audio-recorded. A certificate of confidentiality was obtained from the National Institutes of Health to protect identifiable, sensitive research information from compulsory legal disclosure (eg, sexual assault).

Results

Free-Listing and Web-Based Survey Participants

Free-listing interviews were conducted with 149 students, and data were analyzed from 122 (81.9%) participants (input from 27/149, 18.1% of students was excluded for lack of data on age or because the participants were aged >26 years). Unique item responses were tallied for partners' signals of consent (n=149), students' own signals of consent (n=209), and students' descriptions of a *good* sexual encounter (n=277). Most (119/149, 80%) of the students who participated were undergraduates, and 20% (30/149) were graduate or professional students. Ages ranged from 18 to 26 years, and the mean age was 21 (SD 2.4) years. Approximately 60% (84/149) identified as the female gender, and 40% (61/149) identified as the male gender.

Web-based surveys were completed by 214 students (177/214, 83% undergraduate and 37/214, 17% graduate and professional) from UCLA (43/214, 20%), UCSD (77/214, 36%), and UCSB (94/217, 44%). The participants identified their race and ethnicity as Asian (104/217, 42%), White (83/217, 33%), Latinx or Spanish or Hispanic (34/214, 14%), Black or African American (11/214, 4%), Native Hawaiian (5/214, 2%), and Indigenous or Native American (1/214, 1%). In terms of gender and sexual identity, 61% (131/214) identified as female, 38% (81/214) identified as male, and 1% (2/214) identified as nonbinary. Approximately 76% (163/214) identified as heterosexual or straight, and 24% (43/214) identified as lesbian; gay; bisexual; transgender; queer or questioning; intersex; asexual; and all other sexualities, sexes, and genders (LGBTQIA+).

No consensus was found among students with regard to their understanding of any type of sexual consent. We interpreted this finding to suggest that there is wide variation in students' conceptions of what sexual consent is and how it is signaled by a partner. It also indicates that students may refrain from talking with their peers about how to signal consent or interpret their partner's consent signals. We used these findings to inform the development of our IDI and FGD guides, to include questions to assess students' lived experiences of making (or not making) agreements with partners to participate in a sexual activity, and to inquire about the process of setting personal boundaries and respecting those of a partner.

Interview Participants Enrolled in Phase I

A total of 179 IDIs were conducted with 86 (48%) undergraduate students, 21 (11.7%) graduate and professional students, 34 (19%) staff and administrative members, 27 (15.1%) faculty members, and 11 (6.1%) community stakeholders (Table 1).

A total of 86 undergraduate student IDI participants were recruited from UCLA (26/86, 30%), UCSD (30/86, 35%), and UCSB (30/86, 35%) and included first- (21/86, 24%), second- (20/86, 23%), third- (20/86, 23%), fourth- (21/86, 24%), and fifth-year (4/86, 4.6%) students. The participants were drawn from majors in the humanities, social sciences, and arts (32/86, 37%) as well as science, technology, engineering, and math (54/86, 63%). Slightly more than half (47/86, 55%) identified

as cisgender women; 39% (34/86) identified as cisgender men; and 6% (5/86) identified as agender, nonbinary, or transgender. Most (62/86, 72%) identified as heterosexual, 11% (9/86) identified as bisexual, 8% (7/86) identified as lesbian or gay, 4% (3/86) identified as pansexual, 3% (2/86) identified as nonconforming, and 3% (3/86) identified as asexual or mostly heterosexual. The participants identified as White (30/86, 35%), Asian (20/86, 23%), Latinx or Spanish or Hispanic (14/86, 16%), Black or African American (11/86, 12%), South Asian or Indian (3/86, 3%), Middle Eastern (4/86, 5%), and more than one race (4/86, 5%). Only 3% (2/86) of the participants reported living with a disability.

A total of 21 graduate and professional student IDI participants were recruited from UCLA (8/21, 38%), UCSD (6/21, 29%), and UCSB (7/21, 33%) and included students enrolled in master's degree programs (8/21, 38%) and doctoral degree programs, including doctor of philosophy (9/21, 43%), doctor of medicine (3/21, 14%), and juris doctor (1/21, 5%). Graduate and professional students were from the fields of bioengineering, bioinformatics, biology, communications, economics, education, engineering, fine arts, law, materials, medicine, public health, and sociology. Most (13/21, 62%) identified as cisgender women, 28% (6/21) identified as cisgender men, 5% (1/21) identified as agender, and 5% (1/21) identified as nonbinary. Approximately 57% (12/21) identified as heterosexual, 24% (5/21) identified as bisexual, 9% (2/21) identified as lesbian or gay, 5% (1/21) identified as asexual, and 5% (1/21) identified as nonconforming. By race and ethnicity, the participants identified as White (9/21, 43%), Asian (7/21, 33%), Latinx or Spanish or Hispanic (3/21, 14%), Black or African American (1/21, 5%), and more than one race (1/21, 5%). Approximately 10% (2/21) were living with a disability.

A total of 34 staff members were recruited from UCLA (11/34, 32%), UCSD (13/34, 38%), and UCSB (10/34, 29%) and included health and well-being service providers (7/34, 21%); athletic department staff (8/34, 25%); and staff from student affairs (6/34, 18%), academic departments (3/34, 9%), and student resources (10/34, 29%). Health and well-being service providers included clinicians, therapists from Counseling and Psychological Services, and sexual violence service providers from CARE. Athletic department staff included directors,

coaches, and administrators. Student affairs staff held positions such as Dean of Student Affairs and Student Life Development Specialist. Student resource staff held positions such as Director of the Undocumented Student Services Center. Most staff (23/34, 68%) identified as cisgender women, 26% (9/34) identified as cisgender men, and 6% (2/34) identified as nonbinary. Approximately 58% (20/34) identified as heterosexual, 21% (7/34) identified as lesbian or gay, 16% (5/34) identified as gender nonconforming, and 5% (2/34) identified as asexual. Staff identified as White (18/34, 52%), Asian (2/34, 5%), Latinx or Spanish or Hispanic (5/34, 16%), Black or African American (5/34, 16%), Middle Eastern (2/34, 5%), and more than one race (2/34, 5%). Approximately 11% (4/34) were living with a disability.

A total of 27 faculty members were recruited from UCLA (8/27, 30%), UCSD (9/27, 33%), and UCSB (10/27, 37%) and included people from public health (3/27, 12%); science, technology, engineering, and math (10/27, 38%); and the humanities, social sciences, and arts (14/27, 50%). A range of disciplines were represented, such as Epidemiology, Psychiatry, World Arts and Cultures, Asian American Studies, English, Biology, Pharmacy, Engineering, Literature, Cognitive Science, and Philosophy. Most of the faculty interviewed were full professors (18/27, 65%), followed by associate professors (6/27, 23%) and assistant professors (3/27, 12%). Most chose not to disclose their race and ethnicity, gender identity, and sexual orientation. Thus, we do not report these statistics for this group.

A total of 11 stakeholders were recruited from the communities surrounding UCLA (3/11, 27% of participants), UCSD (4/11, 36% of participants), and UCSB (4/11, 36% of participants). In Los Angeles, we interviewed stakeholders from the Rape Treatment Center at the UCLA Medical Center in Santa Monica, the Center for the Pacific Asian Family, and Peace Over Violence. In San Diego, we interviewed stakeholders from the Institute on Violence, Abuse, and Trauma; Alliance for Hope International; Love on a Leash; and the Center for Community Solutions. In Santa Barbara, we interviewed stakeholders from the office of the Santa Barbara District Attorney Victim-Witness Assistance Program, Stand Together to End Sexual Assault, Domestic Violence Solutions, and an independent trauma therapist who frequently serves students at UCSB.

Table 1. Number of in-depth interviews (IDIs) conducted, classified by University of California campus and participant type (N=179).

Participant type	Campus		
	UCLA[a] (n=56)	UCSD[b] (n=62)	UCSB[c] (n=61)
Undergraduate students (n=86), n (%)	26 (30)	30 (35)	30 (35)
Graduate and professional students (n=21), n (%)	8 (38)	6 (29)	7 (33)
Staff (n=34), n (%)	11 (32)	13 (38)	10 (29)
Faculty (n=27), n (%)	8 (30)	9 (33)	10 (37)
Community stakeholders (n=11), n (%)	3 (27)	4 (36)	4 (36)

[a]UCLA: University of California, Los Angeles.

[b]UCSD: University of California, San Diego.

[c]UCSB: University of California, Santa Barbara.

FGD Participants

A total of 35 FGDs (10/35, 29% at UCLA; 13/35, 37% at UCSD; and 12/35, 34% at UCSB) were conducted with 201 total participants. Of the 35 FGDs, 27 (77%) were completed with undergraduate students, and 8 (23%) were completed with graduate and professional students. Table 2 shows the breakdown by participant type of the FGDs conducted across the 3 campuses.

A total of 27 FGDs (27/35, 77%) were conducted with undergraduate students recruited from UCLA (8/27, 30%), UCSD (9/27, 33%), and UCSB (10/27, 37%). A total of 158 students were involved in these FGDs (36/158, 22.8% from UCLA; 61/158, 38.6% from UCSD; and 61/158, 38.6% from UCSB). Groups with members of sororities and fraternities, National Collegiate Athletic Association athletes, and engineering students were conducted separately by gender identity. Undergraduate *student leaders* included participants involved in student government (eg, the Undergraduate Students

Association Council) and other campus-based leadership positions (eg, the Student Leadership Council). An undergraduate FGD was conducted on the UCLA campus with SVSH prevention leaders, including student interns from the CARE office, members of the Bruin Consent Coalition, and a Title IX policy special interest group. On average, the undergraduate student focus groups had 8 (SD 2) participants.

A total of 8 FGDs (8/35, 23%) were conducted with graduate and professional students recruited from UCLA (2/8, 25%), UCSD (4/8, 50%), and UCSB (2/8, 25%). A total of 43 students were involved in these FGDs (12/43, 28% from UCLA; 22/43, 51% from UCSD; and 9/43, 21% from UCSB). Groups conducted with FGD participants from the liberal arts included master's- and doctoral-level students from the natural sciences, social sciences, arts, and humanities. Health profession students were drawn from graduate programs in medicine, nursing, dentistry, pharmacy, and public health. On average, the graduate and professional student FGDs had 6 (SD 2) participants.

Table 2. Number of focus group discussions (FGDs) conducted, classified by University of California campus and participant type (N=35).

Participant type	Campus		
	UCLA[a] (n=10)	UCSD[b] (n=13)	UCSB[c] (n=12)
Undergraduate students (n=27)			
Sorority and fraternity members (n=5), n (%)	1 (20)	2 (40)	2 (40)
NCAA[d] athletes (n=7), n (%)	2 (29)	3 (43)	2 (29)
LGBTIA+[e] students (n=3), n (%)	1 (33)	1 (33)	1 (33)
Student leaders (n=3), n (%)	1 (33)	1 (33)	1 (33)
Black students (n=2), n (%)	0 (0)	1 (50)	1 (50)
Latinx students (n=2), n (%)	0 (0)	1 (50)	1 (50)
Engineering students (n=2), n (%)	0 (0)	0 (0)	2 (100)
SVSH[f] prevention leaders (n=2), n (%)	2 (100)	0 (0)	0 (0)
General population (n=1), n (%)	1 (100)	0 (0)	0 (0)
Graduate and professional students (n=8)			
LGBTIA+ students (n=2), n (%)	0 (0)	1 (50)	1 (50)
Liberal arts students (n=2), n (%)	1 (50)	1 (50)	0 (0)
Health profession students (n=1), n (%)	0 (0)	1 (100)	0 (0)
Male graduate students (n=1), n (%)	0 (0)	0 (0)	1 (100)
STEM[g] students (n=2), n (%)	1 (50)	1 (50)	0 (0)

[a]UCLA: University of California, Los Angeles.

[b]UCSD: University of California, San Diego.

[c]UCSB: University of California, Santa Barbara.

[d]NCAA: National Collegiate Athletic Association.

[e]LGBTIA+: lesbian; gay; bisexual; transgender; intersex; asexual; and all other sexualities, sexes, and genders.

[f]SVSH: sexual violence and sexual harassment.

[g]STEM: science, technology, engineering, and math.

Student Survivor Interview Participants Enrolled in Phase II (Ongoing)

To date, 15 participants have been enrolled and interviewed from UCLA (5/10, 50%), UCSD (5/10, 50%), and UCSB (5/10,

50%). Recruitment is ongoing. However, as the COVID-19 pandemic shifted the climate in which survivors experience and respond to sexual and other forms of relationship misconduct, we made revisions to our research materials (requiring additional

IRB approvals and delays) to be more salient to survivors' current lived experiences.

Discussion

IPV and sexual violence remain important public health and social justice issues on college and university campuses across the United States. The mission of the UC Speaks Up research is to understand the factors shaping intimate relationships and sexual and interpersonal violence among students at UCLA, UCSD, and UCSB and use the findings to develop and test prevention and response interventions (including policy updates) to improve the health, safety, and well-being of all members of the UCLA, UCSD, and UCSB communities. Access to evidence from each campus will leverage our ability to make specific recommendations for tailoring response systems (eg, advocacy offices for survivors) and primary prevention approaches to ensure they are relevant and acceptable to and meet the needs of all individuals in the campus community, including those who are typically understudied.

The findings will also be used to prepare for rigorous public health prevention research on SVSH across the entire UC system. As the most comprehensive and advanced postsecondary educational system in the world [17], representative survey research is warranted across all 10 UC campuses. However, only 1 UC campus has previously conducted a focused SVSH climate study. We hope this protocol paper and our preliminary results as well as the findings from the UC Speaks Up research will build on the research tools of the MyVoice Working Group [19] and highlight the significant need for implementation of additional SVSH prevention research across the UC system.

We acknowledge several limitations inherent to this project. First, owing to purposive sampling, the samples might not be representative of each campus population. Therefore, our results might not be generalizable to the larger UC population or to other universities (eg, private schools and schools with smaller populations and in more rural settings). Second, some of our study's participant groups (such as undocumented students, male athletes, and fraternity members) were difficult to reach and are not as represented in the sample even with increased efforts using snowball sampling. Thus, their perspectives may not be fully reflected in our findings, and we recommend that future studies consider oversampling these and other hard-to-reach populations to ensure that their unique perspectives are included. The COVID-19 pandemic also introduced a substantial challenge to our research plan and essentially stopped our data collection for the UC Survivors Study. We have tried to compensate for this gap in study flow by resuming fieldwork during the 2021-2022 AY and adapting our research instruments to assess the impact of the pandemic on SVSH.

Notwithstanding the limitations of our ongoing research, we feel the UC Speaks Up Project has and continues to increase our understanding of how we can better prevent and respond to sexual violence and misconduct on the UC campuses as well as at other institutions of higher education in the United States. The COVID-19 pandemic creates new challenges pertaining to social dynamics on college and university campuses, and epidemiological and social science research is currently more important than ever to ensure that SVSH prevention programs and support services can be tailored to meet the changing needs of survivors and their allies.

Authors' Contributions

All authors contributed to this paper. JAW, DS, RFM, JS, and SB had lead roles in the study design. JAW led the writing of all sections of the manuscript. CA, SS, and EP led the implementation of the study and were major contributors to writing the manuscript, specifically the *Methods* and *Results* sections, and the development of the tables. JAW, CA, SS, and EP all contributed to data collection. LO, CA, SS, DS, and RFM reviewed and substantially edited the manuscript. All authors contributed to the refinement of the protocol and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The Web-Based Cultural Consensus Model Survey.
[PDF File (Adobe PDF File), 62 KB - resprot_v11i4e31189_app1.pdf]

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Abbreviations

AY: academic year
CARE: Campus Assault Resources and Education
CCM: cultural consensus modeling
FGD: focus group discussion
HRPP: Human Research Protection Program
IDI: in-depth interview
IPV: intimate partner violence
IRB: institutional review board
LGBTQIA+: lesbian; gay; bisexual; transgender; queer or questioning; intersex; asexual; and all other sexualities, sexes, and genders
SVSH: sexual violence and sexual harassment
UC: University of California
UCLA: University of California, Los Angeles
UCSB: University of California, Santa Barbara
UCSD: University of California, San Diego
VAWC: violence against women and children
WHGE-COE: Women's Health, Gender, and Empowerment Center of Expertise

Protocol

Simulation-Based Learning Supported by Technology to Enhance Critical Thinking in Nursing Students: Protocol for a Scoping Review

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Abstract

Background: Critical thinking is a crucial skill in the nursing profession, so teaching strategies and methodology must be carefully considered when training and preparing nursing students to think critically. Studies on simulation-based learning supported by technology are increasing in nursing education, but no scoping reviews have mapped the literature on simulation-based learning supported by technology to enhance critical thinking in nursing students.

Objective: The proposed scoping review aims to systematically map research on the use of simulation-based learning supported by technology to enhance critical thinking in nursing students.

Methods: The proposed scoping review will use the framework established by Arksey and O'Malley and will be reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension for scoping reviews. A systematic, comprehensive literature search was performed in the LILACS, ERIC, MEDLINE, EMBASE, PsycINFO, and Web of Science databases. Pairs of authors independently selected the articles by screening titles, abstracts, full-text papers, and extract data. The data will be analyzed and thematically categorized.

Results: The development of a comprehensive and systematic search strategy was completed in June 2021. The database searches were performed in July 2021, and the screening of titles and abstracts was completed in September 2021. Charting the data began in February 2022. Analysis and synthesis will be performed sequentially, and the scoping review is expected to be complete by May 2023.

Conclusions: The results of this proposed scoping review may identify gaps in the literature and provide an overview of research on the topic of simulation-based learning supported by technology to enhance critical thinking in nursing students. The research may identify nursing students' reported barriers and enablers for learning critical thinking skills through simulation-based learning supported by technology, and the results may help educators enhance their educational approach through knowledge of students' firsthand experiences and further development of successful teaching strategies in nursing education.

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Introduction

Educational Approaches for Active Learning in Nursing Education

Active teaching methods are recognized as educational approaches by which teachers support students in the development of critical thinking (CT) [1,2]. One strategy for developing CT is to allow nursing students to actively participate in the learning process with the support of technology. Simulation-based learning (SBL) is a teaching strategy that may enhance the integration of theoretical and practical knowledge and the ability to reflect and to give and receive feedback [3,4]. Scientific evidence reveals that active learning strategies are more effective for developing CT skills for students in higher education than passive learning under traditional methods, such as lectures [2,5]. With the advent of the COVID-19 pandemic and its resultant social distancing requirements, the interest in, demand for, and use of technological solutions have increased in nursing education [6].

Critical Thinking in Nursing Education

CT is a crucial skill and a fundamental component of nurses' daily professional responsibilities. Nurses require CT skills to analyze, summarize, and evaluate information and initiate action. CT skills enable nurses to manage uncertainties in nursing practice and contribute to safe and effective care across diverse clinical settings [7-9]. Several definitions and terms for CT are used interchangeably in nursing studies, research, and nursing curricula [10,11]. The core components of CT are to be able to analyze, evaluate, and investigate [12]. Because there is no consensus on the definition of CT in nursing education research, research often looks to other disciplines like philosophy, psychology, and education for clear definitions [10]. A frequently cited definition in nursing studies is the one by a consensus statement of the American Philosophical Association, which defines CT as "a judgment which is purposeful and self-regulatory and results in a process of interpretation, analysis, evaluation, and inference, as well as explanation of the evidential, conceptual, methodological, criteriological, or contextual considerations upon which that judgment is based" [13]. According to Riegel and Crossetti [14], CT is driven by internal motivation, which is reflective in nature and involves self-monitoring and self-correction. This process develops a reflective judgment on what to do, believe, or make sense of in any context.

Several distinct terms are currently used in studies exploring the outcome of CT in SBL, such as *clinical problem-solving*, *clinical decision-making*, *clinical reasoning,* and *handling clinical deterioration* [4,11,15].

In this proposed scoping review, the terms *clinical decision-making*, *analytical thinking*, *creative thinking*, *problem-solving*, *reflective thinking*, *diagnostic reasoning,* and *clinical judgment* are all potential synonyms of CT. Teaching CT is the responsibility of nurse educators [16], and teaching strategies and methodology must be carefully considered to meet the purpose of preparing pre- and postgraduate nursing students to think critically and manage the uncertainty of the nursing profession [10,12,17].

Simulation-Based Learning

Reflection and CT skills may be developed through learning activities with high-quality teaching strategies, such as SBL [7,10]. SBL facilitates learning in a safe environment with the opportunity to gain experience and practice without the risk of doing harm to the patient [3]. Bland et al [18] define SBL as "a dynamic process involving the creation of a hypothetical opportunity that incorporates an authentic representation of reality, facilitates active student engagement, and integrates the complexities of practical and theoretical learning with opportunity for repetition, feedback, evaluation, and reflection." SBL is commonly founded on social constructivism and learning theory, which view knowledge as being constructed in a social context [19]. Within this framework, the traditional teacher-student relationship, in which knowledge is transferred from teacher to student, shifts to a learner-centered, teacher-guided approach [9,20]. SBL can potentially replicate clinical practice, in which the learner must employ clinical reasoning with cognitive, psychomotor, and affective skills [15]. According to the International Nursing Association for Clinical Simulation and Learning (INACSL) Standards Committee [21] self-monitoring, conscious reflection, and insightfulness occur in SBL through debriefing, feedback, and guided reflection. This process may help learners understand their own actual practice; identify knowledge gaps; increase competence; and support the transfer of knowledge, skills, and attitudes. Learners' insights may be developed through conscious reflection that connects actions, thoughts, and beliefs.

In traditional SBL, high-tech modalities, including advanced simulators (eg, life-size patient manikins), replicate real patients and settings in health care [22]. In simulation research, the term *fidelity* traditionally describes the degree to which the advanced simulator looks, acts, and feels like a human being, with an emphasis on technological features and advances that enhance the physical resemblance [23].

Other simulation research focuses on different aspects of realism with a physical, semantic, and phenomenal dimension, but what constitutes realism depends on what makes sense for the individual in a given context or situation [24,25].

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To enhance learning, scholars recommend focusing on learner engagement and correspondence between the simulation technology and the surroundings (the applied context) [23].

Simulation-Based Learning Supported by Technology

Technological solutions to support SBL in nursing education are continually expanding [4], ranging from advanced physical simulators with human features and responses to computer and online games, simulation games, and virtual reality (VR). Simulation gaming for nursing education has emerged in many forms and reportedly offers potential as a teaching strategy for stimulating CT [26,27]. Producers offer specific software that enables virtual computer simulations, and there are online solutions including computer games, virtual simulations, and VR intended for nursing education. Immersive VR uses special headsets that immerse the student in a virtual world [28-30] and has the advantage of replicating the clinical environment and patient-nurse interactions in situations designed to promote specific learning outcomes [26]. Cant and Cooper [29] conclude that internet simulation measures up to other simulation approaches and will likely be a large part of the nursing curriculum in the near future.

SBL supported by technology can ensure equitable learning opportunities by providing the same content and learning environment to all students. The potential for individual training and multiple iterations through technology makes SBL resource-efficient due to its low staff costs [27,31,32]. Due to technological advances, SBL no longer requires a physical meeting space. In virtual meetings, students and teachers can discuss and reflect on dilemmas and situations experienced in simulated or clinical practice. According to the principles of metacognition, this can encourage CT. Technology-supported learning methods can stimulate dialogue between students and teachers, adjusting students' learning focus and ensuring an accurate assessment of learning outcomes [33]. Importantly, in the context of current and future pandemics, technology provides an environment for teaching vital CT skills that is contactless and thus at low risk of spreading infectious disease [32].

Background for the Scoping Review

A literature review by Adib-Hajbaghery and Sharifi [34] found uncertainties about the effect of SBL on the CT of nursing students and nurses. Their findings are supported by a recent systematic review that examined extant evidence of simulation's effectiveness in promoting clinical reasoning skills in nursing education [15]. The authors of this systematic review conclude that insufficient evidence exists to form conclusions. They found a lack of substantial evidence for the cause-effect relationship of simulation training and CT due to the great heterogeneity of the studies, including diverse methods, scenarios, and measurement instruments [15,34]. The heterogeneity of studies makes it challenging to compare results and reach a consensus regarding SBL's effect on CT. Systematic reviews have also noted a lack of comparative studies that could report a quantitative, overall effect of SBL [30,34]. A systematic review of randomized controlled trials (RCTs) found that SBL may improve the acquisition of CT knowledge as well as students' reported satisfaction with teaching, but the authors note a lack of unambiguous evidence of SBL's effectiveness [35].

Reviews have also examined the use of technology in nursing education and SBL with diverse outcomes. A scoping review by Duff et al [28] examined the use of online virtual simulation to enhance clinical reasoning in the education of health care professionals and found online virtual simulation to be comparable or superior to traditional simulation. However, only 3 of the 12 included studies related to nursing education.

A systematic mapping review by Plotzky et al [32] examined the use of VR in nursing education, but the review was limited to the use of VR technology from didactic and technical perspectives and did not report on the outcome of CT. According to a recent systematic review, VR provides educational outcomes similar or superior to traditional SBL practices, but the evidence is limited [36]. Another literature review concluded that most evidence indicates that virtual simulation can effectively improve skills, learning, and CT in nursing education [4], but CT was the least explored outcome, and the search used only two databases, PubMed and CINAHL. Moreover, only articles in English were included, which is an important limitation of the results.

The identified reviews did not thoroughly examine the range and use of technology in SBL to enhance nursing students' CT skills. Furthermore, the identified reviews mainly included research presented in the English language, except two reviews that included studies in Farsi and German. A broad, comprehensive literature review, such as a scoping review that includes papers in several languages (English, Portuguese, Spanish, and the Scandinavian languages) and employs diverse research methods will enable us to examine the nature and range of the currently available research and to identify potential gaps in the research literature [37]. To our knowledge, no scoping review has examined the range of technology used in SBL and how it is used to enhance nursing students' CT skills.

Consequently, this scoping review aims to systematically map research on the use of SBL supported by technology to enhance CT in nursing students. The results may identify potential gaps in research and inform further research on this topic.

Identifying the Research Questions

The scoping review will answer the following research questions:

- What is the range of technology used in SBL to enhance CT skills in nursing education?
- How is technology used in SBL to enhance CT skills in nursing education?
- What do nursing students report as perceived barriers and enablers to enhance CT skills in SBL supported by technology?

Methods

Overview Of Method for Conducting the Scoping Review

The proposed scoping review will follow Arksey and O´Malley´s [37] framework, which includes the following steps: (1) identifying the research questions; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; and (5)

collating, summarizing, and reporting the results. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension for scoping reviews will guide the reporting of the proposed review [38]. The reporting of this protocol is guided by the PRISMA Protocol (PRISMA-P) [39].

Identifying Relevant Studies

The Sample, Phenomenon of Interest, Design, Evaluation, and Research (SPIDER) framework determined the inclusion and exclusion criteria as outlined in Table 1 [40].

Table 1. Eligibility criteria according to the Sample, Phenomenon of Interest, Design, Evaluation, and Research (SPIDER) framework.

Criterion	Inclusion	Exclusion
Sample (S)	• Papers studying undergraduate and postgraduate nursing students.	• Papers studying health care students other than nursing students.
Phenomenon of interest (PI)	• Using SBL[a] supported by technology to stimulate CT[b], clinical decision-making, analytical thinking, creative thinking, problem solving, reflective thinking, diagnostic reasoning, or clinical judgement in educational/institutional contexts. • SBL supported by technology, including manikin-based, virtual reality, online virtual simulation, augmented reality, or computer-based simulation.	• SBL that does not use technology. • SBL using technology but not related to CT or similar concepts. • SBL in clinical practice not related to education.
Design (D)	• Studies with quantitative, qualitative, or mixed-methods design.	N/A[c]
Evaluation (E)	• Undergraduate and postgraduate nursing students' perspectives and experiences regarding the use of technology in SBL to stimulate CT or similar concepts.	• Nurse educators' perspectives and experiences regarding the use of technology in SBL to stimulate CT.
Research type (R)	• Studies of any research type published in Portuguese, Spanish, English, Norwegian, Swedish, or Danish published in peer-reviewed journals.	• Case studies, case reports, clinical guidelines, all types of reviews, and master's and PhD theses, conference proceedings and abstracts, letters, comments, discussion editorials, and book chapters.

[a]SBL: simulation-based learning.

[b]CT: critical thinking.

[c]N/A: not applicable.

Selecting Studies

A systematic search was conducted in the LILACS, ERIC, CINAHL, MEDLINE, EMBASE, PsycINFO, and Web of Science databases on June 28, 2021. Each database was searched from its inception. The database search will be updated approximately 3 months prior to publication.

The search strategy in Ovid MEDLINE, using Medical Subject Headings and text words, was designed by the first research librarian (author MAØ) in collaboration with the rest of the research team and embraced three elements: (1) SBL, (2) technology, and (3) nursing students and nursing education. A second research librarian (KLM) reviewed the search strategy using the Peer Review of Electronic Search Strategies (PRESS) checklist [41]. The search strategy in Ovid MEDLINE is provided in Multimedia Appendix 1. We also performed manual searches in the reference lists of the included papers. We did not perform forward tracking (citation searches). We will conduct the entire search a second time around 3 months prior to submission; most of these studies will probably be identified without using forward tracking.

MAØ exported the identified citations into EndNote to remove duplicates using the method described in Bramer et al [42], and the citations were then exported to the web application Rayyan

for storage, organization, and blinding of the study selection process. A pilot test of 10% of the citations to screen titles and abstracts was performed independently by authors HVS and AAGN, who concluded that the eligibility criteria did not require modification. Pairs of authors (HVS-CFA, SCWL-SAS, MTS-JZ, AGCM-FR, PB-JGM, ALS-CSL, CO-HVS, and IP-AAGN) independently screened paper titles and abstracts to assess whether they met the inclusion criteria. When there was any doubt regarding inclusion, a third author independently assessed the full-text paper, and the decision was based on a negotiated consensus. Further, the same pairs of authors will independently assess whether the full-text papers meet the inclusion criteria. When there is any doubt regarding inclusion, a third author will independently assess the full-text paper, and the decision will be based on a negotiated consensus. The reasons for excluding full-text papers will be recorded, and the study selection process will be recorded using the PRISMA 2020 flow diagram.

Charting the Data

A standardized data collection form will be developed in Microsoft Word for data extraction from the included papers, including authors, year, country, aim, sample, design, technology, simulation procedures, scenario design, and results related to the research question. The data collection form will

be piloted by HVS and AAGN on up to five of the included papers. Their experiences will be discussed with the entire research team, and the data collection form may be revised.

Pairs of authors will extract the data, with one author extracting the data and the other checking its accuracy. Disagreement among pairs of authors will be resolved by an assessment by a third author, and agreement will be based on negotiated consensus.

Collating, Summarizing, and Reporting the Results

HVS, SAS, MTS, and AAGN will analyze the results from the included papers and will use an inductive approach to organize the results thematically, a method previously used in scoping reviews [43,44]. The results extracted from the included papers will be read several times to identify patterns of similarities and differences related to the research questions, and these patterns will be organized in thematic groupings. The preliminary thematic groupings will be discussed with the rest of the research team, and a frequency table showing which papers appear in which thematic groupings will be created. Any new findings from the replicated search will be analyzed to see if they fit according to the thematic groups or if new thematic groupings arise.

Ethics Approval

No ethical board approval is necessary to conduct this scoping review.

Results

The development of a comprehensive, systematic search strategy was completed in June 2021. The database searches were performed in July 2021, and the screening of titles and abstracts was completed in September 2021. Assessment of full-text papers, charting of the data, and summarizing the results began in February 2022. We anticipate that the scoping review will be completed by May 2023.

Discussion

The results of the proposed scoping review will identify and provide an overview of the research on using SBL supported by technology to enhance CT in nursing students. This scoping review may also identify the variety of technological solutions available for nursing education and describe how they are used to enhance the development of nursing students' CT skills. Scoping searches have found reviews on the topic of simulation and CT in nursing education [15,30,34,35], but those reviews do not specifically report on the use of technology to support SBL to enhance CT. Reviews on SBL technologies have also been identified, which often investigate one type of technology or compare the use of technology to traditional SBL [27,29,31].

The outcome of CT is present, but not as the primary outcome for nursing students [28]. The identified reviews do not sufficiently report on the range of technology used and how technology is used in SBL to enhance CT skills in nursing students. Furthermore, the reviews do not adequately reference the outcome of enhancement of CT in nursing students. Strengths and limitations will be thoroughly examined and reported in the proposed scoping review. Limitations may be related to the inclusion criteria, by only including research studies and thus excluding grey literature. Mapping research in multiple languages may add strength to this proposed scoping review, as the exclusion of studies published in other language than English was reported as a limitation in previous scoping reviews [45].

Identifying the status of and gaps in the research in this field may contribute to future research and further the development of successful teaching strategies in nursing education. The findings may inform educators' decisions when choosing technology to support the application of SBL, and identifying nursing students' barriers or enablers to learning CT skills through technology-supported SBL may help educators devise their educational approaches. The results of this scoping review may also interest technology developers and guide the further development of technology-based solutions for SBL aimed at enhancing nursing students' CT in nursing education. The results of this proposed scoping review will be disseminated through publication in relevant peer-reviewed journals in educational or nursing-specific contexts.

Authors' Contributions

HVS, SAS, MTS, and AAGN contributed to developing the protocol. HVS drafted the manuscript's Introduction, Background, Results, and Discussion sections, and SAS drafted the Methods. All the aforementioned authors contributed to reading and editing the manuscript, and the extended group of authors was invited to read and review the draft. All authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy in Ovid MEDLINE.
[DOCX File , 27 KB - resprot_v11i4e36725_app1.docx]

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Abbreviations

CT: critical thinking
INACSL: International Nursing Association for Clinical Simulation and Learning

PRESS: Peer Review of Electronic Search Strategies
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
SBL: simulation-based learning
SPIDER: Sample, Phenomenon of Interest, Design, Evaluation, and Research
VR: virtual reality

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Protocol

Conversational Agents in Health Education: Protocol for a Scoping Review

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Abstract

Background: Conversational agents have the ability to reach people through multiple mediums, including the online space, mobile phones, and hardware devices like Alexa and Google Home. Conversational agents provide an engaging method of interaction while making information easier to access. Their emergence into areas related to public health and health education is perhaps unsurprising. While the building of conversational agents is getting more simplified with time, there are still requirements of time and effort. There is also a lack of clarity and consistent terminology regarding what constitutes a conversational agent, how these agents are developed, and the kinds of resources that are needed to develop and sustain them. This lack of clarity creates a daunting task for those seeking to build conversational agents for health education initiatives.

Objective: This scoping review aims to identify literature that reports on the design and implementation of conversational agents to promote and educate the public on matters related to health. We will categorize conversational agents in health education in alignment with current classifications and terminology emerging from the marketplace. We will clearly define the variety levels of conversational agents, categorize currently existing agents within these levels, and describe the development models, tools, and resources being used to build conversational agents for health care education purposes.

Methods: This scoping review will be conducted by employing the Arksey and O'Malley framework. We will also be adhering to the enhancements and updates proposed by Levac et al and Peters et al. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews will guide the reporting of this scoping review. A systematic search for published and grey literature will be undertaken from the following databases: (1) PubMed, (2) PsychINFO, (3) Embase, (4) Web of Science, (5) SCOPUS, (6) CINAHL, (7) ERIC, (8) MEDLINE, and (9) Google Scholar. Data charting will be done using a structured format.

Results: Initial searches of the databases retrieved 1305 results. The results will be presented in the final scoping review in a narrative and illustrative manner.

Conclusions: This scoping review will report on conversational agents being used in health education today, and will include categorization of the levels of the agents and report on the kinds of tools, resources, and design and development methods used.

International Registered Report Identifier (IRRID): DERR1-10.2196/31923

Introduction

Background

Conversational agents (CAs) are increasingly being used in various industries, including education, entertainment, and health [1]. CAs are also starting to become commonplace in formal health care settings to assist with simple functions, such as appointment scheduling and health monitoring [2,3]. As technology has progressed to enable CAs to engage in natural dialogue, we are starting to see CAs become attractive alternatives for things that have traditionally required human-to-human interaction [4]. This has enabled deployment of CAs to address more complex concerns, such as mental health support [5,6] and patient education [7,8], and in other areas in which the aim is to promote behavior change [9]. One appealing factor is the accessibility of CAs, as they enable people to access information online through a multitude of devices like computers, mobile phones, and voice-assistant hardware, such as Alexa and Siri. It is perhaps then unsurprising that CAs designed to promote health education are beginning to emerge. In the context of this paper, health education is considered education that increases awareness and seeks to favorably influence the attitudes and knowledge related to improving health on a personal or community basis [10].

From Chatbots to CAs

The dictionary defines a chatbot as a "computer program designed to simulate conversation with human users" [11]. The first chatbot ELIZA developed by Joseph Weizenbaum in the 1960s is well established and recorded. ELIZA was an early natural language processing (NLP) chatbot, but made strides in conversational artificial intelligence (AI). It was one of the first AI programs to have passed a restricted Turing test for machine intelligence. It was broadly taken as one of the earliest successes of using intelligence in computers. ELIZA laid the groundwork for current advances in AI chatbot technology; advanced AI CAs, such as Siri and Amazon Alexa, are descendants of ELIZA [12].

Early generations of chatbots used simple pattern matching design techniques and had very basic functionality, which required specific inputs in order to generate outputs [13]. These types of chatbots were also referred to as rule-based chatbots. Later generations of chatbots saw the implementation of NLP. NLP is a subset of AI that is defined as "the ability of a computer program to understand human language as it is spoken and written (referred to as natural language)" [14]. With the introduction of NLP, simple chatbots started to shift into a generation of CAs defined by their ability to have true conversations by generating natural language in a more conversational format. The first wave of CAs emerged around 2016 when social media platforms enabled the creation of chatbots for commercial services. This led to a wave of adoption in industries ranging from health care to shopping as they often replaced the need for any human interaction [15]. Subsequent generations of CAs have progressed with advances in AI and NLP.

Classification of CAs

As CAs have advanced, a wide diversity of terminology has been used. Terms, such as chatbot, virtual assistant, and CA, are found to be used interchangeably, leaving no clear classification method to understand what distinguishes one from another. There are many different ways to classify these initiatives, such as classification based on the depth of information CAs have access to (ie, open or closed domain) [16], the sentimental proximity of the interaction (ie, intrapersonal, interpersonal, or interagent) [1], the ways in which input is received and/or responses are generated [17], or the goal that is trying to be achieved (ie, to inform, converse, or engage the user in a task) [1]. One aim of this review is to help classify the characteristics of CAs, drawing the definitions from industry leaders like Rasa and Artificial Solutions [18-20].

For the purpose of this review, we will use a 5-level classification schema [18] adapted from characteristics detailed by Rasa, a popular open-source CA development platform [21]. The levels are as follows:

1. Level one: The CA does not have conversational ability and lacks the ability to contextualize or have a natural conversation. CAs at this level place the work on the end user. Static web forms and basic notification assistance would fall at this level.
2. Level two: The CA can conduct basic conversation through prebuilt dialogues. There is a heavy reliance on preprogramming of intents and rules. The CA can answer simple FAQs, but unexpected deviation from programmed language will lead to a lack of outcome. CAs at this level are built using rule-based dialogues and have a heavy reliance on conditional statements.
3. Level three: The CA interaction is more linguistic-based and closer to a conversation akin to an encounter between 2 humans. CAs at this level are contextual, allowing for a more flexible, almost natural back and forth conversation. CAs at this level employ NLP and natural language generation. A wide variety of chatbots today are at this level.
4. Level four: CAs at this level are sometimes referred to as consultative assistants. The onus of figuring out what the end user needs is put more on the CA instead of the end user. CAs at this level offer a more personalized experience.
5. Level five: CAs at this level are often an autonomous organization of assistants that can adjust their behavior and pick up cues.

There is no clear dichotomy between these stages, but this gradation provides us with an understanding of where CA technology stands and how it could be leveraged in health education. While scoping reviews exist about CAs in health care [21,22], this scoping review will focus on those being used within health education. The review will also provide a unique

perspective in this research area by classifying interventions using emerging terms from the marketplace.

Objectives and Review Questions

The focus for this review is on *the use of CAs in health education.* This focus was identified after a comprehensive discussion among the protocol authors, which helped clarify the key concepts that we intended to explore. Our objective to categorize the landscape of CAs in health education will be expressed in answering the following review questions:

1. What levels in the cycle are being currently used in health education CAs?
2. What are the resources needed to develop and sustain these CAs?
3. What approaches are taken in designing CAs?
4. For what health education purposes are these CAs being implemented?

Methods

Key Considerations

This scoping review will be guided by the methodology proposed by Arksey and O'Malley [23], with enhancements suggested by Levac et al [24] and Peters et al [25]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) checklist will also provide further details and clarity [26]. As the search for a scoping review is understood to be an iterative process, any deviations from any of the predefined stages in the protocol will be noted and vindicated in the final scoping review.

Eligibility Criteria

We will include articles that report on a CA designed and/or implemented to educate an individual or the public about an area related to health. Included papers must have details on how the CA receives input and provides output in order to enable classification. Peer-reviewed articles, conference papers, and work-in-progress papers will be included. Grey literature will also be included by conducting a google scholar search using evidence-exhaustion and effort-bounded criteria to limit the documents to be screened to the first 100 results, moving to the next hundred if the results continue to meet the eligibility criteria [27].

We will exclude studies that report on the use of CAs in nonhealth education contexts (ie, excluding medical training, medical education, continuing professional development, and educating students). Papers written in languages other than English will also be excluded.

Search Strategy

The search strategy for this protocol was developed in a collaborative effort involving the authors and an information specialist. We aligned on a definition of "health education" by searching the MeSH (Medical Subject Headings) database, and we adopted the definition for the concept of health education that was indexed as a MeSH concept. An initial search of PubMed was conducted using our 2 main concepts of "health education" and "conversational agents." Our list of keywords and our sample search strategy are reflected in Tables 1-3. Relevant papers were identified, and their keyword appendices were consulted to inform our list of keywords [28,29]. To ensure a thorough search strategy, we consulted with an expert in library sciences who helped to ensure our keywords are comprehensive and the select databases are relevant for this review. The databases to be searched are (1) PubMed, (2) PsychINFO, (2) Embase, (4) Web of Science, (5) SCOPUS, (6) CINAHL, (7) ERIC, (8) MEDLINE, and (9) Google Scholar.

Table 1. Keywords for the concept "conversational agent."

Number (#)	Keywords
1	conversational agent*[a]
2	conversational bot*
3	conversational system*
4	conversational interface*
5	chatbot*
6	chat bot
7	chatbot*
8	chatter bot*
9	Chatterbot*
10	smart bot*
11	smartbot*
12	smart-bot*
13	virtual agent*
14	embodied agent*
15	virtual coach*
16	virtual human
17	AI bot*
18	AI-bot
19	AI Assistant*
20	Virtual Assistant*
21	Relational Agent*
22	Interactive Agent*
23	Online agent*
24	Communication agent*
25	Natural Language Generating Agent*
26	Notification Assistant*
27	FAQ Assistant*
28	Contextual Assistant*
29	Personalized Assistant*
30	Autonomous Assistant*

[a]The "*" symbol next to words helps to broaden the search through finding words that start with the same root word.

Table 2. Keywords for the concept "health education."

Number (#)	Keywords
1	Patient Education*[a]
2	Health Education *
3	Health Awareness
4	Patient Awareness Programme*
5	Health Education Programme*
6	Health Advocacy*
7	Community health education*
8	Health Literacy*
9	Patient Communication*
10	Health Outreach*
11	Public Health*
12	Health Promotion*
13	mHealth
14	Mobile Health*
15	Health Teaching*
16	Health Edu*

[a]The "*" symbol next to words helps to broaden the search through finding words that start with the same root word.

Table 3. Sample search strategy.

Search strategy	Database	Results (n)
(("conversational agent*[a]") OR ("conversational system*")) OR ("conversational interface*")) OR ("chatbot*")) OR ("chat bot")) OR ("chat-bot*")) OR ("smart bot*")) OR ("smartbot*")) OR ("smart-bot*")) OR ("virtual agent*")) OR ("embodied agent*")) OR ("virtual coach*")) OR ("virtual human")) OR ("AI Assistant*")) OR ("Virtual Assistant*")) OR ("Relational Agent*")) OR ("Interactive Agent*")) OR ("Communication agent*")) OR (("chatter"[All Fields] OR "chattering"[All Fields] OR "chatters"[All Fields]) AND "bot"[All Fields])) OR ("Chatterbot*")) AND ((((((((((((((("Patient Education*") OR ("Health Education*")) OR ("Health Awareness")) OR ("Health Education Programme*")) OR ("Health Advocacy*")) OR ("Community health education*")) OR ("Health Literacy*")) OR ("Patient Communication*")) OR ("Health Outreach*")) OR ("Public Health*")) OR ("Health Promotion*")) OR ("mHealth")) OR ("Mobile Health*")) OR ("Health Teaching*")) OR ("Health Edu*"))	PubMed	279

[a]The "*" symbol next to words helps to broaden the search through finding words that start with the same root word.

Study Selection and Screening

After the searches in each database have been completed, all identified papers will be imported into EndNote, and duplicates will be removed using the automated features of the tool. As recommended by Levac et al [24], at least two reviewers will independently conduct a title and abstract screening to categorize what literature is eligible for a full review. Before performing a full review of the papers, papers will be uploaded to the Rayyan online platform to undergo screening. An initial review of the titles and abstracts of 5 to 10 articles will be conducted by each reviewer [30]. Results of this initial review will be compared to determine if the eligibility criteria need revision. Any changes to the criteria will be documented in the scoping review publication. After the initial review, the title/abstract of the remaining papers will be screened. Any disagreements between reviewers at this stage will be mediated and resolved with discussion and consultation with a third independent referee. Finally, papers that meet eligibility criteria will undergo a full-text review [30]. The final review will be presented in both a narrative and flow diagram format as recommended by the PRISMA ScR statement [26]. Details of the excluded studies at full-text review and vindication will be appended in the final study.

Data Extraction and Presentation

To guide consistency in our data extraction, a template for charting characteristics, informed by the Joanna Briggs Institute

(JBI) template for results extraction, has been created (Table 4). The characteristics of the chart are derived directly from the objective and review questions for the study. This template will be piloted and refined during the initial review of 5 to 10 studies conducted as part of the initial pilot.

Two reviewers will independently review and chart data for each paper. Data extraction in a scoping review is an iterative process. Therefore, this data charting form will be modified and adjusted to best meet this review's objectives and research questions.

Table 4. Draft charting table.

Type of data	Details of charted data
Article information	Title, authors, date of publication, source of publication, type of study, and country of study
What health education was disseminated through the CA[a]	The data would look at chatbot-targeted health issues. For example, weight management and vaccine hesitancy.
What are the demographics of the CA end user	Age of users, country of user, and health condition (if any)
Outcomes	What outcomes does the paper mention? For example, outcomes relating to the CA or health education will be outlined here.
Resources	What resources were utilized in developing and disseminating the CA (resources including but not limited to human resources, technological resources, knowledge resources, and skill set)?
CA design	This section will extract data regarding "how."
	How the CA was designed? (ie, was there a design framework used, and if so, what?)
	Who designed the CA? For example, health care professionals or computer scientists.
Type of CA	The CA used will be charted to 1 of 5 levels as noted previously
Duration of CA interaction	Is the chatbot used for short-term relationships, or is it only used on a one-off interaction or occasionally when a particular service is needed?
	Long-term relation: Is the CA providing long-term engagement? These chatbots that offer long-term engagement offer recurring updates and remember previous conversations.
Terminology	How is the CA referred to? Is it referred to as a chatbot, CA, AI[b] chatbot, AI assistant, etc?

[a]CA: conversational agent.

[b]AI: artificial intelligence.

Data Analysis

The analysis of the extracted data will be limited to descriptive analysis keeping it under the purview of a scoping review. We will include frequency counts of concepts and studies, which will then be mapped in various illustrations and graphs. Since this is a scoping review, the methodological quality and risk of bias will not be formally appraised or mentioned in the review.

Results

An initial search of the databases was conducted in September 2021, yielding 1305 results after deduplication was completed. We anticipate record screening and data extraction to be complete by mid-March 2022. The extracted results will be presented to fall in line with our review questions and objectives. Our results section will contain 2 broad sections as recommended by Peter et al [25]. The first section will include a PRISMA flow diagram that will detail the study selection process. The PRISMA flowchart is illustrated in Figure 1.

The second section will illustrate results pertaining to our review questions and objectives. A tabulation of information containing basic information of the type of study and extent of literature will be included in this section, along with a map of the extracted data. There will be a diagrammatic illustration that categorizes the types of conversations included. A narrative summary will accompany the illustrations and tables. These data presentation approaches may be further refined at the review stage.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.
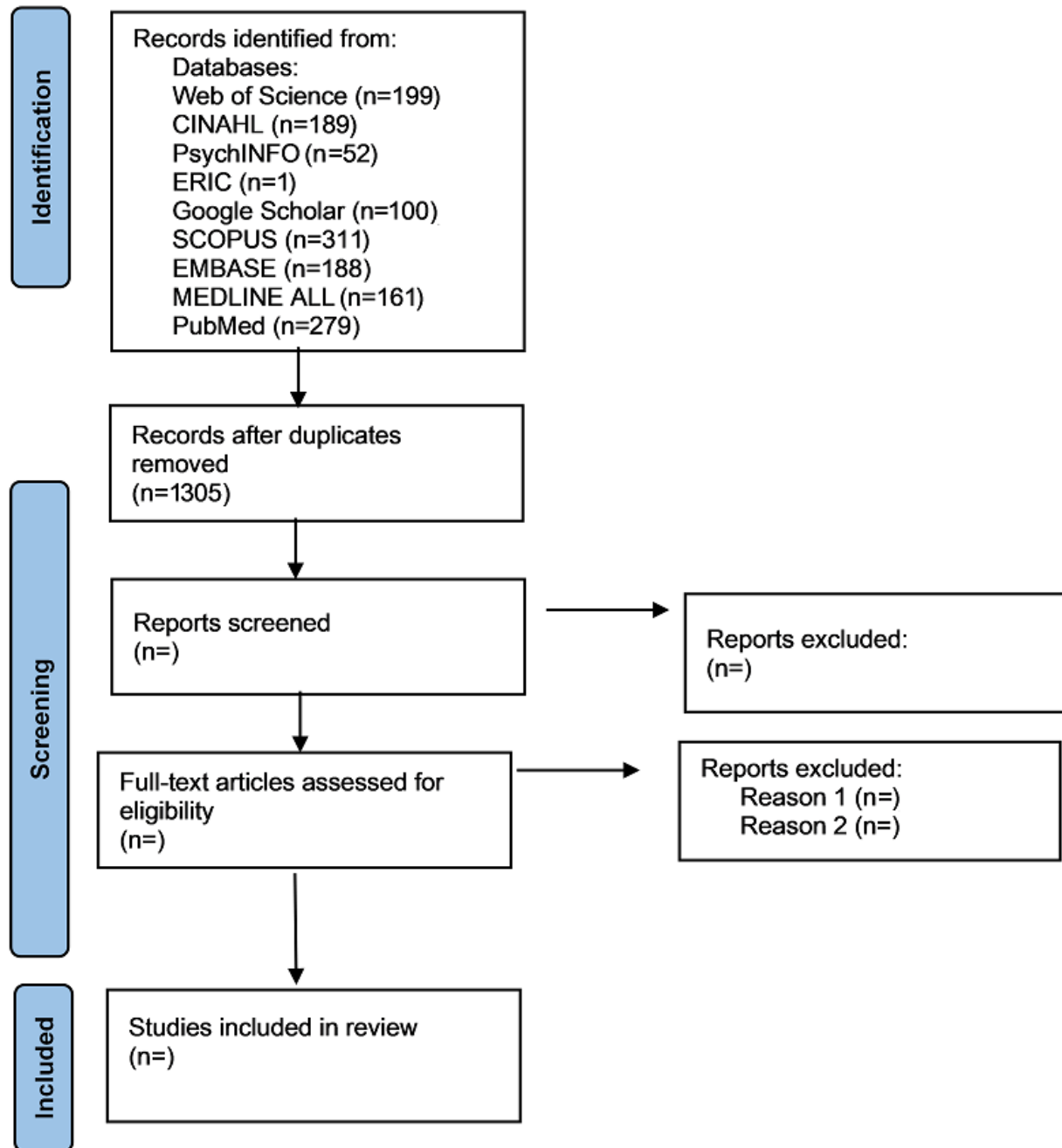
Discussion

Reviewers have previously explored CAs in health. However, to our knowledge, there has been no review conducted in the specific area of our interest (ie, health education). Therefore, this review will provide a map of the literature in this area, and clarify and define the heterogeneous terms found in the literature.

There are several strengths in conducting this scoping review. By categorizing existing CAs in health education into predefined categories, we seek to align on terminology that can promote more clarity in this research space. By reporting on the tools, resources, and design and development strategies undertaken to create CAs in health education, we will help to inform those seeking to develop their own CAs about what is most appropriate for their setting given their available resources, potentially leading to improved CAs and outcomes.

The limitations of this study include those inherent to scoping reviews in that we will not be formally evaluating the quality of the research. We are also limiting our scope to papers that clearly define the input/output method of the CA, which will likely result in the exclusion of papers that do not clearly discuss CA design in detail. We have determined this to be a limitation due to our aim of classifying the interventions, which is not possible with this detail. Finally, this review is limited by the fluency of the reviewers, with restriction of papers to those published in the English language.

Authors' Contributions

MZN, LP, and NZ conceived the study topic and designed the review protocol. MZN and LP wrote the protocol with revisions from RN, YZ, RS, SKW, HAS and NZ.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
CA: conversational agent
MeSH: Medical Subject Headings
NLP: natural language processing
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Problems and Barriers Related to the Use of Digital Health Applications: Protocol for a Scoping Review

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Abstract

Background: The use of mobile health (mHealth) apps is increasing rapidly worldwide. More and more institutions and organizations develop regulations and guidelines to enable an evidence-based and safe use. In Germany, mHealth apps fulfilling predefined criteria (Digitale Gesundheitsanwendungen [DiGA]) can be prescribed and are reimbursable by the German statutory health insurance scheme. Due to the increasing distribution of DiGA, problems and barriers should receive special attention.

Objective: This study aims to identify the relevant problems and barriers related to the use of mHealth apps fulfilling the criteria of DiGA.

Methods: This scoping review will follow published methodological frameworks and the PRISMA-Scr (Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews) criteria. Electronic databases (MEDLINE, EMBASE, PsycINFO, and JMIR), reference lists of relevant articles, and grey literature sources will be searched. Two reviewers will assess the eligibility of the articles by a two-stage (title and abstract as well as full text) screening process. Only problems and barriers related to mHealth apps fulfilling the criteria of DiGA are included for this research. The identified studies will be categorized and analyzed with MAXQDA.

Results: This scoping review gives an overview of the available evidence and identifies research gaps regarding problems and barriers related to DiGA. The results are planned to be submitted to an indexed, peer-reviewed journal in the first quarter of 2022.

Conclusions: This is the first review to identify the problems and barriers related to the use of mHealth apps fulfilling the German definition of DiGA. Nevertheless, the findings can be applied to other contexts and health care systems as well.

International Registered Report Identifier (IRRID): DERR1-10.2196/32702

Introduction

The use of mobile health (mHealth) apps becomes more and more ubiquitous. Health care systems worldwide establish different regulatory frameworks to integrate them into care. mHealth apps are used for many different purposes. For example, app-based vital signs monitoring can serve for (primary) prevention [1], medical adherence apps can lead to more regular medication intake [2], and other apps support coping with chronic diseases such as diabetes [3-5] or mental health problems [6,7].

According to the World Health Organization, digital health solutions can contribute to higher standards of health and better

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access to health care services. The use of digital health allows people worldwide to promote and protect their health and well-being [8]. While opportunities and possibilities are considered certain, the problems and barriers related to the use of mHealth apps often remain unaddressed.

Realizing the potential benefits of digitalization, the national Parliament of the Federal Republic of Germany (Deutscher Bundestag) introduced "the Act to Improve Healthcare Provision through Digitalization and Innovation (Digital Healthcare Act – DVG)" in 2019 [9]. One of the main innovations is the possibility to prescribe predefined mHealth apps, called Digitale Gesundheitsanwendungen (DiGA). These prescribed apps are reimbursable for 73 million people insured under the German statutory health insurance scheme.

Focusing on the following requirements, this text applies the term "Digital Health Application" (DHA) to describe mHealth apps that meet the criteria for DiGA.

In Germany, mHealth apps must fulfill a predefined list of criteria to be regarded as a DiGA [10]. These criteria are as follows: (1) medical device of a risk class lower or equal to IIa; (2) the main function of the app is based on digital technology; (3) the DHA is not only a medium to collect data from a device or to control a device. The app must have a proper main digital function achieving a medical purpose; (4) recognition, monitoring, treatment or alleviation of diseases, or the recognition, treatment or alleviation or compensation of injuries are supported by the DiGA; (5) the purpose of the app is not for primary prevention; and (6) the app is used either by the patient or by the health care provider together with the patient. Therefore, apps only used by health care providers are not assessed as DiGA. DiGA can be considered as "digital assistants" in the hands of patients.

Currently, there are 28 certified DHAs listed in the German DiGA registry, covering a range of indications including mental illnesses such as depression, anxiety disorder, or addiction, as well as physical illnesses such as arthrosis, multiple sclerosis, and diabetes mellitus.

The German DiGA concept is unique, though other countries are considering launching a similar concept. In particular, France has announced to adopt the German system. Therefore, the German system might serve as a blueprint for other countries regarding the integration of DHA in their health care systems.

Reviews on the evidence of problems and barriers related to the use of DHA are sparse. While O'Connor et al [11] identified and synthesized the qualitative literature on barriers and facilitators to engagement and recruitment to digital health interventions [11], Kao and Liebovitz [12] present the current state, barriers, and future directions of consumer mHealth apps. Besides the broad reviews mentioned before, there is a qualitative study by Stiles-Shields et al [13] investigating the barriers to the use of apps for depression. Finally, Meyerowitz-Katz [14] investigated the rates of attrition and dropout in app-based interventions for chronic disease. In their review and meta-analysis, they rather focused on dropout rates in apps for chronic disease than reasons for dropping out.

Ahmad et al [15] planned a scoping review to capture current problems and opportunities in the adoption of mobile apps among older adults. Contrary to this scoping review, our review does not exclude younger users.

The only review focusing specifically on DiGA is part of the German Advisory Council on the Assessment of Developments in the Health Care System report [16]. It focusses on evidence but not on barriers or problems in the context of DiGA.

Considering this research gap, the planned scoping review aims to analyze the following research question: "which problems and barriers related to the use of mHealth apps comparable to the German DiGA concept are addressed in studies?"

The scoping review is part of a wider research project (continuous quality assurance of DHA [QuaSiApps]) funded by the Federal Joint Committee (G-BA) [17].

Methods

Guidance Frameworks

The scoping review will be conducted according to the framework with the 5 (mandatory) stages described by Arksey and O'Malley [18] in 2005 and further developed by Levac et al [19] in 2010. These stages are as follows: (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) charting the data and collating, and (5) summarizing and reporting the results. Following these stages will guarantee a systematic and coherent proceeding. The subsequent preparation of the manuscript will follow the PRISMA-Scr (Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews) by Tricco et al [20]. The protocol was not registered.

Stage I: Identifying the Research Question

The research question, "Which problems and barriers related to the use of mHealth apps comparable to the German DiGA concept are addressed in studies?" was posed. This scoping review will provide a structured overview for further research and inform stakeholders. Furthermore, it serves as one module of our research project, QuaSiApps.

Stage II: Identifying Relevant Studies

The search strategy is predefined according to the Joanna Briggs Institute Manual for Evidence Synthesis [21]. After an initial explorative research and subsequent team discussion, terms and keywords were determined and used to conduct the main search across the included databases (EMBASE, MEDLINE, PsycINFO, and JMIR). Afterward, the reference lists of included studies will be screened, and referenced articles assessed according to the predefined inclusion and exclusion criteria. If they are appropriate, they will be included in the scoping review.

The search was performed following Methodology, Issues, Participants (MIP) [22] scheme including methodology (all methodologies), issues (problems and barriers related to the use of DHA), and participants (focus on patients and health care providers).

Electronic databases EMBASE, MEDLINE, and PsycINFO were searched on June 8, 2021. The used search terms were

combined in the following manner: (*"difficulty"* OR *"obstacle"* OR *"problem"* OR *"issue"* OR *"challenge"* OR *"barrier"*) AND (*"web application"* OR *"mobile application"* OR *"mHealth"* OR *"virtual care"* OR *"healthcare app"* OR *"health care app"* OR *"mobile health"* OR *"health app"*) OR (*"smartphone"* OR *"mobile phone"* OR *"android"* OR *"iphone"* OR *"browser"* AND *"health"*) AND (*"healthcare"* OR *"health care"*).

The respective search terms were restricted to the occurrence in abstract, title, or keyword but expanded by indexing terms (Medical Subject Headings [MeSH] and Emtree). The complete search strategy can be found in Multimedia Appendices 1-3. Due to the thematic focus of JMIR, we added a structured search using the search function as well as relevant themes.

Searching the two databases EMBASE and MEDLINE and carrying out structured research in JMIR provide points of view of many different disciplines, which was deemed necessary in order to depict the multidisciplinary field of mHealth apps. In addition, PsycINFO was searched because a large proportion of certified DiGA in Germany stems from the field of mental illnesses.

Language was restricted to English, German, and French. The research was limited to articles published between January 1, 2015, and June 8, 2021. Further explanation for time restriction is given in the discussion of this protocol.

Apart from the online database research, gray literature sources such as the Federal Institute for Drugs and Medical Devices reports, guidelines, working papers, and industry reports will be searched via institutional websites and Google search engine (Multimedia Appendix 4).

Stage III: Study Selection and Eligibility Criteria

In the first step, the identified citations were uploaded in the literature management program Endnote X9 (Clarivate Analytics), and duplicates were removed. In the second step, 2 reviewers (GG and CS) will decide whether an article is eligible for full-text screening by independently assessing the title and abstract. In a third step, the full-text screening of the included articles and assessment against the exclusion criteria will be conducted by the same 2 reviewers. In this third step, the reasons for excluding studies will also be captured.

Disagreement between the 2 reviewers during the screening process will be resolved through discussion. If necessary, a third person (SN) will resolve emerging conflicts. In case of missing data, the reviewers will contact the authors of the included papers.

To handle the vast magnitude of mHealth apps and to balance between breadth and feasibility, we defined exclusion criteria, which we adjusted in the initial search process. Our final inclusion and exclusion criteria are listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Articles mentioning problems and barriers related to the use of mobile health apps

- A problem term mentioned in the abstract or title was related to the use of mobile health apps

- Publication with focus on mobile health apps

- Examined mobile health apps fulfill the requirements set for Digital Health Application (Digitale Gesundheitsanwendungen)

- Article published in 2015 or afterward

- Language: English, German, or French

Exclusion criteria

- Not valid to answer the research question

- The problem term mentioned in the abstract or title was not related to mobile health apps

- Publication does not focus on mobile health apps.

- Examined mobile health apps fulfill one or more of the following criteria:

- Not used by the patient

- No relation to illness, injury, or handicap

- Primary prevention

- The medical purpose is not achieved through the main digital functions

- Research protocol or conference abstract

- Article published before 2015

- Language other than English, German, or French

Stage IV: Charting the Data

The remaining publications will be included in the scoping review. Relevant information and data such as authors, year, country, study type underlying diseases, and especially problems and barriers related to DHA will be extracted (Table 1).

Table 1. Data extraction.

Author	Year	Study type	Country	Underlying disease	Problems

Stage V: Collating, Summarizing, and Reporting Results

Following the recommendations by Levac et al [19], the fifth stage is divided in the following three distinct steps: (1) analyzing research findings (including descriptive numerical summary analysis and qualitative thematic analysis); (2) evaluating the research findings and extracting an outcome that is in accordance with the research question (the results are reported in a narrative way); and (3) interpreting and discussing the findings with regard to further research questions, practice, and policy.

Besides the narrative reporting, tables and figures will ensure a structured overview about the key findings. The PRISMA-Scr [20] serves to guarantee a systematic reporting of the results.

Results

A coherent search strategy to identify articles focusing on problems and barriers related to the use of DHA and DiGA was developed. The results of our investigation will be presented and published in a systematic scoping review. Therefore, the process of publication selection will be presented using flowcharts, and the extracted data of our research will be systematized in tables and described in a narrative summary.

Data synthesis will not follow the existing themes. Problems and barriers related to the use of DiGA will be grouped in categories defined by the authors. If a problem does not fit to a defined group of problems, a new group will be created. Subsequently, the results and parent categories of problems aim to answer the research question, "Which problems and barriers related to the use of mHealth apps comparable to the German DiGA concept are addressed in studies?"

Discussion

There is a multitude of mHealth apps in nearly every domain of medicine. The opportunities and possibilities of mHealth apps are often discussed, whereas the research on related problems and barriers remain scarce. This scoping review will fulfill two reasons for conducting scoping reviews according to Arksey and O'Malley [18]. First, it summarizes and disseminates research findings to policy makers, practitioners, and consumers. Second, it allows researchers and other stakeholder to identify research gaps in the existing literature.

Our scoping review has some limitations, which cannot be prevented due to resource limitation. The research is restricted to articles published after the year 2015. Evidence gained before the time restriction is only captured if it is incorporated in newer publications. Two facts made the year 2015 a reasonable starting point for the scoping review. On the one hand, previous reviews show that older investigations in the context of mHealth cover mainly text messaging interventions [23]. This was found, for example, for the effectiveness of mHealth interventions focused on health care workers to improve pregnancy outcomes in low- and middle-income countries [24] or the use of mHealth in antenatal and postpartum care and vaccination administration [25]. Text messaging apps do not provide the criteria to be considered as a DiGA. On the other hand, in 2015, Stoyanov et al [26] published the Mobile App Rating Scale (MARS). The MARS is the first tool to assess app quality, which is in direct conjunction with DHA problems.

Further limitations arise from the rather new and rapid advancing technology of mHealth, which also hamper a systematic search. Moreover, the terminology in the field of mHealth apps is not consistent. Even in the most known publications (eg, Mobile "App" Rating Scale [26] and Mobile "Application" Rating Scale [27]), there is no consistency in terminology. While some institutions such as the German Federal Institute for Drugs and Medical Devices use the term "(Digital Health-) Application," a consensus paper recommends the use of "app" instead of "application" [28]. When constructing our search strategy, different terms were pilot tested, and results were compared. In addition, the inclusion of related terms ensures a broad coverage of the topic.

Nevertheless, there still is uncertainty whether all relevant search terms might be covered. This uncertainty also applies to the selection of databases. Medline, Embase, and PsychINFO, the most important databases for classical medical and psychological therapies and devices, are covered. However, these might not cover all relevant journals in the rapidly evolving field of mHealth, and we addressed these limitations by conducting a structured search through JMIR.

A further limitation is made due to the context of the scoping review. The scoping review is one module of the larger research project, QuaSiApps, which aims to develop a generic quality assurance system. Therefore, we could not restrict the research to specific diseases. In order to guarantee research specific to our study and exclude lifestyle, wellness, and fitness apps, we restricted our search to health care.

Exclusion criteria ensured that publications were only included if problems related to mHealth apps were mentioned in the title or the abstract. Other publications describing mHealth apps could include problems or barriers as a secondary aspect. Nevertheless, publications with problems as a central subject are covered.

Conclusion

This scoping review will be the first that provides an overview about potential problems and barriers related to the use of DHA according to the German definition of DiGA. The research findings of this and a further scoping review about the quality of DHA will serve as a first module for the development of a continuous quality assurance concept [29]. In the next step, we will use the research findings to develop a discussion guide to conduct focus groups with users and potential users of DHA.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy; Medline via Embase.
[DOCX File , 18 KB - resprot_v11i4e32702_app1.docx]

Multimedia Appendix 2
Search strategy; Medline via Ovid.
[DOCX File , 18 KB - resprot_v11i4e32702_app2.docx]

Multimedia Appendix 3
Search strategy; PsycINFO via Ovid.
[DOCX File , 18 KB - resprot_v11i4e32702_app3.docx]

Multimedia Appendix 4
Sources of gray literature.
[DOCX File , 15 KB - resprot_v11i4e32702_app4.docx]

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Abbreviations

DHA: Digital Health Application

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DiGA: Digitale Gesundheitsanwendungen
MeSH: Medical Subject Headings
mHealth: mobile health
MIP: Methodology, Issues, Participants
PRISMA-Scr: Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews
QuaSiApps: continuous quality assurance of DHA

Protocol

Evaluation of the Implementation and Effectiveness of a Mobile Health Intervention to Improve Outcomes for People With HIV in the Washington, DC Cohort: Study Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Gaps remain in achieving retention in care and durable HIV viral load suppression for people with HIV in Washington, DC (hereafter DC). Although people with HIV seeking care in DC have access to a range of supportive services, innovative strategies are needed to enhance patient engagement in this setting. Mobile health (mHealth) interventions have shown promise in reaching previously underengaged groups and improving HIV-related outcomes in various settings.

Objective: This study will evaluate the implementation and effectiveness of a clinic-deployed, multifeature mHealth intervention called PositiveLinks (PL) among people with HIV enrolled in the DC Cohort, a longitudinal cohort of people with HIV receiving care in DC. A cluster randomized controlled trial will be conducted using a hybrid effectiveness-implementation design and will compare HIV-related outcomes between clinics randomized to PL versus usual care.

Methods: The study aims are threefold: (1) We will perform a formative evaluation of PL in the context of DC Cohort clinics to test the feasibility, acceptability, and usability of PL and tailor the platform for use in this context. (2) We will conduct a cluster randomized controlled trial with 12 DC Cohort clinics randomized to PL or usual care (n=6 [50%] per arm) and measure the effectiveness of PL by the primary outcomes of patient visit constancy, retention in care, and HIV viral load suppression. We aim to enroll a total of 482 participants from DC Cohort clinic sites, specifically including people with HIV who show evidence of inconsistent retention in care or lack of viral suppression. (3) We will use the Consolidated Framework for Implementation Research (CFIR) and the Reach Effectiveness Adoption Implementation Maintenance (RE-AIM) framework to measure implementation success and identify site, patient, provider, and system factors associated with successful implementation. Evaluation activities will occur pre-, mid-, and postimplementation.

Results: Formative data collection was completed between April 2021 and January 2022. Preliminary mHealth platform modifications have been performed, and the first round of user testing has been completed. A preimplementation evaluation was performed to identify relevant implementation outcomes and design a suite of instruments to guide data collection for evaluation of PL implementation throughout the trial period. Instruments include those already developed to support DC Cohort Study activities and PL implementation in other cohorts, which required modification for use in the study, as well as novel instruments designed to complete data collection, as guided by the CFIR and RE-AIM frameworks.

Conclusions: Formative and preimplementation evaluations will be completed in spring 2022 when the trial is planned to launch. Specifically, comprehensive formative data analysis will be completed following data collection, coding, preliminary review, and synthesis. Corresponding platform modifications are ready for beta testing within the DC Cohort. Finalization of the platform for use in the trial will follow beta testing.

Trial Registration: ClinicalTrials.gov NCT04998019; https://clinicaltrials.gov/ct2/show/NCT04998019

International Registered Report Identifier (IRRID): PRR1-10.2196/37748

Introduction

Background

Despite progress made toward addressing the HIV epidemic within the United States, concerted efforts are needed to address substantial gaps in the care continuum for people with HIV [1]. Retention in HIV care and achievement and maintenance of viral suppression are critical steps of the continuum [2]; however, currently less than half of all people with HIV in the United States are considered retained in care, and even fewer have achieved viral suppression [3,4]. Missed outpatient visits are an important early marker of failure to achieve suppression and are associated with increased mortality [5-7].

National gaps persisting within the HIV care continuum are similar for people with HIV in Washington, DC (hereafter DC), which is a priority jurisdiction of the Ending the Epidemic Initiative [8]. Specific subpopulations of people with HIV have previously demonstrated higher discontinuity of care, including those who are male, Black, younger, uninsured, and with injection drug use as a risk factor for exposure to HIV [9,10]. People with HIV in DC face various barriers to retention in care, including limited transportation, lack of comprehensive medical case management and adherence-related services, absence of a medical home, and gaps in health literacy [11,12].

The DC Cohort

The DC Cohort is the largest citywide prospective cohort of people with HIV in the United States, with 11,700 participants having consented at 15 partnering clinics across DC [13]. The DC Cohort Study is a National Institutes of Health (NIH)-funded study conducted in partnership between the DC Center for AIDS Research (CFAR), DC Department of Health (DOH), and the NIH/National Institute of Allergy and Infectious Diseases (NIAID) as part of the DC Partnership for AIDS Progress [12]. Among the 15 sites, 14 (93%) agreed to participate in the study at the time of funding.

DC Cohort clinics range in size, characteristics, patients, and populations served and include federal, academic, and community-based clinics, as well as pediatric and adult clinics.

Through a network of research assistants (RAs) located at these partner clinics, approximately 450 people with HIV enroll in the DC Cohort annually. DC Cohort participants represent about 75% of people with HIV cared for at these clinics and are demographically similar to the broader HIV population in DC; in 1 interim assessment, 4258 (82%) of 5193 participants were black, 3531 (68%) male, and 1973 (38%) men who have sex with men (MSM) [14].

Mobile Health and HIV

Smartphone accessibility is high overall in the United States [15]. Mobile health (mHealth) interventions developed to encourage self-management and social support and enhance the mental health of people with HIV have been associated with improvement in antiretroviral therapy (ART) adherence and retention in care for at-risk groups [16-25]. A range of retention-in-care services are offered across DC Cohort sites [26,27]; however, no mHealth interventions have been systematically deployed or studied within these sites.

PositiveLinks (PL) is a clinic-associated mHealth platform available to providers (in outpatient settings, including clinical and nonclinical) and patients through a smartphone app. Clinic providers also access a web portal to manage patient cohorts, an online implementation guide, and an online learning management system for training and certification. PL features were designed using psychological theories of behavior change (information-motivation-behavioral skills model [28] and social action theory [29]) and principles of motivational interviewing that encourage self-directed behavior change [30], and are informed by user-based design [31-38]. The PL platform delivers appointment reminders; daily queries ("check-ins") of mood, stress, and medication adherence with self-monitoring feedback; display of recent cluster of differentiation (CD)4 and viral load lab results; access to PL support staff for assistance/troubleshooting; secure communication with providers and clinic staff using in-app messaging; tailored educational resources; and the ability to interact with other users on a secure, anonymous community message board (Figure 1). The PL platform has also been adapted and translated for use in Spanish-speaking populations [39].

Figure 1. Screenshots of the home page and several features of PL. Features shown include a discreet home screen (A) and a dashboard (B), daily queries for medication administration (C), and stress and mood (D), along with discreet push notifications. The "How am I?" screen (E) provides graphical feedback based on user answers to daily queries for self-monitoring. Additional features include a lab results page (F), an anonymous community message board (G), and secure in-app messaging between patients and providers/staff (H). Users can also upload documents that support Ryan White eligibility. PL: PositiveLinks.
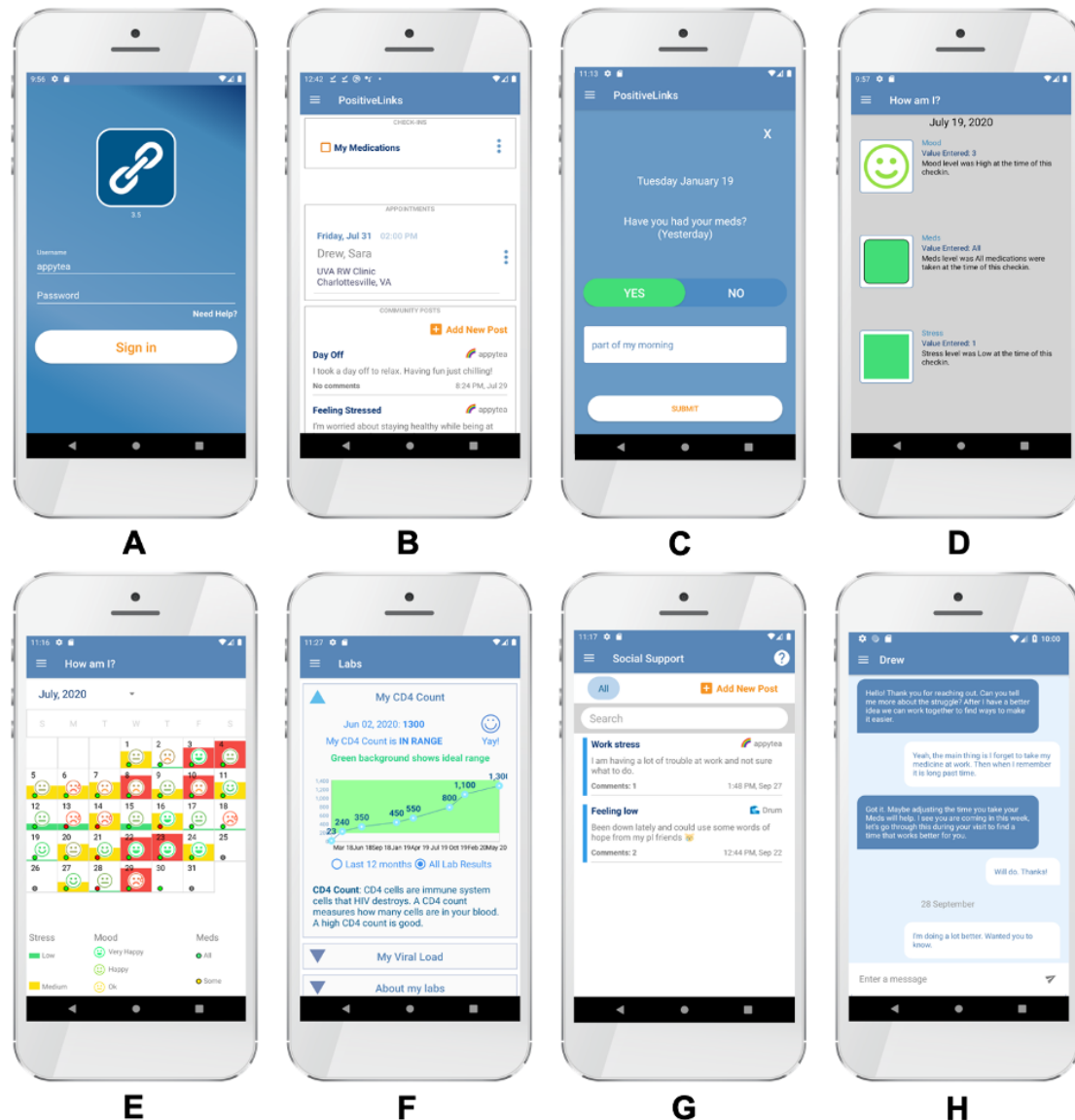
A prospective study of poorly retained people with HIV in Virginia found that PL usage increased retention in care and improved the cohort rate of viral suppression by over 30% at 12 months [40]. Additionally, PL was included as an evidence-based strategy to improve engagement in care for people with HIV in a 2020 update to guidelines by the HIV Medicine Association of the Infectious Diseases Society of America [41]. Although PL is a promising tool for people with HIV, efficacy has not been evaluated with a rigorous randomized trial or in urban populations. We describe a protocol for a cluster randomized controlled trial using a type II hybrid effectiveness-implementation design to test PL against usual care for people with HIV receiving outpatient HIV care in the DC Cohort.

The aims of this study are threefold. We first aim to determine the feasibility, acceptability, and usability of PL within DC Cohort clinic sites in order to tailor the PL platform for use in

this context. Our second aim is to determine the effectiveness of PL in relation to key clinical outcomes of viral suppression, visit constancy, and retention in care. Our third aim is to use validated implementation science frameworks to rigorously measure the success of implementation of the PL program within participating DC Cohort sites and identify site, patient, provider, and system-level factors critical for successful implementation.

Methods

Outcome Measures

Primary outcomes to be evaluated at 12 months following participation include viral suppression (HIV viral load <200 copies/mL), visit constancy (proportion of 4-month time intervals, with 1 visit with an HIV care provider completed in the 12-month period of study participation), and retention in care by the Health Resources and Services Administration

(HRSA)-1 measure (keeping 2 HIV care appointments separated by 90 days within the 12-month time period of study participation) [42].

The primary hypotheses to be tested are that compared to participants at DC Cohort sites randomized to usual care, participants at sites randomized to receive the intervention (tailored PL platform with associated program activities) will demonstrate, on average:

- 15% better viral suppression at 12 months
- 25% greater rate of visit constancy at 12 months
- 25% greater rate of retention in care at 12 months

The study will also test the impact of PL versus usual care on secondary outcomes related to patient psychosocial characteristics, including markers of mental health, stigma, social support, and drug use. Finally, relevant implementation-centered outcome measures identified during the preimplementation evaluation (described in further detail later) will be evaluated during the mid- and postimplementation phases of the study.

Study Aim 1: Formative Evaluation

To determine the feasibility, acceptability, and usability of PL within DC Cohort clinics, we performed a series of focus groups and in-depth interviews with stakeholders.

DC Regional Planning Commission, DC Cohort Executive Committee, and DC Cohort Site Providers

Focus groups were conducted with members of the DC Cohort Executive Committee (DC Cohort site principal investigators (PIs), NIH and DOH representatives; n=10) and the DC Regional Planning Commission on Health and HIV (COHAH; n=50). Both focus groups met online during COVID-19 surges in DC. Members were included in focus groups based on availability to participate; all members were invited to participate and provided informed consent. In-depth interviews were also conducted with 2 providers from 14 DC Cohort sites (eg, clinicians, nurses, case managers, social workers, and support staff; n=28).

Provider focus groups were semistructured. An interview guide designed by the study team was used to collect perspectives on barriers to and facilitators of retention in care and viral suppression, input on app features based on experiences with the population of people with HIV they serve, and potential modifications felt to be most useful for enhancing retention in care. In-depth interviews were also semistructured and conducted using the same interview guides.

People With HIV Receiving Care in the DC Cohort

Focus groups were also conducted with a subset of people with HIV from 14 DC Cohort sites (5 focus groups, n=32 patients representing 8 sites). Eligible people with HIV were those who were aged 16 years or older, were receiving care at a DC Cohort clinical site, spoke English, could provide legal informed consent, and could participate virtually (due to the COVID-19 pandemic restrictions). Participants were identified, recruited, and consented from DC Cohort sites by site RAs. Participants were remunerated with a US $25 gift card. Individual

think-aloud user testing has also been completed (approximately 14/482 [2.9%] expected to enroll). COVID-19 precautions were observed during all sessions. Participants were remunerated with US $50 gift cards and US $10 metro cards. Following the user testing phase, 1 DC Cohort site withdrew from the study and 2 DC Cohort clinics merged, leaving 12 active sites. The site that withdrew cited staffing issues during the COVID-19 era that would present a challenge to fully participate. After user testing, final beta testing to detect any bugs, glitches, or data loss issues will be conducted with an additional 14 participants who will use the DC Cohort PL platform with assistance from their clinic RA for 1 month. People with HIV who participate in the beta testing will be remunerated with a US $50 gift card and a US $10 metro card for each session.

Focus Group Testing Among People With HIV in the DC Cohort

Focus groups were conducted using semistructured interview guides designed to elicit patient knowledge and perspectives surrounding engagement in care and viral suppression, assess comfort with and use of technology and smartphone apps, and elicit perceptions about PL and its potential role in supporting engagement in care. Following demonstration of the PL platform features, interviewers elicited feedback on interest in the app and preferences for particular app features. Brief surveys were distributed at the end of the focus groups and included questions relating to self-reported adequacy of retention in care and care-seeking behaviors, unmet needs, comorbidities, perceptions of the patient-provider relationship, and levels of user experience/comfort with smartphones.

Themes elicited from focus group and in-depth interviews were synthesized by the study team and presented to the DC Cohort Executive Committee, and consensus was reached on app modifications. Requested modifications were then provided to the PL development team.

Think-Aloud User Testing Among People With HIV in the DC Cohort

The modified app was iteratively tested with DC Cohort participants using the think-aloud protocol [43,44]. In total, 14 users provided input during 1-hour task-focused individual sessions and completed surveys at the end of the session, demonstrating how they navigate app features, while voicing their opinions about their experience of PL.

Beta Testing Among People With HIV in the DC Cohort

Investigators and developers discussed modifications to the app based on formative work following a preliminary review. The development team made modifications agreed on by the team. Beta testing of the near-finalized app will be conducted with 14 people with HIV, and the participating DC Cohort site RAs will be assigned to oversee patient enrollment, training on PL use, and ongoing app troubleshooting for the study. Participant interviews will be performed to solicit input after the first week of PL use in order to identify any issues with logins, navigation, functionality, or technical issues. Interviews will be repeated after the 1-month testing period concludes. A postparticipation survey will be performed to elicit feedback on the participants' usage of the app over the 1-month period using the System

Usability Scale [45]. Paradata metrics collected automatically by the app will be reviewed for the period as well. The research and PL development team will review all output from beta testing and make final app modifications.

Formative Data Analysis

All focus groups and interviews were audio-recorded and transcribed verbatim. Analysis of text files will be completed in spring 2022 using qualitative analysis software (Dedoose) with an a priori open coding process to identify themes and categories. Coding will be performed by at least 2 independent RAs to achieve consensus. Descriptive statistics will be used to analyze participant survey data for focus groups, in-depth interviews, and user and beta testing.

Study Aim 2: Cluster Randomized Controlled Trial

This study is a cluster randomized controlled trial whereby 12 clinics will be randomized to PL (n=6, 50%) or usual care (n=6, 50%); see Figure 2. Participants from clinics randomized to PL will receive access to the smartphone app following training on use provided by the site RA. Clinic providers (ie, clinicians, nonclinical care providers, support staff) will have access to the provider online learning management system for training on PL use, the PL provider online portal and smartphone app, and remote assistance provided by the PL program team. On-site administration will be supervised by site RAs. Patients at clinics randomized to PL will be able to use the app for at least 12 months up to the date of trial completion. Participants from clinics randomized to usual care will receive usual clinic retention and medication adherence support services for 12 months. Trial activities will complete in 2025.

Figure 2. Cluster randomized controlled trial recruitment and participant flow diagram. DC: Washington, DC; DOH: Department of Health; PL: PositiveLinks.
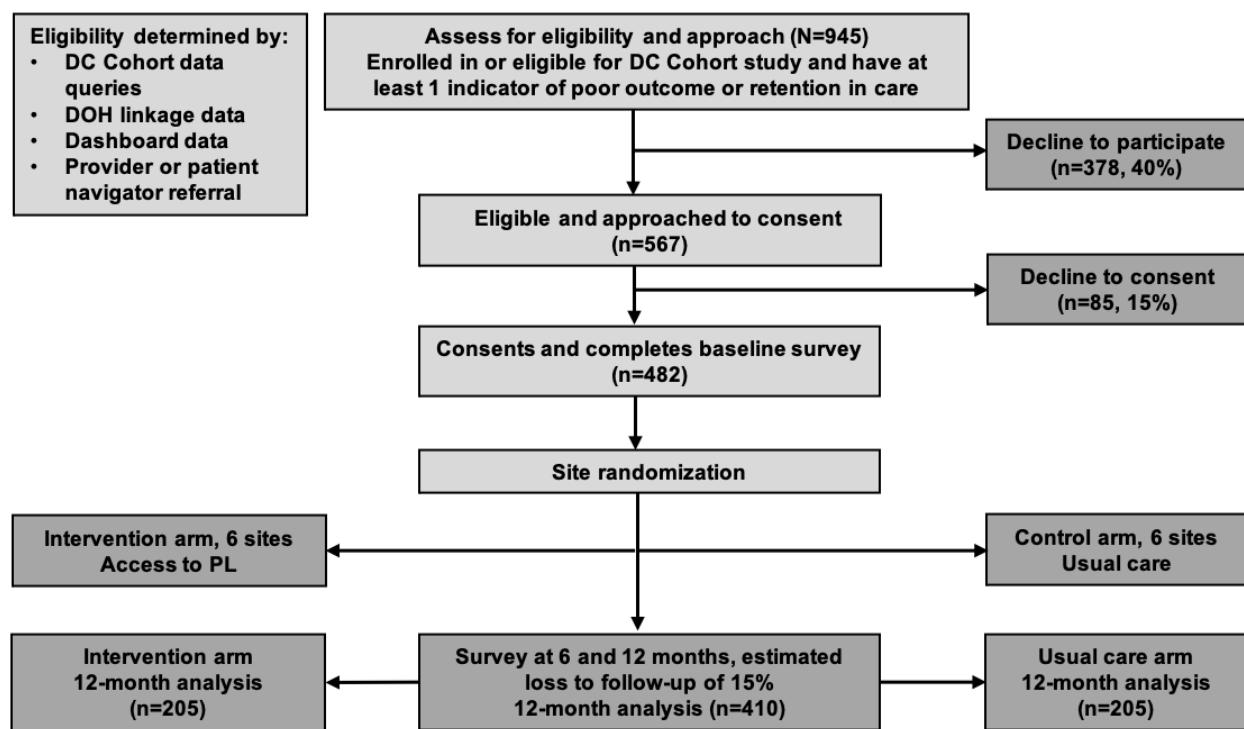
Recruitment

Participants in the cluster randomized controlled trial will be recruited from 12 clinics participating in the DC Cohort Study. Informed consent will be obtained for all DC Cohort participants under a protocol approved by the George Washington University Institutional Review Board (Protocol NCR202829; ClinicalTrials.gov NCT04998019). Inclusion criteria are people with HIV who (1) are enrolled in the DC Cohort study; (2) are aged 16 years or more; (3) if a minor, are in charge of their own HIV care (with waiver of parental consent); (4) speak and read English or Spanish at the fourth-grade level or above; (5) can provide informed consent; (6) plan to reside in the DC metro area for 12 months following enrollment; and (7) have at least 1 of the following putative indicators of poor retention (in order

of priority): (1) detectable viral load, (2) not retained in care, (3) returning to care after a gap of ≥6 months, (4) no visit constancy in the 12 months prior to enrollment, (5) newly diagnosed or initiating HIV care, (6) recently transferred from a different HIV care site, or (7) evidence of simultaneous HIV care receipt at a DC Cohort site and a non-DC Cohort site based on DC DOH surveillance data. Exclusion criteria include people with HIV who are (1) aged below 16 years or if 16-17 years old have a parent in charge of HIV care and (2) unable to provide informed consent. To minimize cross-site contamination, people with HIV receiving care at 2 DC Cohort sites will be excluded. Eligible patients will be identified by the study team with monthly review of the DC Cohort database as well as input from site providers, patient navigators, and RAs. Patients who do not

own a smartphone on enrollment will be provided a study smartphone to use for the duration of the study.

Randomization

In total, 6 clinics will be randomized to the intervention arm, and 6 clinics will be randomized to the usual care arm. Randomization will maximize the balance between arms in terms of clinics' predominant patient population characteristics (adolescent vs adult), panel size (eg, the 2 largest clinics will be randomized, 1 to each arm), and availability of Ryan White Clinical services, with all other clinics randomized to each arm by the study statistician. Given the nature of the intervention, neither researchers nor participants will be blinded to the outcome of randomization of clinic sites.

Sample Size Determination

Sample size calculation and power analysis are based on data from the PL 12-month prospective outcome study [40] showing a 30% increase in viral suppression at 12 months and on DC Cohort data showing that 55% of participants achieved viral suppression within a 12-month period [27]. We would need a mean cluster size of 64 or 768 participants to detect a 15% difference. We would need to enroll 432 participants to detect a more conservative 17.5% increase in viral suppression at 12 months, for 80% power to detect a true difference between PL and usual care as 36 per condition, assuming an intraclass correlation coefficient of .02 and a coefficient of variation of cluster sizes of 0.5. To achieve a sample size with sufficient power, we aim to enroll a total of 482 participants.

We estimate 60% of the people with HIV approached will be interested in the study based on the mean study consent rates for prior DC Cohort studies [46,47]. We plan to approach 945 people with HIV and enroll 482 (51%) participants overall (approximately n=40, on average, per cluster). Based on prior experience in recruiting people with HIV for studies in DC, recruiting 482 people with HIV over 20 months at the 12 clinics (at least 2 people per clinic per month) will be achievable, given the percentage of DC Cohort participants (7839/11,700, 67%) meeting the inclusion criteria. Based on previous experiences with PL and mHealth interventions [16,40], we anticipate approximately 15% participants lost to follow-up, resulting in 410 (85.1%) of 482 participants for analysis at the study endpoint.

Trial Data Collection

At study enrollment, baseline surveys will be completed by trial participants to evaluate specific sociodemographic measures relevant to retention in care [9,10], including age, sex, race, injection drug use, social determinants of health (eg, food insecurity, financial and housing instability), and changes in contact information in the past year. At study enrollment, 6 and 12 months, patients will be surveyed on risk factors for poor retention or lack of viral suppression, including medication nonadherence, self-efficacy, depression, and stressful life events [48] and psychosocial measures relevant to outcomes in PL studies, including experiences with stigma [49], social support, mental health, perceived stress, quality of life, self-efficacy related to substance use, and patient-provider communication. The site RA will administer baseline surveys using REDCap

software during the enrollment visit, while 6- and 12-month surveys will be administered at a clinic visit or over the telephone. All data will be entered into REDCap.

Efficacy Outcomes

All DC Cohort sites have RAs designated to collect and export patient laboratory values (eg, CD4 count, HIV viral load), sociodemographics, comorbid diagnoses, and encounter data into a central database (DC Cohort Study Database). Data exported for our study will be restricted to a 45-day window surrounding each participant's baseline, 6-month, and 12-month dates.

Characterizing Usual Care in DC Cohort Clinics

A standardized site assessment form was distributed as part of DC Cohort Study activities in 2016 to characterize the range of services comprising usual care delivered by DC Cohort clinic sites [27]. Services queried include clinic staffing (size, provider training, work experience), on-site clinical services, and activities to support patient ART adherence or linkage and retention in HIV care. Based on this assessment, the usual care condition across sites ranges from no ancillary support to comprehensive services (case management, adherence support, patient navigation, mental health, substance use, dental services, and food banks). This site assessment form will be redistributed electronically via REDCap to all sites (n=12, 100%) prior to initiation of the trial.

Trial Statistical Analysis

To compare the primary outcomes of viral suppression, visit constancy, and retention in care at 12 months between clusters, we will perform logistic regression using a mixed effects model (MEM), accounting for heterogeneity, including unequal cluster size between sites and correlations between participants from the same clinic site and between repeated measurements on the same participant group [50-52]. The comparisons between the conditions will be adjusted for both individual-level (gender, race, age, mode of HIV transmission) and cluster-level (differences in availability of specific adherence, retention and counseling services provided by sites) characteristics.

The MEM will also compare each secondary outcome of interest (psychosocial characteristics at 6- and 12-month follow-up assessments) between clusters within the PL and usual care arms. Linear regression and logistic regression based on MEMs will be used to analyze continuous outcomes and binary outcomes, respectively, adjusted for the same individual- and cluster-level characteristics as with primary outcome analyses.

Adverse Events

Site RAs will routinely monitor and moderate activity on the PL platform by the respective site's patient panel, including any inflammatory content or disclosure of identifying information posted on the community message board. Should such activity be identified, procedures to notify the site PIs will be instituted to determine whether additional actions are necessary to prevent further dissemination of inappropriate content.

Ethics Approval

Informed consent will be obtained for all trial providers and participants using an approved protocol, with ethical approval provided by the George Washington University Institutional Review Board (Protocol NCR202829; ClinicalTrials.gov NCT04998019).

Study Aim 3: Implementation Evaluation

Implementation of PL will be evaluated in parallel with efficacy of the intervention. Validated implementation science frameworks will be used pre-, mid- and post-PL implementation to determine factors that influence the relative success of the implementation strategy used to recruit, train, and retain patients and providers in the PL intervention. Specifically, we used the Reach Effectiveness Adoption Implementation Maintenance (RE-AIM) framework [53] to identify relevant implementation-centered outcomes during the preimplementation evaluation and will apply the framework mid- and postimplementation to measure and compare implementation success at each step of the implementation strategy executed across DC Cohort sites. The Consolidated

Framework for Intervention Research (CFIR) [54] also guided preimplementation activities, as described later, and will be applied mid- and postimplementation toward identification of relevant barriers and facilitators of implementation success within DC Cohort sites at the patient, provider, clinic, and broader organizational levels.

Preimplementation Evaluation

During the preimplementation period, the DC Cohort Executive Committee, DC Cohort site leadership, and provider concerns related to the process of PL implementation were evaluated in conjunction with formative phase activities (focus groups, in-depth interviews). The output of both rounds of user testing conducted with people with HIV during the formative phase is currently being analyzed for any implementation-related concerns. During the preimplementation evaluation, we also used the RE-AIM framework to identify data points required to evaluate PL implementation based on predefined outcomes of interest across sites (Figure 3). A suite of instruments was then developed to support data collection to adequately capture all identified outcomes of interest and corresponding data points.

Figure 3. RE-AIM framework dimensions. Dimensions of interest for PL implementation in DC Cohort clinics are listed along with corresponding outcome data requiring collection, as well as the instruments that will be utilized. For each framework dimension, outcome measures evaluated using multiple different instruments are denoted with a corresponding symbol matched to the instrument used. DC: Washington, DC; HRSA: Health Resources and Services Administration; ORIC: Organizational Readiness for Implementing Change; PL: PositiveLinks; RE-AIM: Reach Effectiveness Adoption Implementation Maintenance.

RE-AIM Dimension	Outcome Measures	Data Collection Instruments
Reach *How do I reach the targeted population with the intervention?*	Proportion of patients: • Seen at each DC cohort site that are offered enrollment✦ • Completing enrollment and training on PL of those offered✦ • Accessing PL app of those enrolled✧ Patient usage of PL app features over study period✧ Representativeness of patients participating (versus not) in each step (patient demographics)✛	✦Patient Consent Logs ✧PL Platform Data ✛DC Cohort Study Database
Efficacy/Effectiveness *How do I know my intervention is effective?*	HIV viral load suppression (<200 copies/mL) Visit constancy (Proportion of 4-month intervals visit is completed in 12 months) Retention in care (HRSA-1: 2 appointments at least 90 days apart within 12 months) Patient characteristics (eg, patient PL usage, patient demographics)	DC Cohort Study Database
Adoption *How do I develop organizational support to deliver my intervention?*	Proportion of providers (of those employed during study period✩): • Undergoing PL training by study team✚ • Accessing PL web portal for providers✧ Provider and site representativeness: provider characteristics✩, site characteristics (eg, ORIC)◆	✩Provider Baseline, Follow-Up Surveys ✚PL Posttraining Feedback Survey ✧PL Platform Data ◆DC Cohort Site Assessment Form
Implementation *How do I ensure the intervention is delivered properly?*	Fidelity of steps/adaptations performed for patient training✩, provider training✚, provider portal usage✩ Dose of steps (provider usage of PL web portal)✧	✩Provider Baseline, Follow-Up Surveys ✚PL Posttraining Feedback Survey ✧PL Platform Data
Maintenance *How do I incorporate the intervention so that it is delivered over the long term?*	Provider intent/interest to continue using PL following completion of trial✩ Patient and provider PL usage at extended time points✧	✩Provider Follow-Up Survey ✧PL Platform Data

Mid- and Postimplementation Evaluations

During the mid- and postimplementation evaluations, we will conduct in-depth interviews with a subset of site providers and RAs (n=24). Postimplementation, an additional focus group will be repeated with the DC Cohort Executive Committee. We will also conduct 4 focus groups postimplementation with a subset of PL trial participants (32/482 [6.6%] expected to enroll). People with HIV will be sampled to ensure demographic diversity and include a range of users (eg, frequent vs infrequent

users) who will be remunerated with a US $25 gift card and a US $10 metro card. For each interview/focus group conducted mid- and postimplementation, a semistructured interview guide will be used, developed based on our prior application of the CFIR to evaluate PL implementation [55]. Postimplementation interview guides will be updated in an iterative fashion based on analysis of midimplementation feedback.

Implementation Evaluation Data Collection

A suite of data collection instruments relevant to our implementation evaluation and planned for deployment to stakeholders mid- and postimplementation were developed, as described during the preimplementation evaluation (Table 1).

Informed consent to participate in the implementation evaluation phase of the study will be obtained during the trial consent process for patients. Providers will be offered open enrollment in PL across sites randomized to the intervention, and informed consent will be obtained to participate in implementation evaluation activities.

Table 1. Data collection instruments identified during the preimplementation phase to support collection of relevant data points for the implementation evaluation phase of cluster randomized controlled trial.

Instrument	Description of instrument	Frequency and timing of data collection and export
DC[a] Cohort Study Database	Patient laboratory values, encounter data, and sociodemographic data are routinely collected for all people with HIV in the DC Cohort.	Data are collected continuously by site RAs[b] and uploaded/exported to the database monthly for all people with HIV in the DC Cohort, including trial participants.
Patient consent logs	Patient responses are tracked to site RAs, who consent and enroll participants in DC Cohort studies. These logs will be modified for use in the trial to track patient enrollment and completion of various steps of PL[c] program implementation.	Log responses are uploaded and updated within the DC Cohort Study Database by RAs monthly.
DC Cohort site assessment forms	Site assessment forms query various site-level characteristics and will be modified to include items related to PL implementation (eg, site-level use of telemedicine, other mHealth[d] tools). Forms will be deployed electronically and completed by site PIs[e] at the start of the study period.	Interim distribution of the site assessment forms to site leadership (to be completed with site staff/provider assistance) will be performed throughout the study period at a yearly interval.
Provider baseline and follow-up surveys	Surveys will assess provider characteristics of interest, including specialty, time employed at the site, specific training, and baseline technology use. Follow-up survey items include perspectives on provider roles within the program, program adaptations, and individual usage of PL.	Baseline surveys will be distributed to site providers at the start of the study period and then every 6 months to providers newly employed during the study period and consenting to participation. Follow-up surveys will be redistributed to providers at 6-month intervals throughout the study period.
PL posttraining feedback survey	Providers completing the training step of PL implementation will be tracked by completion of a posttraining survey. Feedback elicited will include perceptions of the online learning management system (eg, modules). The survey was modified to include items from the ORIC[f] measure.	An electronic feedback survey immediately follows completion of learning modules via the online learning management system. Survey responses will be exported for mid- and postimplementation evaluations.
PL paradata	Platform paradata metrics include user logins, screens viewed, features used, and screen time. In-app content includes patient responses to daily queries, messages posted on the community message board, and secure messages exchanged between patients and clinic providers.	Paradata metrics are collected and stored in the platform automatically and continuously. In-app content will be exported for analysis for the postimplementation evaluation.

[a]DC: Washington, DC.

[b]RA: research assistant.

[c]PL: PositiveLinks.

[d]mHealth: mobile health.

[e]PI: principal investigator.

[f]ORIC: Organizational Readiness for Implementing Change.

Existing data instruments were identified, including those developed to support the broader DC Cohort Study (DC Cohort Study Database, patient consent logs, site assessment forms), as well as those developed and used for evaluations across different clinic sites implementing PL in various contexts (PL posttraining feedback survey, PL paradata). Modifications to these instruments were planned to further support collection of specific data points required to capture all RE-AIM outcome measures that were elucidated during the preimplementation phase. For example, the PL posttraining feedback survey follows providers' completion of learning modules included in the online learning management system used to train them on how to use PL. For providers in this trial, we plan to modify the survey to include validated items from the Organizational Readiness for Implementing Change (ORIC) measure [56], which assesses

providers' perceptions of the collective psychological readiness of their DC Cohort sites to implement organizational changes necessary to incorporate the PL program within their clinic's activities (a characteristic that can be examined at the level of an individual provider and in aggregate at the site level, which is important for the "adoption" dimension of RE-AIM).

Novel instruments were also designed to complete necessary data collection for corresponding RE-AIM dimensions, including both the provider baseline and provider follow-up surveys. Provider follow-up surveys, for example, probe for shifting roles and adaptations related to program implementation made by providers, different ways in which providers engage with available PL features, and provider perspectives on materials and processes supporting program implementation within the

DC Cohort sites (all relevant to the "implementation" dimension of RE-AIM).

Analysis of Implementation Outcomes

All interviews and focus groups conducted for implementation evaluations will be audiotaped, transcribed, and analyzed using Dedoose, as described for formative data analysis. We will use a deductive approach built around CFIR constructs for analysis of stakeholder interviews, with specific constructs selected from our prior evaluation [55] as the a priori categories to assign codes. Two or more investigators will independently code each interview/focus group. Additional codes will be iteratively added in an inductive fashion following coder consensus. We will analyze PL paradata metrics using Google Analytics to characterize user activity for multiple features over the study period (eg, community message board, daily check-ins, provider messaging), as well as establish any associations between frequency/dose of user activity and differences in primary outcomes.

Descriptive statistics will be used to analyze the proportions of patients and providers completing implementation steps (eg, reach, adoption dimensions of RE-AIM). Pearson correlation and binary logistic regression will be used to for exploratory analysis of associations between patient-specific covariates (eg, demographics) and outcome measures for each dimension (eg, reach, including PL usage by patients). We will also examine associations between site-specific covariates (reach measures attained for their patients, adoption measures achieved for their providers, site-level measures, for example, organizational readiness), and differences in patients' primary outcomes (viral suppression, retention in care) observed on average for sites randomized to PL. Provider survey responses will be analyzed using descriptive statistics for Likert responses and with qualitative analysis, as described before for open-ended responses.

Results

Formative Phase

Interviews and focus groups for the formative phase were completed between April and December 2021. Qualitative analysis of interview and focus group transcripts is ongoing as of March 2022. Preliminary app modification requests have been finalized following consensus reached between study team members and the DC Cohort Executive Committee, and the first round of user testing of the modified app with people with HIV has been completed. Recruitment for beta testing with people with HIV was initiated in February 2022.

Cluster Randomized Controlled Trial

Randomization will occur in spring 2022. Patient recruitment for the cluster randomized controlled trial is planned to start in spring 2022.

Implementation Evaluation

Following completion of the preimplementation evaluation, a series of instruments were designed using the RE-AIM framework to support planned data collection for relevant implementation outcomes during the mid- and postimplementation evaluations. The preimplementation evaluation process, including the design of instruments guided by several relevant implementation science frameworks, and logistical planning surrounding the method and timing of instrument distribution, data export/access, and analysis in conjunction with trial activities, will be described in further detail in a separate publication.

We have previously applied the CFIR toward examination of PL implementation in another cohort seeking care at a Ryan White Clinic in Virginia, using a rigorous process of in-depth interviews with participating stakeholders [55]. CFIR domains (with corresponding constructs) that emerged from our prior evaluation as most relevant to PL implementation included Inner Setting (Compatibility, Access to Knowledge and Information), Outer Setting (Patient Needs and Resources, External Policy and Incentives), Characteristics of Individuals (Knowledge and Beliefs), Innovation Characteristics (Adaptability, Complexity), and Implementation Process (Planning, Engagement of Key Stakeholders). Provider surveys (provider baseline and follow-up surveys) were designed to incorporate items that assess these constructs.

Discussion

Principal Results

This is a novel, large-scale cluster randomized controlled trial with a hybrid efficacy-implementation design examining the impact of the PL mHealth intervention on HIV-related patient outcomes with a direct comparison arm of usual care. Prior work to evaluate the clinical effectiveness of PL has been limited to single-arm prospective cohort studies within a nonurban population in Central Virginia. This project will use a randomized design to test the effectiveness of PL against usual care in a diverse urban cohort of people with HIV not achieving durable viral suppression or retention in care. We hypothesize that compared to usual care, clusters participating in the PL intervention will experience improved rates in viral suppression, visit constancy, and retention in care at 12 months.

Comparison With Prior Work

This study will significantly extend the evidence base for this intervention beyond more rural samples by testing its efficacy in a vulnerable urban sample using a robust study design. Further, evaluation of PL implementation to date has been limited to a small subset of clinics within a nonurban context. This project builds on prior preliminary work using implementation science frameworks to identify best practices for implementing PL in a range of different urban HIV care settings and corresponding determinants of implementation success and will inform future disseminations of PL and other mHealth tools at scale in order to improve the lives and health of people with HIV.

Limitations

Limitations exist in this study design. Although formative work for this distinct patient population to date does not suggest significant changes to the platform will be required based on preliminary review, beta testing is underway and further modifications may be suggested by users. The study research

and development teams will prioritize the most feasible changes prior to trial initiation. DC Cohort sites are heterogenous in the services provided to support patient adherence and retention and the patient populations they primarily serve, presenting a potential challenge in assessment of the impact of PL when implemented in conjunction with variable services across clinics. The usual care condition will require assessment at baseline and periodically throughout the trial, and site-level characteristics must be adjusted for during statistical analyses.

Conclusion

Output from the formative phase is currently being analyzed, and corresponding preliminary modifications to the platform are being tested by people with HIV within the DC Cohort. Modifications will be finalized by the app development team following beta testing. Trial activities are expected to begin in spring 2022.

Authors' Contributions

The cosenior authors are KI and AC. KI, AC, RD, and WC are responsible for study conceptualization and planning; AC and KI, funding acquisition; KI, AC, RD, and ALW, project administration; JH, WC, SC, TF, KI, and AC, investigation; and JH, SC, KI, and AC, manuscript preparation. All authors have reviewed and approved the final manuscript.

Data included in this manuscript were collected by the DC Cohort Study Group with investigators and research staff located at the Children's National Hospital Adolescent (Lawrence D'Angelo) and Pediatric (Natella Rakhmanina) clinics, the Interim Senior Deputy Director of the DC Department of Health (DOH) HIV/AIDS, Hepatitis, STD and TB Administration (HAHSTA; Clover Barnes), the Family and Medical Counseling Service (Michael Serlin); Georgetown University (Princy Kumar), the George Washington University Biostatistics Center (Marinella Temprosa, Vinay Bhandaru, Tsedenia Bezabeh, Nisha Grover, Lisa Mele, Susan Reamer, Alla Sapozhnikova, Greg Strylewicz, and Jiayang Xiao), the George Washington University Department of Epidemiology (Shannon Barth, Morgan Byrne, Amanda Castel, Alan Greenberg, Shannon Hammerlund, Paige Kulie, Anne Monroe, James Peterson, and Bianca Stewart) and the Department of Biostatistics and Bioinformatics (Yan Ma), the George Washington University Medical Faculty Associates (Hana Akselrod), the Howard University Adult Infectious Disease Clinic (Jhansi L. Gajjala) and Pediatric Clinic (Sohail Rana), Kaiser Permanente Mid-Atlantic States (Michael Horberg), the La Clinica Del Pueblo (Ricardo Fernandez), MetroHealth (Duane Taylor), the Washington Health Institute (Jose Bordon), Unity Health Care (Gebeyehu Teferi), the Veterans Affairs Medical Center (Debra Benator), the Washington Hospital Center (Maria Elena Ruiz), and the Whitman-Walker Institute (Stephen Abbott).

Conflicts of Interest

RD, SC, ALW and KI have active consulting agreements with Warm Health Technology, Inc.

Multimedia Appendix 1
CONSORT-EHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1305 KB - resprot_v11i4e37748_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
CD: cluster of differentiation
CFAR: Center for AIDS Research
CFIR: Consolidated Framework for Intervention Research
DC: Washington, DC
DOH: Department of Health
HRSA: Health Resources and Services Administration
MEM: mixed effects model
mHealth: mobile health
NIH: National Institutes of Health
ORIC: Organizational Readiness for Implementing Change
PI: principal investigator
PL: PositiveLinks
RA: research assistant
RE-AIM: Reach Effectiveness Adoption Implementation Maintenance

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