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Corrigenda and Addenda

Proposal

Text Messaging and Home Blood Pressure Monitoring for Patients with Uncontrolled Hypertension: Proposal for a Feasibility Pilot Randomized Controlled Trial

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Abstract

Background: A decrease in blood pressure, even modestly (ie, 2 mmHg), lowers cardiovascular morbidity and mortality. Low patient adherence to antihypertensive medication is the most significant modifiable patient-related barrier to achieving controlled blood pressure. Preliminary studies have shown that SMS text messaging and home blood pressure monitoring (HBPM) can be effective in promoting medication adherence and blood pressure control. The best strategy to engage with older patients of low socioeconomic status who are low adopters of technology and disproportionally affected by uncontrolled hypertension is still unknown.

Objective: The objective of this study is to improve blood pressure control in the older, low socioeconomic status population. The study will test two aims: First, we aim to evaluate the feasibility of conducting a randomized controlled trial by using an SMS-based approach among nonadherent, older patients of low socioeconomic status who have uncontrolled hypertension. Feasibility will be assessed in terms of recruitment rates per month (primary outcome); patient acceptability will be evaluated by monitoring retention rates and SMS response rates and using the validated Systems Usability Scale (secondary outcomes). Second, we aim to estimate the effects of the SMS approach on lowering blood pressure and adherence to antihypertensive medications.

Methods: We will recruit 24 patients of low socioeconomic status with uncontrolled hypertension (systolic BP>140 mmHg or diastolic BP>90 mmHg) showing low medication adherence and taking at least two antihypertensives, who have presented to two outpatient clinics of Wake Forest Baptist Health (Winston Salem, North Carolina, USA). Participants will be randomly assigned to either SMS and HBPM (n=12) or usual care and HBPM (n=12) intervention. Clinicians adjusting the patients' medications will be blinded to the study assignment. Text messages will be sent from a secure platform to assess medication adherence and HBPM on a weekly basis. The content and delivery frequency of the proposed SMS intervention are based on input from three focus groups conducted in Spring 2019. Participants in both study arms will receive education on HBPM and using an HBPM device. We hypothesize that we will successfully recruit 24 participants and the intervention will be acceptable to the participants. It will also improve medication adherence (assessed by question Medication Adherence Questionnaire scores) and blood pressure control.

Results: Our study was funded in July 2020. As of May 2021, we have enrolled 6 participants.

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Conclusions: Our findings will help design a larger efficacy trial to advance the field of eHealth delivery systems particularly for older adults of low socioeconomic status. This study addresses a highly significant topic and targets a population of high morbidity and mortality that has been traditionally underrepresented in clinical trials.

Trial Registration: ClinicalTrials.gov NCT03596242; https://clinicaltrials.gov/ct2/show/NCT03596242

International Registered Report Identifier (IRRID): PRR1-10.2196/18984

KEYWORDS

Introduction

The successful implementation of the American College of Cardiology/American Heart Association (ACC/AHA) hypertension guidelines based on the SPRINT (Systolic Blood Pressure Intervention Trial) findings will lead to improvements in the health of the American population and reduce the risks posed by heart disease and stroke [1]. Heart disease is the United States' leading cause of death [1,2]. These guidelines have lowered the blood pressure (BP) thresholds and recommended incorporating home blood pressure monitoring (HBPM). Low patient adherence to antihypertensive medication is the most significant modifiable patient-related barrier to achieving controlled BP [3]. Medication nonadherence contributes to poor BP control that can lead to further cardiovascular complications, including coronary heart disease and heart failure. Furthermore, hospitalization rates are significantly higher among patients with poor medication adherence [4-6]. Objective measures of medication adherence include electronic monitoring of medication administration (eg, Medication Event Monitoring System, prescription records, and dose counts). These measures are expensive, labor intensive, and difficult to incorporate in routine clinic flows. Subjective measures of adherence include physician reports, self-report, and adherence scales. The 8-question Medication Adherence Questionnaire (MAQ) has been well validated to identify adherence among patients with hypertension, and the scores have been shown to correlate well with a range of objective adherence measures [7].

Preliminary studies have shown that SMS text messaging and HBPM can be effective in promoting medication adherence and BP control [8-11]. When HBPM is used in the surveillance of hypertension, it is more cost effective than office visits in the long run, as it reduces the number of unnecessary return visits and antihypertensive drugs administered to chronic users [12]. The best strategy to engage with older, nonadherent patients of low socioeconomic status who are most affected by uncontrolled hypertension is still unknown. The potential of SMS text messaging to engage patients in their own health care has been met with great enthusiasm because of the relatively low cost, transportability, and the widespread use of this technology [8,13]. Internal medicine and nephrology clinics are two outpatient clinics of Wake Forest Baptist Health Winston-Salem, North Carolina, United States. The demographics of older patients visiting those clinics include predominantly African American patients (60%) who are dual Medicare/Medicaid recipients (60%), suggesting that most of them are of low socioeconomic status. Between November 2018 and November 2019, a total of 8170 patients were seen in the two clinics, of which 5889 patients had uncontrolled hypertension (systolic BP [SBP]>130 mmHg or diastolic BP [DBP]>80 mmHg). Among those, 1840 patients with uncontrolled hypertension were adults over the age of 60 years. These numbers are aligned with the literature, with studies reporting hypertension control rates are lower in patients of lower socioeconomic status [2,14]. In 2018, we surveyed a random sample of 50 patients in the outpatient clinic, and 85% of the sample had access to a cellular phone with SMS capability (CL Campos, MD, unpublished data, March 2017). Therefore, developing and evaluating mobile health tools such as SMS to implement clinical guidelines is essential and particularly relevant in settings like our clinic, where the burden of cardiovascular disease and poor adherence to medications is exceptionally high. Using SMS to support this patient population is logical because of its low cost and widespread use [10]. Self‐monitoring has been shown to be pivotal in the management of patients with other chronic diseases such as diabetes [15]. This pilot study aims (1) to evaluate the feasibility of conducting a full-scale randomized controlled trial of a patient-centric, bidirectional SMS with HBPM intervention for older adults of low socioeconomic status with uncontrolled hypertension (BP>130/80 mmHg) who presented at two clinics at Wake Forest Baptist Health, and (2) to explore intervention effects in BP and medication adherence in both groups.

Methods

Sample Characteristics

Twenty-four participants aged 60 years and older will be randomized to either the monitoring intervention or to receive usual care and education; they will be followed-up for 12 weeks. See Figure 1 for patient flow during usual care. The clinicians in the study will identify patients with uncontrolled hypertension during their visits to the clinic. Nurses rooming the patients will record their BP by using an automated BP monitor following the AHA guidelines [16]. The study coordinator will approach prospective patients, that is, those who are 60 years and older, have uncontrolled hypertension (ie, SBP>130 mmHg or DBP>80 mmHg), and have two or more BP medications on their medication list. Nurses will interview the participants in a private room and those with less than college education and with an MAQ score of 0 to 6 will be classified as *nonadherent* and will be invited to participate in the study. The MAQ cut-off score of ≤6 was chosen for this study because it has been used in previous studies and serves a highly sensitive tool for identifying medication nonadherence [17-19]. Low education

has been used a proxy for low socioeconomic status [2]. The study coordinator will assess the potential participant's phone ownership, text messaging ability, text messaging willingness, and receptivity to the intervention (and record all this information). Participants will be excluded if they have end-stage renal disease (on hemodialysis or peritoneal dialysis), a kidney transplant recipient, unable to afford BP medications, institutionalized (hospice or nursing home care) or unable or unwilling to provide consent to participation in this study (ie, dementia or cognitive impairment), or diagnosed with a terminal illness (eg, cancer, chronic respiratory failure, or requiring oxygen support). Participants who are unable to pay for their medications will be excluded as the study will not provide BP medications. The sample size of 12 patients in each group was chosen based on the feasibility and budget [20] (Figure 2).

Figure 1. Usual care patient flow. DBP: diastolic blood pressure; SBP: systolic blood pressure.

Office visit 1

1. Rooming by nurse
- Blood pressure measured with automated blood pressure machine following American Heart Association guidelines
- Medication reconciliation
- Blood pressure re-check if SBP>140 or DBP>90 after 5 minutes
2. Clinician visit
- Medication reconciliation
- Medication adjustment if warranted
- Recommendation on home blood pressure monitoring

Office visit 2- Follow up visit at two weeks (at clinician discretion)

1. Nurse visit
- Blood pressure measured with automated blood pressure machine following American Heart Association guidelines
- Medication reconciliation
- Blood pressure re-check if SBP>140 or DBP>90 after 5 minutes
- In-basket message to clinician with normal blood pressure results or if SBP>140 or DBP>90 then
2. Clinician visit
- Medication reconciliation
- Medication adjustment if warranted

Office visit 3 at 12 weeks

3. Nurse rooming
- Blood pressure measured with automated blood pressure machine following American Heart Association guidelines
- Medication reconciliation
- Blood pressure re-check if SBP>140 or DBP>90 after 5 minutes
4. Clinician visit
- Medication reconciliation
- Medication adjustment if warranted

Figure 2. Study algorithm. BP: blood pressure; HBPM: home blood pressure monitoring; MAQ: Medication Adherence Questionnaire.
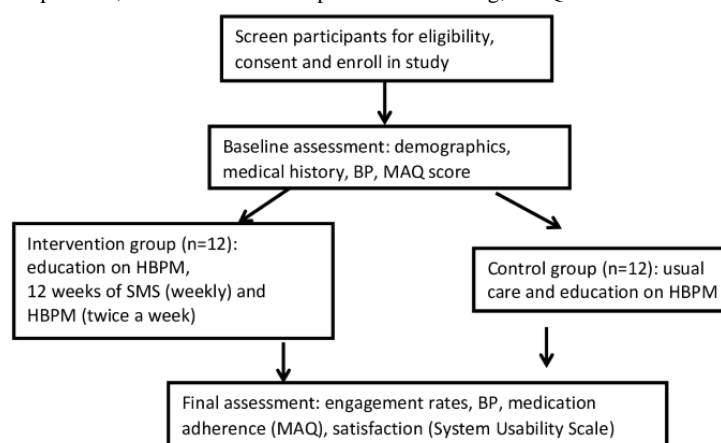
Study Intervention

Participants will be randomized to the two study groups by using a computer-based random number generating algorithm. Baseline demographic characteristics of the participants will then be collected. All participants will receive a previously validated Omron Bp785n 10 Series arm blood BP monitor and printed instructions in English or Spanish (as per the AHA) on how to perform HBPM [16]. Participants will be instructed on checking their BP at home at least twice a week [21,22]. Text messages used in the intervention were vetted by patients with hypertension in three focus groups held in the Spring of 2019. A programmer will build the SMS text messaging system to be used for the study intervention by using the Research Electronic Data Capture (REDCap)/Twilio platform, keeping a record of the participants contacted via SMS (sent and received messages). Twilio is a cloud communication platform that embeds messaging directly into REDCap. An example of the SMS system is as follows:

- Adherence checkpoint: *Good morning! Did you take your blood pressure medications today?*
  - "No" response: *Let's try to stay on top of taking them daily! You can do this!*
  - Additional prompt: *Did you fill your prescription?*
    - If no, alert to study coordinator to place phone call to determine barrier to filling BP medication.
  - Additional prompt: *Did you have any side effects from your blood pressure medication?*
    - If yes, phone call to determine side effect from BP medication.
  - "Yes" response: *Keep it up! [Thumbs up emoji]*
- Self-monitoring phase: *Have you been checking your BP? What is the top number? Bottom number?*

If the participants report SBP below 90 mmHg and or above 180 mmHg and/or DBP below 50 mmHg and/or above 120 mmHg on more than one occasion, those numbers will be considered to be outside of the threshold range. These thresholds are made based on the recommendations by AHA/ACC hypertension guidelines, which designate a hypertensive urgency to be 180/120 mmHg or higher and hypotension urgency to be 90/50 mmHg or lower [23]. The study coordinator will be alerted with any outlier BP recordings, who in turn will alert clinicians through an in-basket message in the electronic medical record (Wake One). The patient will then receive an SMS and a phone call and will be prompted to make a clinic visit.

Patients who do not show up to the follow-up visit will be contacted via phone to assess adherence barriers. The study coordinator will create a telephone encounter in the patient's electronic health record to document their discussion and route it to the patient's primary care provider. Patients who refuse participation in the study will be asked for the reason, and their responses will be recorded to determine any barriers to participation. The study coordinator will attempt to contact patients who miss follow-up visits every week up to three times; if the patient still cannot be contacted after three attempts, the patient will be considered "lost to follow-up." Participants will receive a stipend to compensate them for their time in participating in the study.

Blinding of Outcomes Assessments

The personnel performing the outcome assessments will be blinded to the participants' study assignments.

Statistical Analysis

All statistical analyses will be performed using SAS 9.3 To accomplish Aim 1, we will examine the number of participants enrolled into the study at each study clinic by month over the course of recruitment phase, as well as the average and overall number of participants enrolled per month within each clinic. These rates will assist us in determining the feasibility of recruiting a sufficient sample for the larger trial, and it will potentially inform protocol adjustments. We will estimate additional indicators for feasibility throughout the trial, including measures of retention of participants through the 12 weeks and adherence to the protocol within each group, as well as acceptability of the intervention as measured by the questionnaire (Table 1). We will quantify missing data and dropouts, and we will examine the reasons for ineligibility and discontinuation in the study. For Aim 2, we will examine all data distributions and calculate summary statistics by group using an intention-to-treat approach. Although we will not have adequate statistical power for testing our hypotheses of improved BP control and medication adherence as a result of the intervention, we will conduct an exploratory analysis of any

treatment effects (Table 1). An important end product of the trial will be our estimates of variance and correlation for these and other potential outcomes of interest for the larger trial. These estimates will be compared with estimates from studies similar to ours but focusing on other populations and will be used to inform power for the larger trial.

Table 1. Evaluation and outcomes.

Outcome and evaluation	Method	Baseline	During the 12-week intervention	At week 12	Expected outcome
Primary outcome: Feasibility					
Recruitment	Track number of enrolled participants per week	✓	✓		24 patients will be recruited in 4 months. The team will learn from the study findings and adjust the protocol to achieve goals.
Secondary outcomes					
Protocol adherence	SMS response rate/week BP[a] measurement transmission/week		Weekly		Monitoring of adherence to protocol
Acceptability	Systems Usability Scale (SUS) questionnaire. • Track participant discontinuation and loss to follow-up • Track proportion of patients screened but excluded because they did not own a phone with SMS capability • Track participant discontinuation and loss to follow-up • Informal comments from participants	✓	Weekly	✓	Monitoring of acceptability; the SUS yields a single score on a scale of 0 to 100. An SUS score >68 would be considered above average.
Exploratory outcomes					
Systolic BP and diastolic BP change	BP will be measured per clinic protocols and extracted from the patient's electronic medical record. The average change will be calculated and reported in mmHg.	✓		✓	Systolic BP and diastolic BP will improve
Medication adherence	8-item Morisky Medication Adherence Questionnaire (MAQ)	✓		✓	MAQ scores will improve

[a]BP: blood pressure.

Data Safety and Monitoring

The proposed study presents small risks to participants. They will receive usual medical care. The principal investigator will be responsible for the overall monitoring of the data and safety of the study participants. We will use REDCap, a secure online platform designed for research, to collect all patient data. Participants' demographics (including their education level), comorbidities, number of medications, number of BP medications prescribed, and BP measures will be extracted from Wake One records when available. The level of education will be confirmed verbally with each participant during consent process. Only one participant identifier will appear in the data collection forms.

Results

Our study began recruitment in September 2020, and the anticipated completion date for the recruitment phase is March 31, 2021. This study is funded by CTSI Pilot funding from Wake Forest Baptist Health. This trial has been registered in ClinicalTrials.gov (Identifier: NCT03596242).

Discussion

The proposed study will evaluate the feasibility of conducting a randomized controlled trial of a new patient-centric SMS delivery system tailored primarily for older adults of low socioeconomic status demonstrating nonadherence to antihypertensive medication. The SMS system was designed with the input of three focus groups composed of older minority patients with hypertension. The study is distinctive in its ability to recruit and test the implementation in a population particularly affected by medication nonadherence and uncontrolled hypertension. To engage patients in health care is considered a key strategy to improve patients' adherence, clinical outcomes, and satisfaction about the care received [24-26]. If successful, a larger efficacy trial will help advance the eHealth delivery

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system particularly for underrepresented minority patients in the context of BP management. Reducing disparities is a key component of promoting health equity. Assessing interventions aimed to reduce health care disparities are needed to counteract social risk factors in order to achieve health equity [27-29].

We intend to publish the findings of this study. If successful, we will plan to conduct a larger efficacy randomized controlled trial. The dissemination of these results will help improve BP control in this patient population. In addition, our long-term goal is to develop an automated patient-centric system that will improve monitoring of BP and medication adherence in other ambulatory clinics, to help improve BP control rates among older adults with uncontrolled hypertension who visit other primary care clinics at Wake Forest Baptist Health.

Conflicts of Interest

None declared.

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Abbreviations

ACC: American College of Cardiology
AHA: American Heart Association
BP: blood pressure
REDCap: Research Electronic Data Capture
DBP: diastolic blood pressure
HBPM: home blood pressure monitoring
MAQ: Medication Adherence Questionnaire
SBP: systolic blood pressure
SPRINT: Systolic Blood Pressure Intervention Trial

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Protocol

Effects of Providing Tailored Information About e-Cigarettes in a Web-Based Smoking Cessation Intervention: Protocol for a Randomized Controlled Trial

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Abstract

Background: There is an ongoing debate whether electronic cigarettes (e-cigarettes) should be advocated for smoking cessation. Because of this uncertainty, information about the use of e-cigarettes for smoking cessation is usually not provided in governmental smoking cessation communications. However, there is an information need among smokers because despite this uncertainty, e-cigarettes are used by many smokers to reduce and quit tobacco smoking.

Objective: The aim of this study is to describe the protocol of a randomized controlled trial that assesses the effect of providing tailored information about e-cigarettes compared to not providing this information on determinants of decision making and smoking reduction and abstinence. This information is provided in the context of a digital smoking cessation intervention.

Methods: A randomized controlled trial with a 6-month follow-up period will be conducted among adult smokers motivated to quit smoking within 5 years. Participants will be 1:1 randomized into either the intervention condition or control condition. In this trial, which is grounded on the I-Change model, participants in both conditions will receive tailored feedback on attitude, social influence, preparatory plans, self-efficacy, and coping plans. Information on 6 clusters of smoking cessation methods (face-to-face counselling, eHealth interventions, telephone counselling, group-based programs, nicotine replacement therapy, and prescription medication) will be provided in both conditions. Smokers in the intervention condition will also receive detailed tailored information on e-cigarettes, while smokers in the control condition will not receive this information. The primary outcome measure will be the number of tobacco cigarettes smoked in the past 7 days. Secondary outcome measures will include 7-day point prevalence tobacco abstinence, 7-day point prevalence e-cigarette abstinence, and determinants of decision making (ie, knowledge and attitude regarding e-cigarettes). All outcomes will be self-assessed through web-based questionnaires.

Results: This project is supported by a research grant of the National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu). Ethical approval was granted by the Ethics Review Committee Health, Medicine and Life Sciences at Maastricht University (FHML-REC/2019/072). Recruitment began in March 2020 and was completed by July 2020. We enrolled 492 smokers in this study. The results are expected to be published in June 2021.

Conclusions: The experimental design of this study allows conclusions to be formed regarding the effects of tailored information about e-cigarettes on decision making and smoking behavior. Our findings can inform the development of future smoking cessation interventions.

Trial Registration: Dutch Trial Register Trial NL8330; https://www.trialregister.nl/trial/8330

International Registered Report Identifier (IRRID): DERR1-10.2196/27088

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Introduction

Background

Tobacco smoking is a major public health threat, contributing to increased morbidity and mortality [1]. In the Netherlands, tobacco smoking is responsible for more than 19,000 deaths per year [2]. Many smokers report that they want to quit smoking, but only about 4% of smokers trying to quit without assistance succeed in their cessation attempts [3,4]. Most smokers find it hard to quit smoking because of the highly addictive nature of nicotine [5], and while they smoke for the nicotine, their probability of dying prematurely increases owing to the by-products of burnt tobacco (eg, tar) [6]. In this paper, we will describe the study protocol for a randomized controlled trial assessing an intervention aimed at quitting combustible cigarette smoking and the potential added effects of providing tailored information on electronic cigarettes (e-cigarettes).

e-Cigarettes for Smoking Cessation

e-Cigarettes, also called as electronic nicotine delivery systems, are handheld electronic devices that generate aerosols by heating a liquid that usually contains nicotine, flavorings, and other compounds [7]. Because e-cigarettes do not burn tobacco, users are not exposed to the damaging substances of combustible tobacco [7]. However, it is important to note that, although e-cigarette aerosols generally contain fewer toxic chemicals than cigarette smoke, all tobacco (and related) products, including e-cigarettes, carry risks [8]. Smokers who want to quit smoking can use e-cigarettes as an aid for smoking reduction, cessation, and relapse prevention [7,9]. e-Cigarettes may be advantageous over nicotine replacement therapy because they are able to provide nicotine effectively and mimic the smoking experience [10]. Using e-cigarettes for smoking cessation can be considered as a tobacco harm reduction strategy [11]. There is an ongoing debate whether e-cigarettes should be advocated for smoking cessation [12]. A recent Cochrane systematic review concluded that the current evidence provides moderate certainty that e-cigarettes with nicotine are superior to e-cigarettes without nicotine and nicotine replacement therapy concerning smoking cessation [7]. Reviews on the effectiveness of using e-cigarettes for smoking cessation stress that more evidence is needed to be confident about the effects [7,8,13-15]. Furthermore, e-cigarettes developed quickly in recent years and findings from studies conducted with past generations of e-cigarettes (eg, cigalikes, battery pens) are not applicable to state-of-the-art e-cigarettes (eg, pod mods) [8]. Hence, more randomized controlled trials are needed to gain insight into the effectiveness of e-cigarettes for smoking cessation.

Information Need on e-Cigarettes

In line with this ongoing debate, e-cigarette users, smokers, and nonusers reported that they have unanswered questions regarding e-cigarettes [16]. They raised questions about the harmfulness of e-cigarettes, especially compared to cigarette smoking, about the long-term health effects of e-cigarette use, and about e-cigarettes as a smoking cessation method. e-Cigarette users also report a lack of knowledge regarding the ingredients of e-cigarettes and its health effects [17]. Furthermore, incorrect risk perceptions regarding e-cigarette use and tobacco smoking are held by smokers. For instance, only half of the smokers believe that the use of e-cigarettes is less harmful than smoking tobacco [18], and fruit or candy flavors in e-cigarettes are perceived as less risky compared to tobacco flavors [19]. Thus, there is an information need regarding e-cigarettes, especially among smokers who may benefit from e-cigarettes as an aid in smoking cessation.

Decision Making on e-Cigarettes

Owing to the uncertainty surrounding e-cigarettes, it is important that smokers have sufficient knowledge about e-cigarettes when deciding whether to use them. An informed choice is often defined based on relevant knowledge and the congruence between attitudes and conducted behavior [20]. These conceptualizations of informed decision making employ cut-off points in order to dichotomize constructs into positive and negative outcomes (eg, sufficient knowledge or not). These cut-off points are chosen arbitrarily, indicating that there is neither evidence for the choice of these cut-off points nor evidence that there is an underlying dichotomy at all [21]. Furthermore, individuals who score values close to the cut-off points but on opposite sites (eg, on a scale from 1-10, if 5 is considered to be the cut-off point, individuals who score values close to the cut-off point but on opposite sites would then for instance score 4.9 and 5.1) are categorized as being very different, while in reality being quite similar [21]. In this research, we will avoid dichotomizing continuous variables by examining the constructs of decision making separately.

Research Goal

The goal of this study will be to assess the effect of tailored communication about e-cigarettes in a digital smoking cessation intervention on determinants of decision making, smoking reduction, and smoking cessation. In the context of a tailored eHealth program, smokers will be randomized into 1 of the 2 conditions—either receiving detailed tailored information about e-cigarettes or not. Information provision about e-cigarettes can have differential effects on smoking behavior, including favorable effects (eg, decreased number of tobacco cigarettes smoked, increased number of tobacco-abstinent participants) as well as unfavorable effects (eg, decreased number of tobacco-abstinent participants). Differences between conditions in the number of dual users (ie, people using e-cigarettes and smoking tobacco cigarettes) will be examined as well. Regarding decision making, we hypothesize that participants in the intervention condition will have more knowledge about e-cigarettes directly after the intervention compared to participants in the control condition. We did not formulate a hypothesis for the determinant attitude as neither a more positive nor a more negative attitude is directly associated with improved decision making. Regarding smoking behavior, we hypothesize

that participants in the intervention condition will have smoked less tobacco cigarettes (adjusted for baseline measurement) in the past 7 days at the 6-month follow-up compared to participants in the control condition.

Methods

Study Design

A randomized controlled trial will be conducted and the results will be reported according to the CONSORT-EHEALTH checklist [22]. Participants will be 1:1 randomized into either the intervention condition or the control condition. Participants

in both conditions will receive the same underlying digital smoking cessation intervention. The 2 conditions differ in the provision of information about e-cigarettes. Smokers in the intervention condition will receive detailed tailored information on e-cigarettes whereas smokers in the control condition will not receive that information. Measurements will be conducted at 3 points in time. A baseline questionnaire will be conducted at the start of the intervention. A first follow-up questionnaire will be conducted directly after completion of the intervention (ie, postintervention). A second follow-up questionnaire will be conducted at 6 months from the baseline. All questionnaires will be web-based and self-assessed. Figure 1 shows the study design.

Figure 1. Flowchart of the study design.
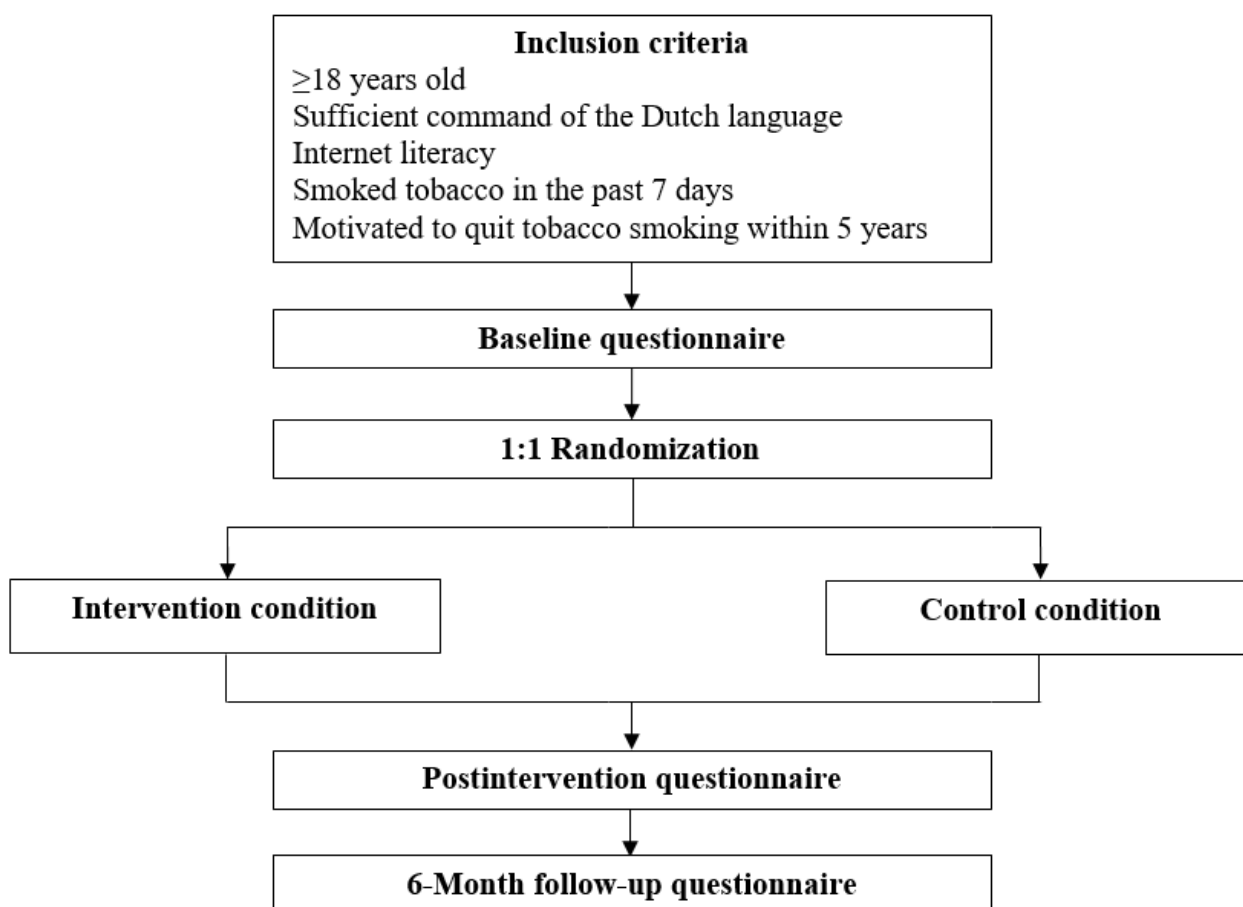
Participants and Recruitment

Inclusion criteria were that participants are at least 18 years old, have sufficient command of the Dutch language, have necessary internet literacy to use the intervention, have smoked tobacco in the past 7 days, and are motivated to quit tobacco smoking within 5 years. Participants were recruited using multiple strategies. A Dutch research agency was consulted in order to recruit smokers from their participant pool. Google Ads were used to recruit people who were searching the Google search engine for terms around smoking cessation. Social media and smoking-related forums were approached to recruit members of those channels. Moreover, flyers were distributed door-to-door in the Maastricht region, the Netherlands. Incentives were provided to participants who took part in the

intervention and who answered all the questionnaires (baseline, postintervention, 6-month follow-up). Ten gift vouchers of €25 (US $1=€0.83) were raffled off among all participants who were recruited organically. Participants stemming from the research agency collected points within the system of the research agency, which could be exchanged for gift vouchers or donations. Interested individuals were directed to an external intervention website. Potential participants were informed that they would receive tailored smoking cessation advice during the intervention. The nature of tailoring was explained to clarify that the advice will be based on the answers participants provide to the questions during the intervention. The aim of this study was stated as exploring the opinion of smokers on the intervention. e-Cigarettes were not mentioned in the participant information text. Potential participants were informed about the

possibility to withdraw from the study at any time without providing any reason. Participants did not need to register on the intervention website in order to limit the participation burden. After giving web-based informed consent, the inclusion criteria were verified by a short questionnaire. The intervention would take about 20 minutes (including the baseline and postintervention questionnaire). Answering the 6-month follow-up questionnaire will take about 3 minutes.

Sample Size Calculation

The sample size was calculated using the ufs package [23] in R. Acknowledging that the accurate estimation of effect sizes is more important than relying on *P* values, we based our sample size calculation on accuracy in parameter estimation for Cohen *d* [24]. Unfortunately, we cannot infer the effect size from earlier research since we are not aware of any prior studies assessing the influence of providing information about e-cigarettes in a digital intervention on decision making and smoking cessation. Thus, we assumed a small effect size as it is usually found in digital health research on smoking cessation interventions [25]. Taking into account the small effect size of Cohen *d* of 0.2, a margin of error (half-width) of 0.15, and a confidence level of 95%, a total sample size of 687 participants is required.

Intervention

The intervention will be a digital computer-tailored smoking cessation intervention that will be partly based on an earlier developed intervention at Maastricht University [26-28]. Compared to generic information, computer-tailored interventions provide highly individualized information that is tailored to the motivational and behavioral characteristics of the recipient [29]. According to the elaboration likelihood model, information that is perceived as personally relevant is expected to lead to more in-depth processing and, in turn, to more sustained attitudinal and behavioral changes [30]. The computer-tailored intervention will be based on the I-Change model [31,32], a comprehensive model that integrates various social-cognitive theories (see Figure 2). During the intervention, participants in both conditions will receive tailored advice on the pros and cons of quitting smoking (ie, attitude), social influence, preparatory plans, self-efficacy, and coping plans concerning smoking cessation. Participants will be able to decide based on their own interests and needs on which determinants of smoking cessation they would like to receive tailored advice.

The information for the tailoring process is gathered by means of questionnaires that the recipient has to fill in during the intervention. Subsequently, a computerized process, employing if-then rules, selects appropriate feedback messages from a pool of all messages based on the answers that the recipient has given in the questionnaires [29,33].

The items of the questionnaires are based on previous research [27,28] (Elling and de Vries, unpublished data, 2021) and are reported in Multimedia Appendix 1. The pros and cons of quitting smoking (eg, "If I stop smoking, my physical fitness will improve") will be assessed by 16 items. Social influence will consist of 2 components with 2 items each: social modeling (eg, "Does your partner smoke?") and social support (eg, "Does your partner support you when you decide to quit smoking?"). Figure 3 illustrates an example of tailored advice for social support. Preparatory plans (eg, "I am planning to stop smoking completely without cutting down on cigarettes first") will be assessed by 5 items. Self-efficacy (eg, "I find it difficult not to smoke if I am stressed") will be assessed by 11 items. Coping plans (eg, "I have made clear plans to make sure that I will not smoke if I am stressed") will be assessed by 11 items, reflecting the same situations as assessed for self-efficacy. After answering and receiving information on the determinants of smoking cessation, participants in both conditions will be able to indicate about which 6 clusters of smoking cessation methods they want to receive information (face-to-face counselling, eHealth interventions, telephone counselling, group-based programs, nicotine replacement therapy, and prescription medication).

All advices concerning the pros and cons of quitting smoking, social influence, preparatory plans, self-efficacy, and coping plans will be presented in the form of spoken animations with little on-screen text in order to increase user experience and user engagement [34] (Elling and de Vries, unpublished data, 2021). A screenshot of an example of a webpage of the intervention with an animation is shown in Figure 4. All texts will be written in simple language and no hyperlinks to other resources will be presented. The website will be developed employing responsive web design and will thus be accessible on all common devices (eg, computer, smartphone) with all types of screen sizes. A second screenshot of a typical webpage presenting 2 questions of the tailoring process is shown in Figure 5.

Figure 2. I-Change model [34].
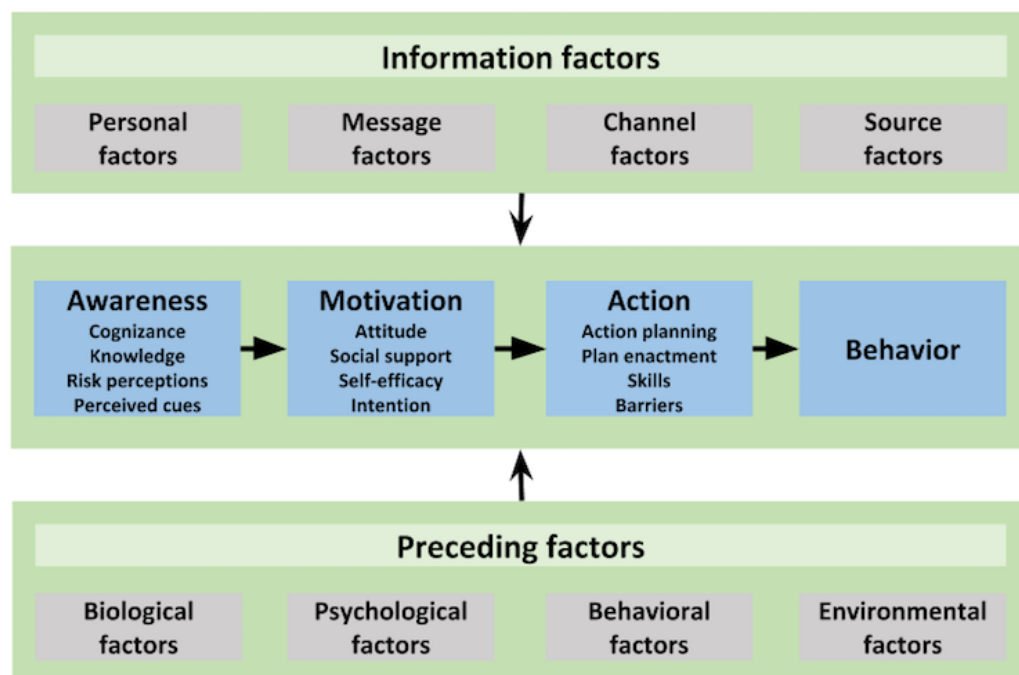
Figure 3. An example of tailored advice about the social influence of the partner.
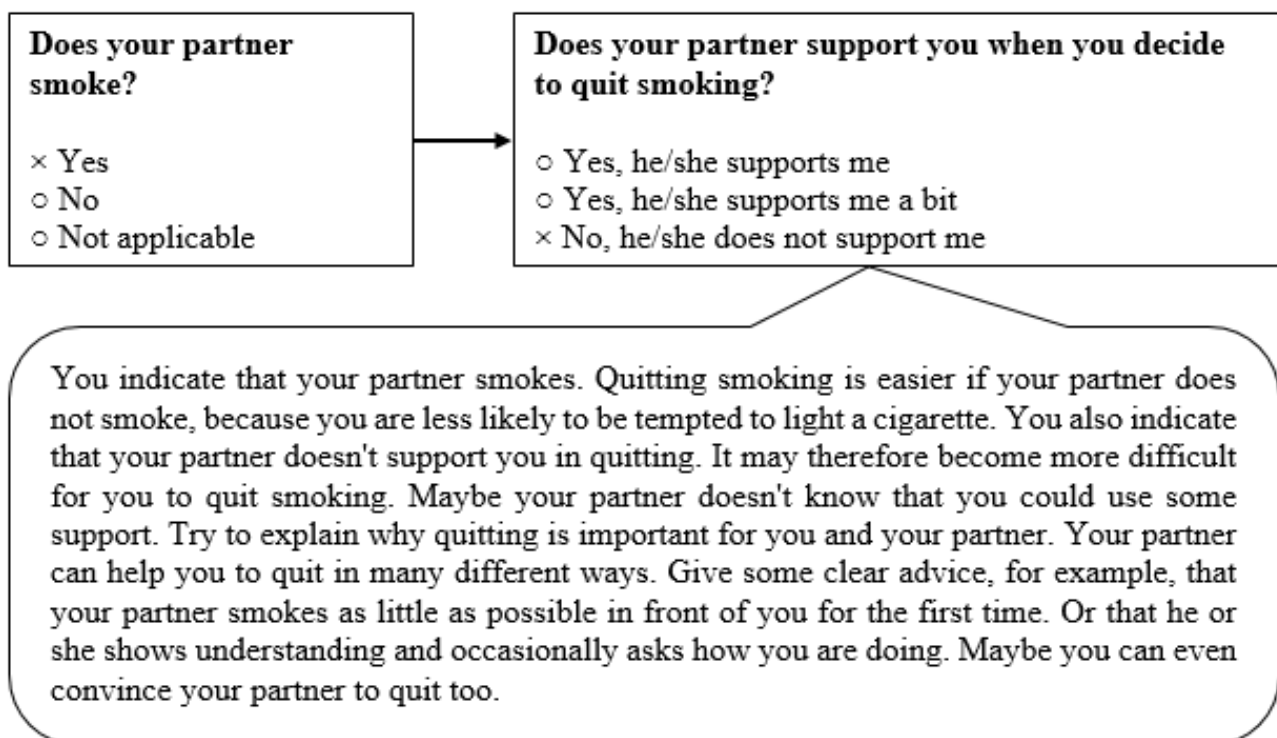
Figure 4. Screenshot of a webpage of the intervention showing an animated video advice.
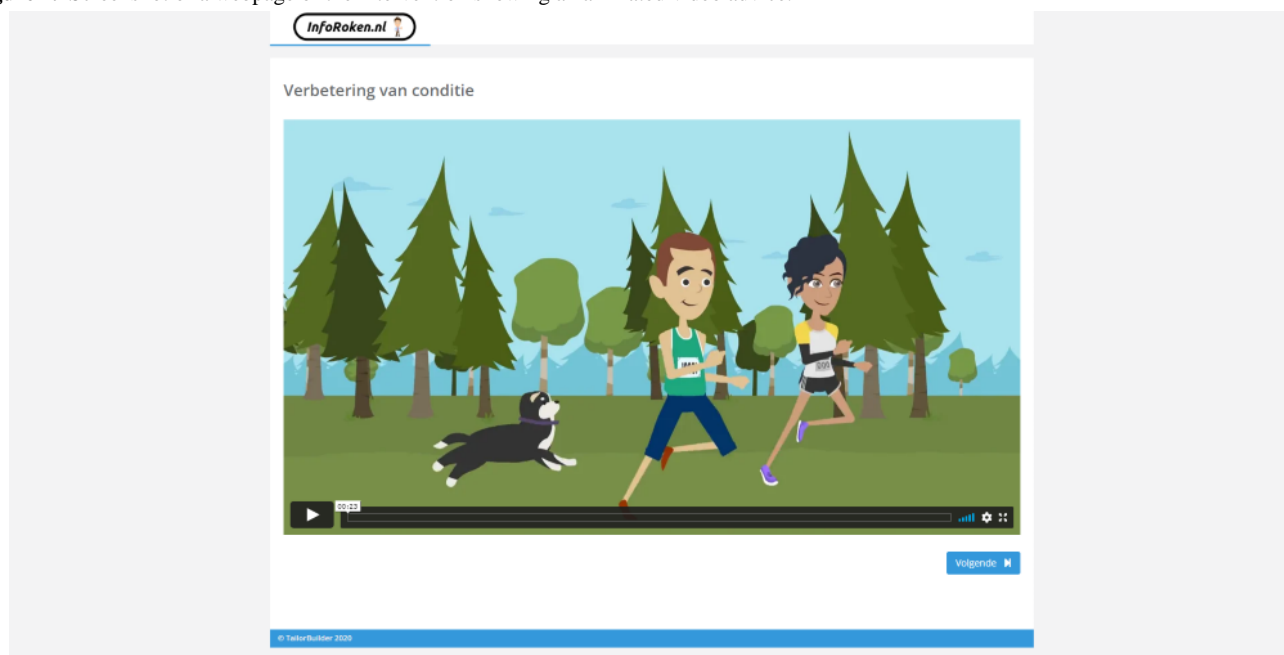
Figure 5. Screenshot of a webpage of the intervention showing 2 questions with answer options.

Tailored Information on e-Cigarettes

Participants in the intervention condition will receive tailored information on e-cigarettes based on 5 items (Do you know what an e-cigarette is? How harmful do you think e-cigarettes are compared to tobacco cigarettes? Do you think e-cigarettes are helpful in quitting smoking? Do you think using e-cigarettes is difficult or easy? Have you seen reports in the media about illnesses and deaths in the United States related to the use of e-cigarettes?). These items were developed by the research team and evaluated for comprehensibility and clarity by a

communication expert of the National Institute for Public Health and the Environment. In general, the information will convey the message that, for smokers, the use of e-cigarettes is less harmful than continuing smoking tobacco cigarettes. However, it will be highlighted that this does not mean that using e-cigarettes is harmless. Regarding smoking cessation, it will be stressed that e-cigarettes are especially interesting for smokers who have tried to quit several times but have not succeeded. The possibility to (gradually) decrease the nicotine content of the e-cigarette liquid in order to cope with nicotine withdrawal symptoms will be discussed. The outbreak of lung

injury associated with e-cigarette use in the United States of America will be discussed in detail. Participants in the control condition will receive a short text explaining that e-cigarettes are not actively recommended for smoking cessation ("A rather recent method that can be used to quit smoking is the e-cigarette. There is still a lot of uncertainty surrounding the e-cigarette. The e-cigarette is therefore not actively recommended as a method to quit smoking in the Netherlands."). This short text is aimed to resemble the status quo of communication on e-cigarettes in smoking cessation interventions in the Netherlands.

Measures

All items of the baseline questionnaire, postintervention questionnaire, and 6-month follow-up questionnaire are reported in Multimedia Appendix 2.

Smoking Reduction and Abstinence

The primary outcome of this study will be the number of tobacco cigarettes smoked in the past 7 days [35]. Secondary outcomes will be the average number of tobacco cigarettes smoked per day [36], 7-day point prevalence tobacco abstinence [37], and 7-day point prevalence e-cigarette abstinence [37]. If participants indicate to have used an e-cigarette, the nicotine content of the e-cigarette will be assessed. All outcomes will be assessed at baseline and at 6-month follow-up.

Smoking Cessation Methods

The *intention to use a smoking cessation method* (split-up per method) will be assessed directly after the intervention on a 5-point Likert scale ranging from 1=definitely do not to 5=definitely do. At the 6-month follow-up, we will assess which smoking cessation methods were actually utilized (ie, *smoking cessation method chosen*) on a dichotomous scale (yes/no). The following methods will be assessed: face-to-face counselling, eHealth interventions, telephone counselling, group-based programs, nicotine replacement therapy, prescription medication, and e-cigarettes. Participants can also indicate to have used another smoking cessation method or to not have used any smoking cessation method at all.

Determinants of Decision Making

Determinants of decision making will be assessed by 2 constructs: knowledge and attitude. Knowledge about e-cigarettes (eg, There are less harmful substances in e-cigarettes compared to tobacco cigarettes) will be measured by 7 items with response options being 1=True, 2=False, and 3=I do not know. Correct answers will be coded as 1 and incorrect answers and the option I do not know as 0. The sum of the correct answers is the overall score for the construct knowledge. Attitude on e-cigarettes (eg, I think that using e-cigarettes is better for my health than smoking cigarettes) will be measured by 10 items on a 5-point Likert scale ranging from 1=I totally disagree to 5=I totally agree. All items will be assessed directly after the intervention.

Process Evaluation

A process evaluation will be conducted by assessing an *overall grade* for the intervention [27], asking open questions about positive and negative aspects of the intervention, and by

analyzing system usage data [27]. An *overall grade* will be measured by 1 item on a scale ranging from 1=very bad to 10=very good. The open questions (eg, What do you like about the intervention?) will be asked to capture aspects that are perceived as both positively and negatively. The overall grade and the open questions will be assessed directly after the intervention. The time spent on the intervention website and the device (eg, smartphone, tablet, desktop) of the users will be measured using the TailorBuilder software (OverNite Software Europe BV). The time spent on the website will be provided per condition, whereas the device used will be reported for all participants together.

Demographics and Smoking Characteristics

We will assess the demographics by asking for *gender* (0=male, 1=female, 3=not on the list), *age*, and *education level* (1=low, 2=intermediate, 3=high). *Addiction level* will be assessed by the Fagerström Test for Nicotine Dependence [38]. The 6 items of the scale will be summed into an overall score ranging from 0 to 10. We will classify the dependence level as 0-2=low, 3-4=moderate, 5-6=strong, and 7-10=very strong. Addiction level will be measured at baseline. The *intention to quit smoking* will be assessed by 2 items. First, participants will be asked when they are planning to quit smoking (1=within 1 month, 2=within 6 months, 3=within 1 year, 4=within 5 years) [39]. Second, participants will be asked to indicate whether they are planning to quit smoking within 1 year on a 5-point Likert scale ranging from 1=definitely do not to 5=definitely do. The intention to quit smoking will be measured at baseline and after the intervention for every participant and at 6-month follow-up for participants who indicated that smoking cessation was not successful.

COVID-19 Pandemic and Smoking Behavior

The COVID-19 pandemic coincides with the recruitment and follow-up period of this research project. Participants are influenced by the pandemic in numerous ways, including the information that tobacco smoking may increase susceptibility to and severity of COVID-19 [40]. Thus, we included 15 items about smoking-related beliefs and behavior in times of COVID-19. These items are reported in Multimedia Appendix 3.

Analyses

The focus of all the analyses will be on the effect size accompanied by the confidence interval [41]. Multiple imputations will be conducted to account for the missing observations at 6-month follow-ups. Sensitivity analyses will be conducted for complete cases and intention-to-treat [42]. The primary outcome (number of tobacco cigarettes smoked in past 7 days) will be tested by analysis of covariance [43,44]. The dependent variable will be the number of tobacco cigarettes smoked weekly at the 6-month follow-up. The number of tobacco cigarettes smoked weekly at baseline will be included as the covariate. The independent variable will be the condition. The average number of tobacco cigarettes smoked per day will be tested similarly. Logistic regression analyses will be performed to assess the effect of the intervention condition and control condition on 7-day point prevalence tobacco abstinence

and 7-day point prevalence e-cigarette abstinence. Analyses of variance will be performed to test for differences in the determinants of decision making (knowledge and attitude on e-cigarettes) between conditions. Addiction level will be included as a covariate in additional sensitivity analyses. Previous research suggests that the addiction level needs to be considered when assessing the effectiveness of e-cigarettes for smoking reduction and cessation [45]. The open questions will be analyzed per question. Codes for recurrent themes will be created and reported in a table with example quotes and the number of times a theme was addressed.

Results

The study is registered in the Netherlands Trial Register [46]. Ethical approval was granted by the Ethics Review Committee Health, Medicine and Life Sciences (FHML-REC) at Maastricht University (FHML-REC/2019/072). This project is supported by a research grant of the National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu). Recruitment began in March 2020 and was completed by July 2020. We enrolled 492 smokers in this study. The results are expected to be published in June 2021.

Discussion

Governmental public health institutes inform the public about smoking cessation. Usually, only information on the *best* option to quit smoking is provided, which is complete smoking cessation using evidence-based smoking cessation methods. Smokers may not follow this advice and they may do nothing about cessation, thereby making it the *worst* option. Smokers may also seek alternative advices for the *second best* option, which can be using e-cigarettes for smoking reduction and cessation. However, information about e-cigarettes is mostly not included in governmental smoking cessation interventions. Including information on e-cigarettes in smoking cessation interventions can yield different effects, which can be both favorable and detrimental to smokers specifically and public health in general. On the one hand, communication about e-cigarettes could lead to more people quitting smoking with the help of e-cigarettes, thereby reducing the number of people choosing the worst option. On the other hand, communication about e-cigarettes could lead to more people choosing the second best option who would otherwise have chosen the best option. This protocol describes a randomized controlled trial that aims to investigate the effects of including tailored information about e-cigarettes on decision making and smoking behavior. These findings can inform the development of future smoking cessation interventions, in particular, and communication about the second best option, in general.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Determinants of smoking cessation tackled in the intervention.
[DOCX File , 27 KB - resprot_v10i5e27088_app1.docx]

Multimedia Appendix 2
Items of the baseline, postintervention, and 6-month follow-up questionnaires.
[DOCX File , 34 KB - resprot_v10i5e27088_app2.docx]

Multimedia Appendix 3
Questionnaire items about smoking-related beliefs and behavior in times of COVID-19.
[DOCX File , 26 KB - resprot_v10i5e27088_app3.docx]

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Abbreviations

e-cigarette: electronic cigarette

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Protocol

A Nurse Case Management HIV Prevention Intervention (Come As You Are) for Youth Experiencing Homelessness: Protocol for a Randomized Wait-list Controlled Trial

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Abstract

Background: Youth experiencing homelessness are more likely than housed youth to experience premature death, suicide, drug overdose, pregnancy, substance use, and mental illness. Yet while youth experiencing homelessness are 6 to 12 times more likely to become infected with HIV than housed youth, with HIV prevalence as high as 16%, many do not access the prevention services they need. Despite adversities, youth experiencing homelessness are interested in health promotion programs, can be recruited and retained in interventions and research studies, and demonstrate improved outcomes when programs are tailored and relevant to them.

Objective: The study aims to compare the efficacy of a nurse case management HIV prevention and care intervention, titled Come As You Are, with that of usual care among youth experiencing homelessness aged 16 to 25 years.

Methods: The study is designed as a 2-armed randomized wait-list controlled trial. Participants (n=450) will be recruited and followed up for 9 months after the intervention for a total study period of 12 months. Come As You Are combines nurse case management with a smartphone-based daily ecological momentary assessment to develop participant-driven HIV prevention behavioral goals that can be monitored in real-time. Youth in the city of Houston, Texas will be recruited from drop-in centers, shelters, street outreach programs, youth-serving organizations, and clinics.

Results: Institutional review board approval (Committee for the Protection of Human Subjects, University of Texas Health Science Center at Houston) was obtained in November 2018. The first participant was enrolled in November 2019. Data collection is ongoing. To date, 123 participants have consented to participate in the study, 89 have been enrolled, and 15 have completed their final follow-up.

Conclusions: There is a paucity of HIV prevention research regarding youth experiencing homelessness. Novel and scalable interventions that address the full continuum of behavioral and biomedical HIV prevention are needed. This study will determine whether a personalized and mobile HIV prevention approach can reduce HIV risk among a hard-to-reach, transient population of youth at high risk.

International Registered Report Identifier (IRRID): DERR1-10.2196/26716

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Introduction

HIV Risks Among Youth Experiencing Homelessness

A number of systemic barriers and risk behaviors drive high HIV infection rates among youth experiencing homelessness. Youth experiencing homelessness have earlier sexual debuts; are more likely to have multiple sexual partners; and trade sex for food, shelter, money, drugs, or alcohol [1,2]. They are more likely to use substances before sex, are less likely to use condoms, and are overrepresented by youth who identify as men who have sex with men; each of these characteristics increase risk for HIV [3,4], and those who trade sex are at high risk for HIV infection as they are rarely able to negotiate condom use due to the power dynamics [5] and often lack knowledge about biomedical advances in HIV prevention such as preexposure prophylaxis and nonoccupational postexposure prophylaxis [6]. In a recent 7-city (Houston, Denver, St. Louis, Phoenix, Los Angeles, San Jose, New York City) study of 1427 youth experiencing homelessness (58% male, 81% youth of color, 31% lesbian, gay, bisexual, transgender, queer [LGBTQ]), 71% of participants had little to no knowledge of preexposure prophylaxis [7]. Reassuringly, 53% of study participants had undergone HIV testing in the preceding 3 months [7]. Unfortunately, youth experiencing homelessness experience sexual assault and forced sex at high rates (22% and 24% respectively); yet only 29% received a postsexual assault examination which is when they could have received nonoccupational postexposure prophylaxis and sexually transmitted infection (STI) treatment [8]. The Society for Adolescent Health and Medicine has recommended the development of screening tools, skill-building interventions, and accessible preexposure prophylaxis delivery models for all youth and young adults, particularly those experiencing disparities [9].

Implications of Mental Health and Substance Use on HIV Risk

HIV risk among youth experiencing homelessness is further exacerbated by multiple comorbid conditions, including mental illness and substance use. Suicide is one of the leading causes of death among youth experiencing homelessness [10], with suicide attempt rates ranging from 12% to 48% [11-13]. Rates of depression and posttraumatic stress among youth experiencing homelessness vary across studies with ranges from 8% [14] to 61% [15] and 5% to 48% [16-18], respectively. A recent study [19] found that 42% of youth experiencing homelessness reported being moderately to severely stressed, 48% experienced mental distress, 48% had depression, and 23% had posttraumatic stress. Depression among youth experiencing homelessness may be due to a lifetime of adversity, abuse, neglect, and housing instability [20,21]—all of which can lead to inhibition and riskier sexual decision making and behavior [22]. Furthermore, rates of substance use are twice those of housed

youth [3,23]. In one study [24], 86% of youth experiencing homelessness (n=173) met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, criteria for a substance use disorder compared with only 14.2% in the general young adult population [25]; drug overdose is a leading cause of death among youth experiencing homelessness [10]. HIV prevention efforts should address mental health and the intersection of substance use and sexual behaviors.

Barriers to Health Care Access

Youth experiencing homelessness are underserved by the health care system for several reasons. Structural barriers include transportation, lack of health insurance, and costs [26]. Youth also suggest that fear of or past experiences of being judged, dismissed, or discriminated against by health care professionals reduce utilization [27]. Other barriers to health care access include fear of social service agency notification or legal intervention, lack of familiarity with health care resources, and lack of affordability [28]. As a result, youth experiencing homelessness often interact with the health care system at lower rates than their housed peers and frequently overutilize emergency departments for care while experiencing reduced access to prevention services [3]. Therefore, it is essential to increase access to and availability of HIV prevention services, and these services should be colocated with other service programs to foster trust and increase accessibility for youth experiencing homelessness [29-31]

Interventions for Youth Experiencing Homelessness

A recent systematic review [32] of interventions to prevent HIV among youth experiencing homelessness highlighted the paucity of HIV prevention research and concluded that more research is necessary. Interventions for youth experiencing homelessness should include the full continuum of behavioral and biomedical HIV prevention, including HIV and STI screening and treatment, preexposure prophylaxis, and nonoccupational postexposure prophylaxis [33]. Engagement in these prevention services requires interventions to increase preexposure prophylaxis awareness, screen for preexposure prophylaxis eligibility, promote condom use, provide assistance with health care navigation that includes care for mental health and substance use issues [34], and address transportation and health insurance challenges. Individuals impacted by mental illness, homelessness, and substance use have greater preexposure prophylaxis uptake and adherence when these abovementioned issues are also addressed [35]. Nurse case management is an evidence-based strategy that has been effective in addressing the multifaceted and complex health and social challenges of HIV prevention among youth experiencing homelessness [27,36-38]

Nurse Case Management

A nurse-led intervention allows for multiple HIV prevention services to be delivered during a single visit (eg, preexposure

prophylaxis, nonoccupational postexposure prophylaxis, lab draws, STI testing and treatment), which may increase adherence. This is particularly important as being homeless can decrease effectiveness of linkages to care [39] as opposed to providing that care at the point of contact. Nurse case management has been efficacious in reducing drug use among methadone users [40] and youth experiencing homelessness [41], improving hepatitis B vaccination rates [42], and facilitating HIV care coordination [43]. This comprehensive approach of simultaneously addressing concomitant problems (eg, mental health, substance use, and housing needs), incorporating the full continuum of behavioral and biomedical HIV prevention, is a promising strategy for engaging youth experiencing homelessness in HIV prevention. Given the widespread integration of nurses into current HIV programs serving youth experiencing homelessness, nurse-led interventions are likely scalable and can be integrated into existing HIV prevention programs.

To further engage youth experiencing homelessness, they should be met "where they are" [35] and interventions should be implemented in collaboration with existing health and social service providers by colocating the study activities at drop-in centers, shelters, and service providers that are highly used by youth experiencing homelessness. This strategy is particularly important given that past-month use of a drop-in center has been shown to predict HIV and STI testing [44], increase service utilization, and improve HIV-related outcomes [31]. These findings support the potential of delivering HIV prevention in drop-in centers and shelters to connect youth experiencing homelessness to other underutilizing services and health care. Moreover, drop-in centers may be a preferred HIV prevention service location of youth experiencing homelessness [31]. By integrating the delivery of HIV risk reduction interventions into already-established social services, we may enhance HIV prevention, increase retention, and improve access to mental health, substance use, and housing services.

Motivational Interviewing and Behavior Feedback

Nurse-led interventions can also integrate evidence-based strategies that have proven effective in increasing motivations for behavior change. Increasing motivation is particularly important for populations that are potentially overwhelmed by multifaceted and complex health and social challenges. Motivational interviewing is a person-centered counseling style that aims to strengthen a person's motivation and commitment to change and addresses ambivalence about behavior change [45]. Motivational interviewing has been successfully used with youth to improve uptake of and adherence to health behaviors resulting in reduced alcohol [46] and substance use [47], and increased condom [48] and contraceptive use [49]. Youth experiencing homelessness are self-reliant, can be challenging to engage, and may be distrustful of adults due to past trauma and victimization on the streets [50,51]. Motivational interviewing strategies can strengthen the relationship between the youth experiencing homelessness and providers to evoke participant driven HIV prevention goals [52].

Behavioral feedback technology might also increase motivation to change behavior as tailored and targeted feedback could

further engage youth experiencing homelessness. Smartphone-based daily ecological momentary assessments have been used with youth experiencing homelessness. Instant feedback enhances cognitive appraisal of health-seeking and coping behaviors and increases motivation in youth experiencing homelessness [52,53]. Like many adolescents and young adults, youth experiencing homelessness underestimate their HIV risk [7], suggesting that self-monitoring may assist in aligning their behaviors with their perceived HIV risk. Immediate self-monitored behavioral feedback has been found to increase condom use [52,54]. A high number of youth have phones, and young adults, in general [55-57], and youth experiencing homelessness, specifically, have a preference to use technology [58]. A review [59] of 42 studies showed high ecological momentary assessments completion rates (78%) among youth. Prior studies [60] have found similar high adherence rates (82%-87%) with homeless and vulnerable populations.

Objectives

This study describes the design and implementation of a nurse case management intervention (Come As You Are) efficacy trial with youth experiencing homelessness aged 16 to 25 years who received the active intervention or usual care. The intervention aims to increase uptake of HIV prevention strategies (eg, pre- and postexposure prophylaxis uptake, HIV testing, STI screening and treatment, sober sex, and condom use) when compared with usual care youth experiencing homelessness immediately postintervention and 3, 6, and 9 months postintervention. The study also aims to determine whether the intervention improves mental health symptoms, substance use, and housing status. Additionally, we will assess whether health seeking, coping, HIV risk perception, pre- and postexposure prophylaxis barriers and facilitators, and condom self-efficacy mediate the effect of the intervention on uptake prophylaxis, condom use, and HIV/STI testing. This protocol paper describes the study design, intervention, recruitment, and retention strategies.

Methods

Study Design

This study uses a 2-armed randomized controlled trial design with a wait-list control group to determine the efficacy of the intervention compared to usual care. The primary outcomes are the uptake of HIV prevention strategies (preexposure prophylaxis and nonoccupational postexposure prophylaxis, HIV and STI testing, and condom use). Secondary outcomes of the intervention include the impact on mental health, substance use, and housing status. Follow-up surveys are conducted immediately after the 3-month intervention period and 3, 6, and 9 months postintervention (Figure 1).

Participants are randomly assigned to the intervention or wait-list control arm using a computer-generated blocked 2:1 allocation. By the end of the recruitment period, we anticipate that 300 participants will be randomized to the intervention arm and 150 randomized to the wait-list control arm. Participants are informed in which group they are allocated after completing the baseline survey.

Figure 1. Study flow diagram. CAYA: Come As You Are.
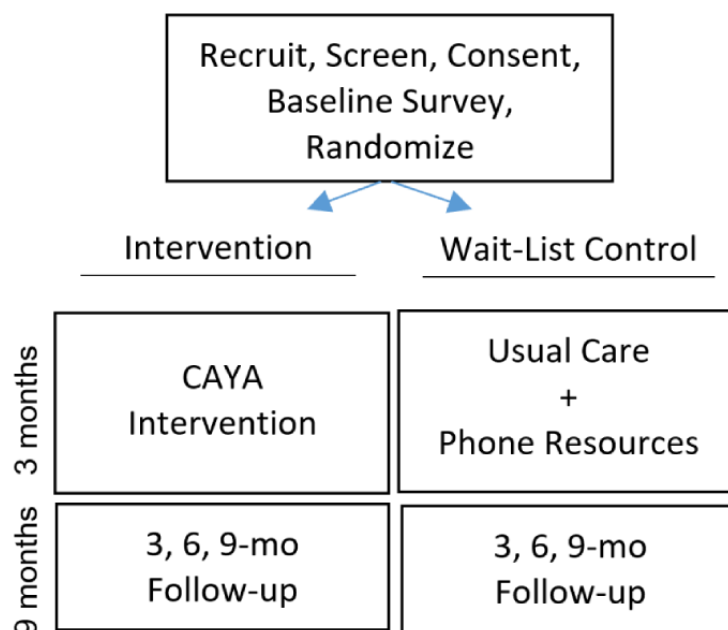
Recruitment

Utilizing numerous recruitment sites in Houston—drop-in centers, shelters, local youth experiencing homelessness service locations, clinics, federally qualified health care centers in locations with a high concentration of homelessness, magnet (eg, hot meal) events, mobile clinics, and street outreach—will increase generalizability of the findings by including a sample of both connected and disconnected youth experiencing homelessness. These recruitment sites serve young men, women, families, and LGBTQ youth. We make use of group-based study introduction sessions, flyers, and recruitment letters at the agencies, clinics, street outreach, and the website and Facebook pages of the agencies and Homeless Youth Network of Houston. We have used these methods successfully in previous studies [61]. The research staff will maintain a consistent, weekly presence at the recruitment sites throughout the study to facilitate both recruitment and follow-up efforts. In response to COVID-19 physical distancing requirements and shelter closures, we are also using snowballing participant referral techniques and online advertisements.

Inclusion and Exclusion Criteria

Our sample is limited to youth, 16 to 25 years old, to align with youth homelessness services providers and adolescent risk behavior studies [7], current guidelines for preexposure prophylaxis and nonoccupational postexposure prophylaxis use [62,63], and evidence that experiencing homelessness as a young adult under 26 years of age is associated with heightened sexual risk behaviors and substance use [33]. Individuals are eligible to be included if they (1) are 16 to 25 years old, (2) speak English, (3) are experiencing homelessness, and (4) are not planning to move out of the Houston metropolitan area during the study.

Experiencing homelessness is defined as having slept on the streets, in a place not meant for habitation, in a shelter, hotel or motel, or with someone where they cannot stay for more than 30 days (eg, couch surfing). Youth experiencing homelessness may stay in emergency shelters or on the streets (eg, parks and tent cities); in abandoned or vacant buildings or apartments; temporarily with friends, family, or acquaintances; or in rented hotel or motel rooms [35], and they can go to great lengths to stay hidden from the dangers of victimization [50]. This broad definition of homelessness aligns with the McKinney-Vento Homeless Assistance Act of 1987 [64], which allows us to account for the transiency and instability of housing experienced by youth experiencing homelessness and increases the generalizability of the study findings.

Youth with very low literacy (Rapid Estimate of Adult Literacy in Medicine-Short Form [65] health literacy assessment score <4)[1] are excluded from the study due to the need to independently read the daily smartphone-based assessments. Additionally, youth who are noticeably intoxicated or experiencing acute mental distress are encouraged to be screened for enrollment at a later time to assure safety and acute needs are met prior to enrollment. Youth are connected to services at the recruitment sites for acute needs.

Study Enrollment

Due to the transient nature of the study population, study participants are being enrolled in a stepwise process that takes place over the course of 3 weeks. The first step entails a thorough review of the consent form and collection of contact information including a photo, and the second step consists of baseline data collection. During the third step, participants receive the study phone and are notified of study group assignment. Intervention participants receive the first intervention session on the same day that they receive the study phone. During the COVID-19 pandemic, consenting and the baseline survey are being completed remotely as needed to reduce the face-to-face study visits to only 1 enrollment visit.

Intervention Description

The *Come As You Are* intervention is based on the Comprehensive Health Seeking and Coping Framework (CHSCF; Figure 2), which describes how the nurse and client work together to mutually develop goals and strategies to improve health in a context of nonjudgmental acceptance. Accomplishment of goals occur by addressing cognitive appraisals (clarifying misconceptions), promoting health seeking, and addressing knowledge and coping behaviors that incorporate the situational, personal, social, and resource needs affecting health. The intervention involves coordinated, individualized, comprehensive care delivered by a nurse that includes a comprehensive health assessment, mutual care plan development, prevention education, and health and social service navigation [36-38,41]. An individualized, rather than group based, intervention was chosen for this study due to the heterogeneity of youth experiencing homelessness and their risk behaviors and the challenges associated with group session designs, including low attendance [66]. The intervention has 2 main components: 6 face-to-face sessions with a study nurse and a behavioral assessment and feedback app. Additionally, booster calls are made monthly for 3 months following the last face-to-face session. This intervention is guided by the CHSCF [67] and uses motivational interviewing [45,68] strategies to promote behavior change and uptake of HIV prevention strategies by facilitating goal setting and evoking change talk.

Figure 2. Motivational interviewing enhanced case management. CAYA: Come As You Are; HIV: human immunodeficiency virus; PrEP: preexposure prophylaxis; nPEP: nonoccupational postexposure prophylaxis; STI: sexually transmitted infection.
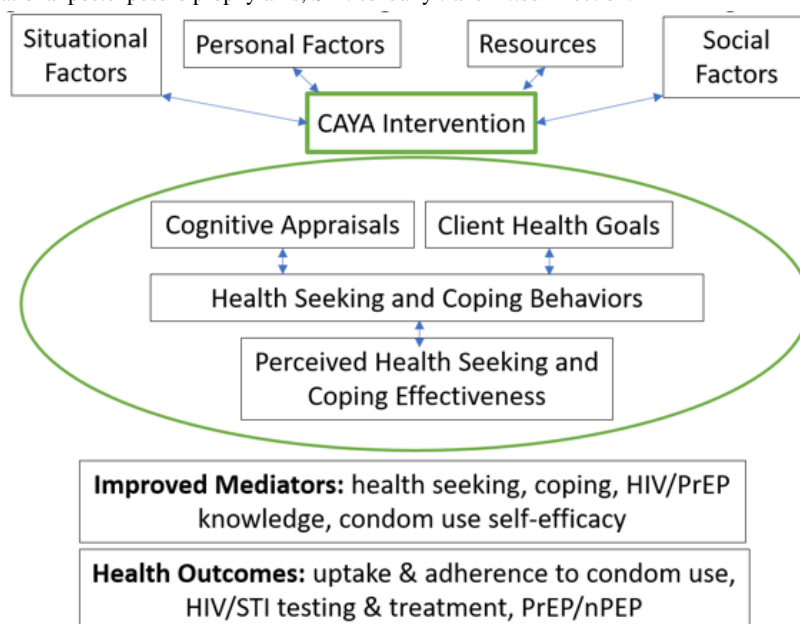
Come As You Are Intervention Group

Face-to-Face Sessions

The 6 biweekly 1-hour face-to-face sessions are designed to meet the complex, individual, multilevel health and social needs of homeless youth to align with extant literature demonstrating the strong connection between HIV risk behaviors and mental health, substance use, and housing [69]. During each session, the nurse uses motivational interviewing strategies to assess current mental health, substance use, and housing needs to establish a plan of care to assist youth in generating HIV prevention behavioral goals while addressing barriers. During these sessions, the nurse conducts an HIV risk profile and preexposure prophylaxis eligibility assessment and guides discussions about goal attainment strategies (Table 1). Six sessions allow for the development of the nurse-client relationship and for adequate time to establish, monitor, and maintain HIV prevention goals [70]. The motivational interviewing strategies allow the sessions to be youth-driven and tailored to the individual's needs based on their current HIV risk behaviors, HIV status, behavioral goals, and motivation level. In response to the challenges experienced during the COVID-19 pandemic, the nurses also offered to conduct these individual sessions via videochat or phone call as needed (when shelter-in-place orders are enacted or service sites are closed) to protect their clients.

Table 1. Come As You Are session description.

Number	Session title	CHSCF[a] constructs	Discussion topics	Session goals
1	Introduction and needs assessment	Situational, personal, social factors, and resources	Review HIV[b] risk behavior and prevention strategy (condoms, HIV/STI[c] testing, treatment, preexposure prophylaxis, nonoccupational postexposure prophylaxis) knowledge, attitudes, beliefs, and self-efficacy	Establish rapport; assess HIV risk, preexposure prophylaxis eligibility
2	HIV prevention strategies and goal setting	Nursing goals	Review personal HIV risk; use motivational interviewing to discuss risk reduction and prevention strategies; evoke change talk	Select HIV prevention goals and action plan
3	Behavioral feedback and goal alignment	Health seeking and coping behaviors	Identify gaps between goals and behaviors (eg, self-management, coping, health care engagement); evoke change talk	Revise/reinforce plan to meet/maintain HIV prevention goals
4	Addressing facilitators and barriers	Perceived behavior adherence and coping effectiveness	Review goals and action plan; use motivational interviewing to discuss personal HIV prevention behavior change facilitators and barriers; evoke change talk	Revise/reinforce HIV prevention goals and action plan to increase facilitators
5	Establishing a medical home	Immediate health outcomes	Review goals and action plan; discuss local clinic preferences and schedule well-check as indicated; evoke change talk and behavioral maintenance	Revise/reinforce HIV prevention goals, action plan, follow-up care plan
6	Moving toward health and wellbeing	Long-term health outcomes	Review goals and action plan; identify additional health, housing, work, and education needs and goals; evoke change talk and behavioral maintenance plans	Reinforce HIV prevention goals and action plan

[a]CHCSF: Comprehensive Health Seeking and Coping Framework.

[b]HIV: human immunodeficiency virus.

[c]STI: sexually transmitted infections.

HIV Risk Profile and Preexposure Prophylaxis Eligibility Assessment

HIV status is assessed at baseline using a rapid, finger stick HIV test. During the first intervention session and at the beginning of each subsequent session, the nurse uses a screening tool developed from the Centers for Disease Control and Prevention 2014 Clinical Practice Guidelines to assess preexposure prophylaxis eligibility. This screener is used to assess preexposure prophylaxis eligibility based on the participants' HIV risk behaviors (eg, having an HIV-positive sexual partner, a recent bacterial STI, number of sex partners, a history of inconsistent or no condom use, injection drug use, or trade sex) to determine whether recent behaviors warrant preexposure prophylaxis as a possible intervention for HIV prevention. preexposure prophylaxis and HIV clinical care guidelines and standing orders under the supervision of a health care provider are incorporated into the 6 nurse sessions. The care plan for these participants includes coordinating access to, uptake of, and adherence to preexposure prophylaxis, and promoting HIV-preventing behaviors (eg, HIV/STI testing, using condoms, reducing sexual partners, reducing intravenous drug use, engaging in sober sex, and avoiding trade sex). When a youth is HIV-negative and preexposure prophylaxis–eligible, the nurse discusses what preexposure prophylaxis is, how it works, its risks and benefits, and the implications of its use (eg, follow-up lab work and appointment schedule) to promote shared decision making. When participants are interested in receiving preexposure prophylaxis, the nurse works with the preexposure prophylaxis navigator who accompanies the youth to the preexposure prophylaxis appointment to begin lab work and assists with completing an application form to cover preexposure prophylaxis medication costs.

HIV Prevention Goal Setting

The nurse uses motivational interviewing strategies to evoke youth-driven HIV prevention goals and behavior change talk. Each session includes personalized HIV prevention education (ie, personal risk behaviors and prevention strategies) and goal setting. Session appraisals help align the youth's goals with their current behaviors and evoke personal motivation to adopt and maintain HIV prevention strategies. For youth who are not preexposure prophylaxis–eligible, the nurse promotes the adoption or maintenance of other HIV prevention strategies (ie, condom use).

Behavioral Interface

Building on the goal setting, participants in the intervention group complete a brief, daily ecological momentary assessment on their study-issued phone during the 3-month intervention delivery period. The ecological momentary assessment asks about sexual risk behaviors, sexual urges, stress, affect, social interactions, coping, and circumstances from the prior day (eg, where did you stay last night, sexual activity, substance use), and it takes less than 5 minutes to complete. Once the daily ecological momentary assessment is completed, the data populate a behavioral goal interface accessible by password on the study-issued smartphone (Figure 3). This interface provides a visual display based on the participant's HIV prevention goals, and their behaviors as reported in the daily ecological momentary assessment. It allows the nurse and youth to review how current behaviors align with the health goals established during the Come As You Are session and facilitates discussion about the barriers and facilitators that impeded or enhanced uptake and adherence to HIV prevention strategies.

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Figure 3. Example behavioral interface.
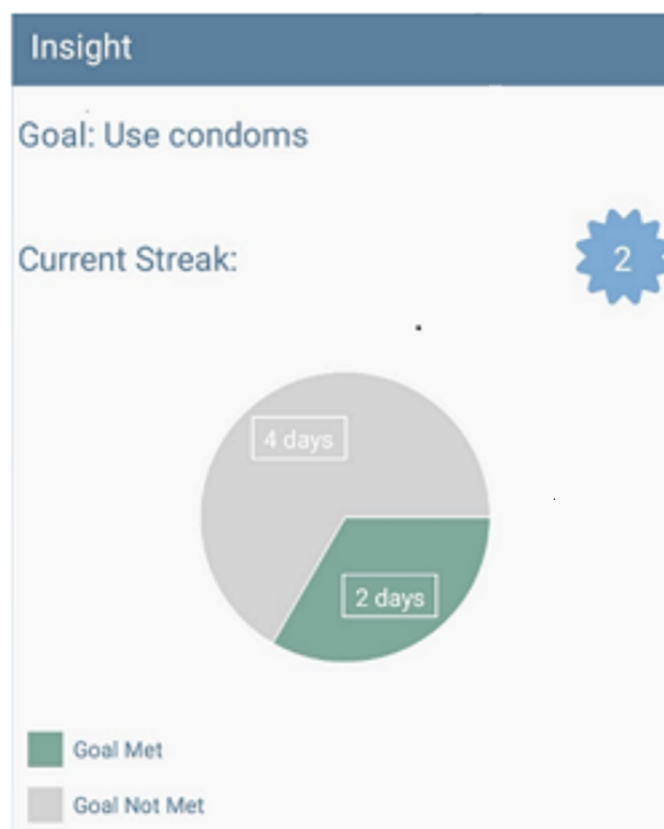
Booster Calls

After the face-to-face intervention sessions are completed, the team makes monthly booster calls to intervention participants on the study-issued phone for 3 months following the end of the individual sessions. During these calls, the team members inquire about the uptake and adherence to the HIV prevention strategies outlined during the Come As You Are sessions, asks if there are any other needs that they can address for the participant at that time, and helps the participant access and navigate services (ie, shelters, mental health counseling, health care) as needed.

Wait-list Control Group

Youth in the control condition receive usual care from the recruitment sites including assistance with housing, food and clothing needs; basic health assessments and health care; limited anticipatory guidance; access to mental health counseling; substance use treatment referrals; and preexposure prophylaxis or nonoccupational postexposure prophylaxis referrals. Youth receiving usual care also receive a study phone and complete the baseline, 3-, 6-, and 9-month follow-up surveys. After the 12-month study period is completed, youth in the control group are invited to access the full Come As You Are intervention.

A Community Advisory Group and Youth Working Group provided input on study procedures, protocol implementation and will be active in the interpretation and dissemination of the findings to the community. These groups assisted in the development of study procedures, survey items, and recruitment materials. Additionally, they oversaw the creation of a local homeless resource guide to be given to all participants at the time of enrollment and preprogrammed into the study-issued phones. This guide contains location and contact information for local shelters, meals, social, legal, and education services, and clinics. These resources are available in paper version and preloaded to the phones (ie, suicide hotline, shelter contacts) for all participants. The Community Advisory Group are current service providers for youth experiencing homelessness. The Youth Working Group members are youth with lived homelessness experiences between the ages of 18 to 25 years.

Data Collection Procedures

Data collected include baseline and follow-up survey data, HIV and STI test data, and data from smartphone-based daily ecological momentary assessments. Assessments are collected at baseline, at the end of treatment (3 months postbaseline), and 3, 6, and 9 months postintervention using REDCap (Vanderbilt University). The surveys are done in person or through a link to the survey sent to the participant via text message or email. The baseline survey assesses demographics (eg, age when first experiencing homelessness, duration experiencing homelessness, race and ethnicity, sexual orientation, gender identity), psychosocial factors, sexual behaviors, substance use, and mental health. The end of treatment assessment for the intervention group contains intervention process outcome items including what participants found to be the most and the least helpful, what made it easy or difficult to attend sessions. HIV and STI test data are collected at baseline, at the end of treatment, and 3, 6, and 9 months postintervention. Table 2 outlines measures used for primary outcomes. Youth with a positive STI test receives treatment and care coordination from the Healthcare for the Homeless Houston program, shelter

clinics, or their medical home when preferred. Youth who test positive for HIV during the study will be linked to HIV care at a local clinic by the nurse.

Table 2. Outcome measures.

Construct	Scale or measure	Cronbach α
Aim 1 outcomes		
Prophylaxis uptake	Preexposure prophylaxis uptake; nonoccupational postexposure prophylaxis uptake (NCM report, chart review)	—[a]
Condom use	Youth Risk Behavior Survey [71] (condom use at last sexual encounter)	—
HIV[b]/STI[c] test uptake	Rapid HIV test; gonorrhea, chlamydia, syphilis tests	—
Aim 2 outcomes		
Mental health	Kessler Psychological Distress Scale [72,73]	—
Housing status	In a shelter, apt/house, with someone, outside, in a car	—
Substance use	Texas Christian University Drug Screen II [74,75]	.89
Exploratory outcomes[d]		
Health care engagement	Health care utilization, Medical Mistrust Index 2.1 [76]	—
Condom-use self-efficacy	Condom Control beliefs [77]	.74-.83
HIV risk perception	Perceived Risk of HIV scale [78]	.88
Preexposure prophylaxis facilitators and barriers	Facilitators and Barriers to Preexposure Prophylaxis Use [79]	—
Health seeking	General Help Seeking Questionnaire [80]	.83
Coping	Derived from Ways of Coping Questionnaire [81]	—

[a]No data.

[b]HIV: human immunodeficiency virus.

[c]STI: sexually transmitted infections.

[d]Possible mediators based on Comprehensive Health Seeking and Coping Framework.

For HIV testing, we use the INSTI HIV-1/HIV-2 Rapid Antibody Test (99.5% sensitivity, 100% specificity; Biolytical Laboratories Inc)[82]. Urine specimens are collected and transported on the same day to a local clinic to test for *Chlamydia trachomatis* and gonorrhea (*Neisseria gonorrhoeae*), and results are shared with participants via phone call or in person. Blood samples are tested for syphilis (*Treponema pallidum*) using an antibody rapid immunochromatographic test (Syphilis Health Check, Trinity Biotech plc)[83]. Due to restrictions on in-person study visits during the COVID-19 pandemic, additional options for STI testing, including going to conveniently located partner clinics or receiving an at-home STI testing kits, are being provided to study participants as attrition mitigation strategies.

Results

Institutional review board approval (Committee for the Protection of Human Subjects HSC-SN-18-0993) was obtained in November 2018. The first participant was enrolled in November 2019. Data collection is ongoing—to date, 130 participants have consented to the study, 110 have enrolled, and 15 have completed the final follow up—and expected to conclude in 2022.

Discussion

This study will provide essential data on the efficacy of a 2-component nurse case management HIV prevention intervention (ie, nursing visits and smartphone based behavioral monitoring and feedback) among youth experiencing homelessness. Findings from the study will significantly contribute to the field of HIV prevention in a marginalized and hard-to-reach population. The intervention is designed to be scalable within the practical parameters of care currently provided through the Health care for the Homeless programs across the nation.

This project is innovative in several ways. It addresses the underutilized role of nurses, the most trusted professionals in the United States [84], in the HIV prevention team. Consequently, nurses' abilities to provide HIV prevention services may reduce the need to refer youth experiencing homelessness to other health care providers, which can decrease referral no-show and treatment plan nonadherence. Combining nurse case management with motivational interviewing and behavioral feedback can potentiate motivation for adopting HIV prevention behaviors and address the full continuum of behavioral and biomedical HIV prevention with youth experiencing homelessness. If found to be effective, this intervention can be applied to improve existing youth

experiencing homelessness HIV prevention program, maximizing the available resources and potential outcomes.

The eponymous intervention capitalizes on the "come as you are" approach endorsed in clinical guidelines [85] put forth by the National Healthcare for the Homeless Council and aligns with NIH and Ending the HIV Epidemic High Priority areas [86] for reducing HIV through behavioral prevention and access to services in high HIV prevalence and substance-using, high-risk populations. Additionally, the intervention facilitates coordination with youth experiencing homelessness service providers to meet mental health, substance use, and housing service needs and connects youth to the health care services, such as HIV and STI testing and treatment.

The potential benefits of study participation include increased knowledge about HIV transmission and increased uptake of prevention strategies. Participants may become more aware of how thoughts and feelings can affect one's behaviors and improve uptake and adhere to HIV prevention goals. Research staff are provided with comprehensive lists of resources available to youth experiencing homelessness and receive extensive training on how to make referrals to appropriate resources if a participant indicates that they need services they are not otherwise receiving. Participants will have access to resources and contact information for services that will be preprogrammed into the study-issued smartphones provided to all participants throughout the duration of the study. Participants in the intervention arm may also benefit from linkages to care provided through the Come As You Are intervention. Through the HIV and STI testing offered to all participants, youth may become aware of a positive result and receive necessary treatment and linkages to care that they may not have otherwise received. If efficacious, this scalable intervention has the potential to be disseminated to young people experiencing homelessness across the country without requiring significant investments in infrastructure, equipment, or staff resources. Some potential challenges related to whether youth have access to a phone are present, though studies suggest that smartphone use among youth experiencing homelessness is similar to that in the general population, ranging from 47% to 78% [87,88]. Given the implementation of this study during the COVID-19 pandemic, there are unique learning opportunities related to executing a randomized control trial focused on HIV prevention during a global pandemic with youth experiencing homelessness.

Conflicts of Interest

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Abbreviations

CHSCF: Comprehensive Health Seeking and Coping Framework
COVID-19: coronavirus disease 2019
HIV: human immunodeficiency virus
LGBTQ: lesbian, gay, bisexual, transgender, queer
STI: sexually transmitted infection

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Protocol

Communication Intervention Using Digital Technology to Facilitate Informed Choices at Childbirth in the Context of the COVID-19 Pandemic: Protocol for a Randomized Controlled Trial

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Abstract

Background: In Brazil and other low- and middle-income countries, excess interventions in childbirth are associated with an increase in preterm and early-term births, contributing to stagnant morbidity and mortality of mothers and neonates. The fact that women often report a negative experience with vaginal childbirth, with physical pain and feelings of unsafety, neglect, or abuse, may explain the high acceptability of elective cesarean sections. The recognition of information needs and of the right to informed choice during childbirth can help change this reality. The internet has been the main source of health information, but its quality is highly variable.

Objective: This study aimed to develop and evaluate an information and communication strategy through a smartphone app with respect to childbirth, to facilitate informed choices for access to safer and evidence-based care in the context of the COVID-19 pandemic.

Methods: A randomized controlled trial, with 2 arms (intervention and control) and a closed, blind, parallel design, will be conducted with a smartphone app designed for behavior and opinion research in Brazil, with women of reproductive age previously registered on the app. After completing an entry questionnaire to verify the eligibility criteria and obtaining ethical consent, approximately 20,000 participants will be randomly allocated to the intervention and control groups at a 1:1 ratio. Participants allocated to the intervention group will be invited to engage in a digital information and communication strategy, which is designed to expand evidence-based knowledge on the advantages and disadvantages of options for labor and childbirth and the safety of the care processes. The information is based on the guidelines of the Ministry of Health and the World Health Organization for a positive childbirth experience and has been updated to include the new challenges and disruptions in maternity care within the context of the COVID-19 pandemic. The control group will receive information regarding disposable and reusable diapers as a placebo intervention. The groups will be compared in their responses in generating the birth plan and the entry and exit questionnaires, regarding responses less or more aligned with the guidelines for a positive childbirth experience. A qualitative component to map information needs is included.

Results: The digital trial started recruiting participants in late October 2020, and data collection has been projected to be complete by December 2020.

Conclusions: This study will evaluate an innovative intervention that has the potential to promote better communication between women and providers, such that they can make better choices using an approach suitable for use during the COVID-19 pandemic.

Trial Registration: The Brazilian Clinical Trials Registry U1111-1255-8683; http://www.ensaiosclinicos.gov.br/rg/RBR-3g5f9f/

International Registered Report Identifier (IRRID): PRR1-10.2196/25016

Introduction

Improvement of Maternal and Neonatal Health: a Permanent Challenge

Nationwide and worldwide studies have indicated, for many years, the need to act in order to reduce maternal and neonatal mortality, especially because a significant proportion of deaths can be avoided with adequate and timely assistance, considering the family planning continuum, prenatal care, childbirth assistance, and postnatal care [1-3]. Many sociohistorical, economic, and cultural factors interact, and the issue of maternal mortality remains poorly addressed, primarily in low- and middle-income countries such as Brazil. Thus, national and international stakeholders search for interventions that may contribute to significantly reduce maternal and neonatal mortality [1,3,4].

There have been advancements in the past decades in Brazil, with health professionals' training, research, and improved access to prenatal care and childbirth assistance at health care facilities [5]. However, quality of care remains limited by non–evidence-based practices, within the context of increased use of inappropriate technology, which may be simultaneously harmful and costly [5]. At the health system level, in networks and facilities, women's and families' safety and well-being cannot be taken for granted, since recent studies have reported disrespectful practices in childbirth care [6,7], and in Brazil, infant and maternal mortalities have increased, raising public concern regarding maternity services [8]. In some scenarios, the uncertainties imposed by the COVID-19 pandemic in 2020 threaten the availability of medical resources and health care services, and studies have reported that Brazil has the highest COVID-19 mortality rates in the obstetric population [9,10].

Maternal and Neonatal Morbidity and Mortality and Childbirth Care in Brazil

In Brazil, monitoring and regulation of obstetric interventions is limited. For example, the cesarean section rate remains as high as 55% since 2015, with rates of >80% in the private sector. This major surgery, when properly indicated and performed in a timely manner, protects the mother's and the infant's lives [11,12]. However, if performed without adequate reason, caesarean sections unnecessarily increase the risk to both mothers and neonates. In other words, unnecessary cesarian sections increase maternal and neonatal morbidity and mortality,

as well as other negative outcomes, over the short and long term [13,14].

Several indicators show excess of interventions in childbirth care in Brazil, such as amniotomy (39.1%), fundal pressure (36.1%), episiotomy (53.5%), and oxytocin augmentation (36.4%) [5]. Simultaneously, pathological conditions are not adequately addressed, such as early identification of gestational hypertension, syphilis, and other infections during pregnancy. This is rather incompatible with current nationwide developments and with the presence of a universal health system.

Obstetric care can be characterized as a combination of "too little too late" with "too much too soon," a reference to the insufficient and delayed use of necessary resources with the excessive and inopportune use of technology, potentially resulting in harm [15]. Abuse of unnecessary interventions has also been verified in the private sector, especially with high rates of caesarean sections. Furthermore, owing to the fact that in the private sector, a greater proportion of neonates are born in the early preterm period (37-39 weeks), neonatal admissions to intensive care units are more frequent, as are the cases of transient tachypnea, hypoglycemia, jaundice, and breastfeeding problems [5].

The main causes of neonatal death are prematurity (30.3%), congenital malformation (22.8%), and infection (18.5%), and mortality rates vary widely between regions. Late preterm infants (which accounts for 17.1% of all neonatal deaths) present a 9-fold greater chance of neonatal death compared to those born at term. In this context, it is recommended to improve the quality of prenatal care and to prevent iatrogenic prematurity, largely in cases of cesarean sections performed without technical indication [16]. Evidence- and rights-based care can reduce infant mortality by decreasing preventable neonatal deaths. This comprises deaths from intrapartum asphyxia, an important component of preventable neonatal deaths in the country [16].

Resources to Increase Women's Control Over Their Experience and Information Available on the Internet

During pregnancy, women seek information and want their needs to be heard, but educational materials, prenatal consultations, and support groups may not be sufficient or adequate [17]. Women can gather information from different sources such as their relatives, friends, the internet, and popular media [18-21]. Television shows and other popular media

resources frequently resort to "experts" or other sources of information that are not scientifically validated. This influences women's expectations and decisions regarding many aspects of their health, including childbirth fears and desires [19-23]. Incomplete information about cesarean sections is often disseminated, which "can lead women to underestimate important maternal and perinatal risks associated with this mode of parturition" [24]. A recent systematic review reported that there are few campaigns aimed at the general public to reduce the rates of cesarean sections [25].

The large volume of information available on the internet and its heterogeneity impact women's curiosity about certain topics, often to the detriment of others [26]. On Brazilian Portuguese webpages, the quality of information on cesarean sections varies from regular to poor, with low reliability and comprehensiveness [27]. This can cause anxiety among women [28], especially if the information is not discussed with health professionals [29] or confronted with other sources. To change this situation and contribute to increasing women's satisfaction, one possibility is to encourage the use of a birth plan, which improves their communication with health professionals and makes women more aware of their options [30].

In a systematic review in 2019, two trials observed that birth plans had a protective effect in promoting positive birth experiences in line with women's perception. The quality of the studies was considered low, and the review concludes that more high-quality randomized studies are needed to assess the hypothesis that the use of the birth plan contributes to improving women's satisfaction and promoting a more positive birth experience [31].

Digital Technologies and Health Research

More than half of the world's population has access to the Internet. In Brazil, a survey in June 2020 by the Getúlio Vargas Foundation of São Paulo [32] revealed that there are 190 million computers—including desktop, notebook, and tablet devices—currently in use in the country, which corresponds to 9 computers for every 10 inhabitants (90% per capita usage). Although approximately 25% of the population, especially the oldest and poorest individuals, remain digitally excluded, there are overall 234 million smartphones currently in use. In addition, considering notebook and tablet devices, there are 342 million portable devices currently in use; that is, 1.6 portable devices per inhabitant.

Throughout the 2010s, mobile phones spread digital health communication in low- and middle-income countries in South East Asia, sub-Saharan Africa, and Latin America, including Brazil. In the field of reproductive health, the establishment of opportunities for continuous communication, and complementary to institutional care for prenatal care, postpartum care and reproductive planning are associated with better perinatal outcomes [33,34], increased confidence and satisfaction with childbirth [35], increased knowledge of obstetric interventions such as uterine fundal pressure, episiotomy, and labor augmentation with oxytocin, increased perception of being better prepared for the childbirth experience [36], reduced anxiety [37], and reduced perinatal mortality [33]. Recent literature reviews revealed evidence of the effectiveness

of digital interventions focused on pregnant and postpartum women, suggesting the need for more large-scale clinical trials [38,39].

To our knowledge, this will be a pioneering study, with population sampling in the country, assessing the preparation of a birth plan tool and women's choices related to a safer and more positive childbirth experience.

Emergence of the COVID-19 Pandemic: New Priorities Arise

On February 26, 2020, the first case of COVID-19 was reported in Brazil, and the disease was declared a pandemic by the World Health Organization on March 11, 2020. Since then, COVID-19 has monopolized the news and significantly modified the daily life of the population. Of note, Brazil ranks third worldwide with respect to the number of cases (>5 million) and deaths (>150,000) so far [40], while being amid a major political crisis. In addition, researchers in Brazil have observed an elevated COVID-19 mortality rate in the Brazilian obstetric population (12.7%), reporting 124 deaths among pregnant or postpartum women in June 2020, which is possibly the highest rate reported worldwide [9].

Innovative interventions have the potential to promote better communication between women in reproductive age and health care providers, such that they can make better choices. This study aims to develop and evaluate an information and communication strategy for a smartphone app on childbirth to facilitate informed choice for access to safer, more satisfactory, evidence-based assistance, in the context of the COVID-19 pandemic.

Methods

Study Design

This study is a randomized controlled trial, with 2 parallel arms (intervention and control) and a closed (only registered app users can participate) and blind design (only the participants are unaware of whether they are in the intervention or control arms). It is registered on the Brazilian Registry of Clinical Trials as "Communication intervention to improve informed choice at childbirth: a randomized controlled trial using digital technology in the context of the Covid-19 pandemic" with the World health Organization unique trial number U1111-1255-8683. The work is being conducted under a program supported by the Brazilian Ministry of Health (Programa de Apoio ao Desenvolvimento Institucional do Sistema Único de Saúde 25000.028646/2018-10).

Study Setting

The study will be conducted through the restricted segment of a smartphone app. This app has been especially designed for behavior and opinion research in Brazil and will be used for participant recruitment, assessment of eligibility criteria, delivery and control of the intervention, and data collection.

Currently, the app has registered approximately 1,360,000 active users. Of them, 98,518 have accessed the internet in the past 14 days (September 2020); these individuals will be primarily invited to participate at the recruitment stage, reaching women

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with different socioeconomic and demographic characteristics in all States of Brazil.

All communication with participants will be carried out within the native and private environment of the app. Engagement will be voluntary, and participants will be financially reimbursed for the value of mobile internet use. The estimated compensation for participation in this study was set between R $5.00 and R $10.00 (US $0.92-$1.84), depending on the extent of participation, to cover the cost of mobile internet usage.

The stages of the study conducted through the app will be comprised of interactive questionnaires (called "missions" in the app), which are opportunities for engagement through direct communication with users. The questionnaires are as follows:

1. Eligibility criteria filter: the filter has 7 questions related to the study variables (intention to have biological children, number of children, those born through normal delivery, year of birth of the oldest child, race, education, and occupation) (Multimedia Appendix 1)
2. Invitation to participate in the study: information on the study and the investigators, objective of the study, and the dynamics of the missions (Multimedia Appendix 2)
3. Questionnaire to complete and validate the informed consent form: split across different screens, digitally validated by the participant (Multimedia Appendix 3)
4. Entry questionnaire: prospecting of values and preferences associated with the intended care (Multimedia Appendix 4)
5. Questionnaires on childbirth (intervention group) (Multimedia Appendix 5) or on diaper use (control group) (Multimedia Appendix 6)
6. Exit questionnaire: similar to the entry questionnaire (Multimedia Appendix 4)
7. Birth plan questionnaire (Multimedia Appendix 7)

Participants

All women of reproductive age (18-49 years old) registered on the app will be notified of the invitation to participate in the study in order of priority.

Eligibility Criteria

To be included in this study, a participant must be a registered user on the app; identify as a woman; be classified under class A, B, C, D, or E in accordance with the Brazil Criteria of 2015 of the Brazilian Association of Research Companies [41]; be aged between 18 and 49 years; and be pregnant or have biological children of any age or intend to have biological children in the future.

Exclusion Criteria

Women without children and with no intention of having children in the future will be excluded from the study.

Recruitment

A filter questionnaire will be administered to all women registered on the app and aged between 18 and 49 years, from all Brazilian States and socioeconomic strata. Those who are pregnant or have biological children of any age or intend to have biological children in the future will be notified of the invitation questionnaire to participate in the study. Thereafter, the informed consent questionnaire will be sent to all women who agree to participate in the study. The following stage comprises the entry questionnaire, and all women who digitally provide informed consent will be invited to answer it.

These questionnaires will account for sociodemographic data in addition to those already available on the app's registry; type of health care assistance and funding (public or private, birth place including the hospital or health care institution, or professional including obstetricians and gynecologists, midwives, and nurse-midwives); clinical-obstetric characteristics (parity, mode of previous delivery, and the presence of a risk diagnosis); perception of safety in childbirth (for the mother and the neonate); and the perception of satisfaction or suffering expected during childbirth (for the mother and the neonate).

Allocation and Randomization

Users will be recruited through the app, which is voluntarily installed by the user. Registrations are carried out organically, with no active screening for users and no advertising. Once registered, the new user answers questions related to his/her socioeconomic data. Missions will be sent to the profiles of users of all social classes (paired to represent the composition of the Brazilian population in the 5 regions of the country) and aged between 18 and 49 years.

Randomness in the sample is guaranteed in the program architecture of the missions, ensuring that those who undertake 1 mission will not be able to access the other mission, by blocking the mission ID through the execution of filters. On the app screen, the respondent sees only the name of the mission, with no indication of whether that participant is in the intervention or the control arm. To guarantee greater confidentiality and not induce interests or scams, we assigned the same name to the 2 missions: "Being a mother is making choices." To balance the sample, the statistician team distributes the sample on the basis of the "n" defined for the study, thus generating a balance between the geographical region and economic class.

Intervention

The intervention was developed on the basis of the guidelines for childbirth care from the Ministry of Health and the World Health Organization [42-44] updated with reference to the COVID-19 pandemic [45-47]. It is an educational resource to promote women's knowledge of labor and childbirth care, as well as evidence-based choices for childbirth, which have been shown to protect maternal safety and satisfaction. The intervention consists of dummies, questions, and information cards developed and illustrated especially for this study by author BFF, a graphic artist specialized in maternal health.

The intervention presents information regarding the available models of care for childbirth, including information on care provider staff, obstetric practices in labor and childbirth, procedures for perinatal safety, skin-to-skin contact and breastfeeding in the first hour of life, and COVID-19 prevention procedures (Figure 1). The intervention requires the interaction and engagement of participants with the contents presented in a unique electronic "route" format, which will be available for

engagement in a restricted segment of the app for 48 hours. After answering all questions, the women will be directed to 1 of the 6 cards with profiles associated with "childbirth styles" (Multimedia Appendix 8).

Figure 1. Screenshot of the app-based intervention: typical childbirth care and COVID-19.

Control or Comparator

Participants allocated to the control group will receive informative content on models of disposable and cloth diapers that are widely available in the Brazilian market. The theme of disposable diapers versus ecological diapers was selected for the control arm of this trial because it is related to choices in the maternity experience, without interfering with information on labor and birth provided in the intervention arm. The illustrated cards were developed on the basis of the following themes: advantages and disadvantages of each type of diaper; risks of allergies and dermatitis; chemical materials and components; ecological aspects used in manufacturing; decomposition, use of water; and practicality and costs (Multimedia Appendix 6).

Birth Plan

The birth plan is a structured means of reflecting on the desired care for labor and birth, including an assessment of possibilities and uncertainties arising from the COVID-19 pandemic. It allows assessing the understanding of the intervention through questions on topics such as companionship, mobility, episiotomy, the Kristeller maneuver (fundal pressure), and augmentation with oxytocin. Upon completing the questionnaire (Multimedia Appendix 7), the participant sees her consolidated birth plan and is encouraged to take a screenshot to save this information.

Participants in both the intervention and control arms will be invited to elaborate a birth plan, and we will compare the differences in engagement and the responses.

Adherence and Study Withdrawal

During recruitment, women of reproductive age will receive app notifications to take part in the study until sample size requirement is fulfilled. Throughout the study, the app will notify participants whenever they have to respond to a questionnaire, and they can save it to respond to it in the next 48 hours. This is intended to guarantee participant engagement in the study, as far it is comprised of 7 questionnaires.

Participants can opt out from the study at any time, withdrawing their consent to participate or simply by the digital act of "aborting a mission."

Outcomes

Primary Outcomes

The primary outcome measures (Table 1) will be the following:

1. Preference reported for the gestational outcome (for a healthy woman and neonate) the safety of which is determined on the basis of evidence: waiting for spontaneous onset of labor; waiting for the full 39 weeks; preference for vaginal childbirth; preference for cesarean delivery after labor; preference for elective cesarean delivery; or indifference.
2. Differences between the responses in the elaboration of the birth plan, aligned with the information provided in the intervention, in accordance with the Ministry of Health guidelines.
3. Knowledge of the COVID-19 pandemic's impact in childbirth care and alternatives available.

Table 1. Outcomes of interest and definitions.

Endpoints	Definitions
Engagement in the intervention	Proportion of invited women who finish the missions
Reduced interest in elective cesarean section	Reduction in the proportion of women who intend to schedule an elective cesarean section
Increased engagement in seeking protagonism or informed choice	Proportion of women who develop a birth plan
Knowledge of the safest, most effective options associated with a more positive experience	Safer, more effective choices associated with a more positive experience in the exit survey and the birth plan
Engagement or desire to elaborate and share the experience and concerns	Elaboration of a narrative of the experience, doubts, and expectations regarding childbirth
Knowledge of the options available during the COVID-19 pandemic	Responses compatible with the information offered

Participant Timeline

As the entire study will be carried out through a smartphone app, the study duration is shorter than that of regular trials. The first questionnaire (eligibility criteria filter) will be accessible to app users for 14 days. Once the user completes the questionnaire and is considered eligible for the study, her participation will last approximately 12 days (Multimedia Appendix 9).

Parameters for Calculating the Sample Size

The sample size was calculated in accordance with the following parameters:

1. Study population size: in total, 32,000 women of reproductive age registered through the app (data collected from July 2019 before the onset of the COVID-19 pandemic).
2. Prevalence of the outcome of interest: a prevalence of 2.6% (Murcia, Spain) and 3% (São Paulo, Brazil) in the delivery rate of the birth plan to the obstetric care service.
3. Estimated impact of the intervention: a previous study that aimed to verify the effectiveness of a crowdsourcing strategy in promoting testing for hepatitis among men who have sex with men in China achieved a rate of 72.1% for the visualization of the multimedia components of the intervention. An increase in the number of tests performed was reported among 17.4% of the participants and confirmed by sending pictorial evidence of the examination

among 7.9% of the participants [48]. In this study, a 20% impact on the outcome of preference for the elective cesarean section was estimated.
4. Margin of error and safety: considering that part of the parameters used during sampling was estimated from other studies and the possibility of loss to follow-up among a portion of the recruited women, a type I error (α) margin of 1% was adopted with a 99% confidence level, along with a safety margin for type II error (β) of 20%.

Thus, at least 9068 participants in each group will be required to demonstrate the effect of the educational intervention on the outcome measures of interest [49]. We expect to have 10,000 participants in each group. Expected recruiting numbers (approximate, depending on engagement) are detailed in Multimedia Appendix 9.

Data Collection Methods

Collection of data on outcomes, baseline characteristics, birth plan, and other trial data will be collected automatically by the app. All study questionnaires were developed specifically for this study, and screenshots are available in Multimedia Appendices 1-8.

Pilot Intervention and Adjustments

A pilot intervention was conducted with 1000 participants prior to the final study for final adjustment of the questionnaires' linguistic adequacy and to evaluate the optimal sequence of

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missions to be administered to the participants. Engagement in the study questionnaires was higher than expected.

Data Management

For this study, a series of data management procedures will be implemented to ensure data protection, safety, privacy, and confidentiality. Data management will target the following three aspects: participant data treatment by the app's parent company, relevant information transfer to researchers, and data set maintenance by all teams. It is worth mentioning that in compliance with security measures established by the general data protection law [50,51] and the resolutions of the National Council of Health for human experimentation [52], researchers will receive only the variables of interest for the study.

At the individual level, the collected data will be computed directly in the parent company's system. This will include the following: verification of the individual's registration, deidentification of the data and separation of the population data for this study from the rest of the platform data, and the creation of an individual cloud to store the data for this specific study. Only the variables of interest in the deidentified data of the study participants will be used.

When accepting the app's terms of use and privacy policy, all users have their data automatically pseudo-anonymized (ie, unidentifiable). These data include the following: personal data collected upon registration; complementary data captured during app use, such as a version of the smartphone's operating system or device model; and all user responses during interventions.

At the level of database management by the researchers, the file will be initially processed within the app's servers, where the raw data files will also be stored and will not be used for any purpose other than this study.

Data Analysis Plan

Statistical Analysis

CONSORT (consolidated standards of reporting trials) guidelines will be used in reporting the results. An intention-to-treat analysis will be performed to compare data from the study's entry and exit surveys. This approach promotes a pragmatic assessment of the potential benefits of the intervention, as it incorporates loss to follow-up in the analyzed data of the intervention group.

Sociodemographic characteristics will be analyzed using descriptive statistics; between-group comparisons will be performed using chi-square analysis or a 2-tailed t test. For all group comparisons, the results shall be expressed as an effect (or relative risk for binary outcomes), corresponding 2-sided 99% confidence intervals ($\alpha=1\%$; power=80%), and associated P values. Adjusted analyses using baseline variables shall be performed using regression analysis to determine the continuing influence of key baseline characteristics on the outcomes, including female app users in the public and private sectors, cesarean sections, and vaginal delivery. The analyses will be conducted using the R statistical analysis software (The R Foundation) [53].

Qualitative Analysis

Audio narratives (entry and exit questionnaires and birth plan) will be automatically transcribed and analyzed in accordance with Bardin thematic analysis [54], using the Qualitative Solutions Research NVivo software (version 12.0, QSR International). A priori categories will include the following: feeling informed to make choices, feeling physically and emotionally secure, factors influencing satisfaction or dissatisfaction, desire to do something differently, and information needs. A posteriori categories are expected to emerge, as experience is considered an expansive learning opportunity [55].

Data Monitoring and Auditing

Since this is an educational intervention with low risk among participants, no data monitoring committee has been contemplated. There will be no independent review of trial processes (data auditing) during its execution, as the whole trial will last less than a month and routine data quality management will be performed.

Potential Risks to Participants

In this type of study, minimum risks are expected for the participants, such as the following: fatigue during the missions due to the long duration of the study or the lack of motivation with the topic of interest in the questionnaires; and discomfort or embarrassment if the participant is unaware of any term or situation presented during the study, despite efforts to adapt the language.

Another risk is the loss of data confidentiality, which will be minimized with protection measures by the researchers, as outlined during data collection and management. At the app level, users have preserved and guaranteed the rights to their data under the terms of the Brazilian General Data Protection Law.

Results

The digital trial started recruiting participants in late October 2020, and data collection has been projected to be completed by December 2020.

The study will be conducted in accordance with Resolutions 466/2012 and 510/2016 of the National Health Council [52,56]. Information regarding personal interest will be obtained exclusively for the study, and privacy, confidentiality, and preservation of the participants' identity will be ensured. Furthermore, the protection of data of all users of the digital platform, where the intervention will be applied, comply with the procedures outlined in accordance with the Brazilian General Data Protection Law.

Participation in the study must be voluntary and will be confirmed only after digital validation of the informed consent form. The study was approved by the institutional review board of Hospital Israelita Albert Einstein (project# 4194-20) and by the National Commission for Ethics in Research of the National Health Council of the Ministry of Health (CAAE: 32840920.7.0000.0071).

App users will individually provide consent to participate in the study. The risk to confidentiality will be minimized through protection measures by the researchers. All participants' personal data and responses to participation will be kept private and confidential, thus guaranteeing anonymity, and at no time will participant identity be disclosed.

The data will be accessed only by the investigators. Since this is an educational intervention, it is of low risk, and no adverse effects are expected, and no compensation for study participation is contemplated.

Discussion

There are presently no intentions to implement major protocol modifications; in case they occur, relevant parties will be solicited.

No restrictions are anticipated among investigators and sponsors to communicate trial results. We expect to disseminate the outcomes to the general public, health providers, and through scientific publications by means of a joint collaboration of the School of Public Health, University of São Paulo, with Sociedade Beneficente Israelita Brasileira Hospital Albert Einstein. The research teams from both institutions will author the resulting publications, with no intention to use professional manuscript writing services.

We will request authorization from the sponsor to grant public access to the complete protocol, anonymized participant-level data set, and the statistical code, 2 years after the completion of the study for both research and educational purposes, and to explore new hypotheses arising from the study.

If successful, this educative intervention (which can be used outside of the smartphone app) will be made publicly accessible after the dissemination of results, with proper credit and recognition.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Eligibility criteria filter questionnaire screenshot.
[PNG File , 83 KB - resprot_v10i5e25016_app1.png]

Multimedia Appendix 2
Invitation questionnaire screenshot.
[PNG File , 66 KB - resprot_v10i5e25016_app2.png]

Multimedia Appendix 3
Informed consent questionnaire screenshot.
[PNG File , 59 KB - resprot_v10i5e25016_app3.png]

Multimedia Appendix 4
Entry and exit questionnaire screenshot.
[PNG File , 121 KB - resprot_v10i5e25016_app4.png]

Multimedia Appendix 5
Intervention questionnaire screenshot.
[PNG File , 125 KB - resprot_v10i5e25016_app5.png]

Multimedia Appendix 6
Control questionnaire screenshot.
[PNG File , 146 KB - resprot_v10i5e25016_app6.png]

Multimedia Appendix 7
Birth plan questionnaire screenshot.
[PNG File , 128 KB - resprot_v10i5e25016_app7.png]

Multimedia Appendix 8
Childbirth styles screenshot.
[PNG File , 168 KB - resprot_v10i5e25016_app8.png]

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Multimedia Appendix 9
Schedule of enrolment, interventions, and assessments.
[PDF File (Adobe PDF File), 34 KB - resprot_v10i5e25016_app9.pdf]

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Protocol

Evaluation of the My Diabetes Care Patient Portal Intervention: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: My Diabetes Care (MDC) is a multi-faceted intervention embedded within an established patient portal, My Health at Vanderbilt. MDC is designed to help patients better understand their diabetes health data and support self-care. MDC uses infographics to visualize and summarize patients' diabetes health data, incorporates motivational strategies, provides literacy-level appropriate educational resources, and links to a diabetes online patient support community and diabetes news feeds.

Objective: This study aims to evaluate the effects of MDC on patient activation in adult patients with type 2 diabetes mellitus. Moreover, we plan to assess secondary outcomes, including system use and usability, and the effects of MDC on cognitive and behavioral outcomes (eg, self-care and self-efficacy).

Methods: We are conducting a 6-month, 2-arm, parallel-design, pragmatic pilot randomized controlled trial of the effect of MDC on patient activation. Adult patients with type 2 diabetes mellitus are recruited from primary care clinics affiliated with Vanderbilt University Medical Center. Participants are eligible for the study if they are currently being treated with at least one diabetes medication, are able to speak and read in English, are 21 years or older, and have an existing My Health at Vanderbilt account and reliable access to a desktop or laptop computer with internet access. We exclude patients living in long-term care facilities, patients with known cognitive deficits or severe visual impairment, and patients currently participating in any other diabetes-related research study. Participants are randomly assigned to MDC or usual care. We collect self-reported survey data, including the Patient Activation Measure (R) at baseline, 3 months, and 6 months. We will use mixed-effects regression models to estimate potentially time-varying intervention effects while adjusting for the baseline measure of the outcome. The mixed-effects model will use fixed effects for patient-level characteristics and random effects for health care provider variables (eg, primary care physicians).

Results: This study is ongoing. Recruitment was closed in May 2020; 270 patients were randomized. Of those randomized, most (214/267, 80.1%) were non-Hispanic White, and 13.1% (35/267) were non-Hispanic Black, 43.7% (118/270) reported being 65 years or older, and 33.6% (90/268) reported limited health literacy. We obtained at least 95.6% (258/270) completion among participants through the 3-month follow-up assessment.

Conclusions: This randomized controlled trial will be one of the first to evaluate a patient-facing diabetes digital health intervention delivered via a patient portal. By embedding MDC into Epic's MyChart platform with more than 127 million patient records, our intervention is directly integrated into routine care, highly scalable, and sustainable. Our findings and evolving patient portal functionality will inform the continued development of MDC to best meet users' needs and a larger trial focused on the impact of MDC on clinical end points.

Trial Registration: ClinicalTrials.gov NCT03947333; https://clinicaltrials.gov/ct2/show/NCT03947333

International Registered Report Identifier (IRRID): DERR1-10.2196/25955

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Introduction

Background

Diabetes is a leading cause of several highly morbid and costly conditions, including chronic kidney disease, cardiovascular disease, and visual impairment [1]. Attention to diabetes self-management behaviors can help patients avoid or delay many diabetes-related complications; however, consistent engagement in self-care behaviors is challenging for many patients [1,2]. Patient activation (ie, knowledge, skills, and confidence in managing one's own health) is vital to achieving optimal diabetes self-management and is associated with lower health care costs [3-5].

Patient portals are computerized tools that can connect patients with electronic health data maintained by their health care system. Patient portals can provide an engaging and convenient means for patients to track and visualize health data, obtain education and guidance, and connect patients and doctors [6]. Research has shown that patient portals offer a promising platform to increase patient activation, enhance care, and promote self-management while overcoming the limitations of costly and difficult-to-scale face-to-face interventions [7,8]. We recently applied a user-centered design sprint methodology and key strategies for patient engagement to develop a patient portal intervention called My Diabetes Care (MDC; formerly Diabetes Dashboard) [9].

MDC is embedded within an established patient portal, My Health at Vanderbilt (MHAV), at Vanderbilt University Medical Center (VUMC) [10]. MDC is a multi-faceted intervention designed to help patients better understand their diabetes health data and support self-management [9]. MDC uses infographics to visualize and summarize patients' diabetes health data; incorporates motivational strategies (eg, social comparisons); provides literacy-level appropriate educational resources; contains secure messaging capability; and links to a diabetes online patient support community and diabetes news feeds, highlighting new discoveries, medicines, and recipes. MDC was founded on the well-established Chronic Care Model adapted for eHealth—eHealth Enhanced Chronic Care Model (eCCM) [11]. By leveraging elements within the model's 5 domains (self-management support, delivery system design, decision support, clinical information systems, and eHealth education), MDC has the potential to create more informed and activated patients, leading to improved outcomes (Figure 1).

Figure 1. The eHealth Enhanced Chronic Care Model with key aspects of My Diabetes Care shown in italics under the corresponding domain.
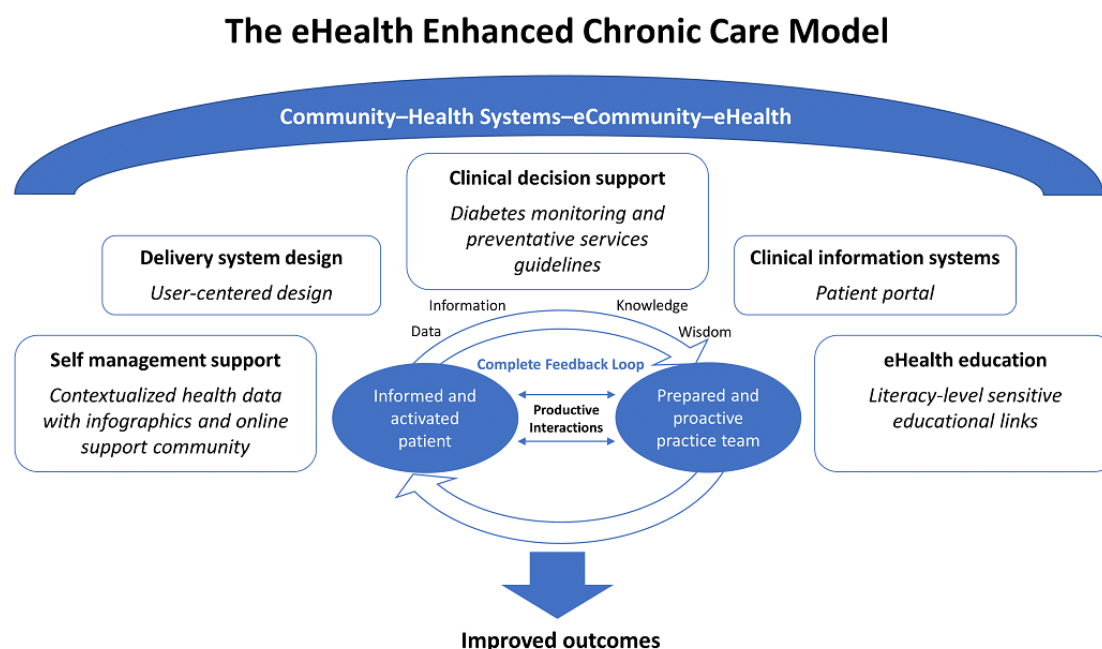
A 1-month usability study of MDC among 60 patients found that participants, including those with limited health literacy, highly rated MDC's usability and acceptability [12]. User experience data showed that most participants found that the infographics and links to literacy-level appropriate diabetes health information helped them better understand their diabetes health data. Participant feedback also identified areas for improvement, including adding information about diabetes medications and links to diabetes news feeds, highlighting new discoveries, medicines, and recipes. Consistent with the eCCM, the study also found a significant pre-post increase in patient activation scores among the study participants. However, a larger randomized controlled trial (RCT) is needed to assess MDC's impact on patient activation more definitively.

Objectives

This study aims to evaluate the effects of MDC on patient activation in adult patients with type 2 diabetes mellitus (T2DM). In addition, we plan to explore secondary outcomes, including system use and usability, and the effects of MDC on diabetes self-efficacy, knowledge, self-care, medication adherence, distress, and clinical endpoints. The study will serve as a pilot for a larger definitive trial evaluating the effect of MDC on clinical endpoints.

Methods

Study Design

To achieve this objective, we are conducting a 6-month, 2-arm, parallel-design, pragmatic pilot RCT of MDC. Participants in both arms are told the purpose of the study is *to determine satisfaction with 2 versions of MHAV among patients with diabetes*. One version is the currently available version of MHAV. The second version of MHAV contains the MDC intervention. Participants in both arms complete the study questionnaires at 3-time points: T_0=baseline, T_1=3 months, and T_2=6 months.

The study protocol is registered with ClinicalTrials.gov (ID NCT03947333) and is being conducted in accordance with the principles outlined in the CONSORT (Consolidated Standards of Reporting Trials) Statement, extension for pragmatic trials [13]. Pragmatic trials are designed to evaluate the real-world effectiveness of interventions in routine practice environments [14]. Unlike a strictly controlled trial, participants in our study are not constrained to receive a controlled *dose* of the intervention [14]. Due to necessity, participants are not blinded to the intervention, and we do not attempt to control participants' communication or information-seeking behaviors beyond the 2-arm randomization described here. The Vanderbilt University institutional review board approved this study.

Recruitment and Eligibility

Participants are recruited from 14 VUMC-affiliated adult primary care clinics located throughout Middle Tennessee (4 urban and 10 suburban clinics). An electronic health record (EHR; Epic Systems Corp) stores all clinical data. Patients receive access to their clinical data via an integrated and highly adopted patient portal, MHAV, that is accessible on desktops and via a native mobile app for iOS and Android mobile operating systems.

Participants are eligible for the study if they are a patient at a participating primary care clinic and have T2DM, are currently being treated with at least one diabetes medication, are able to speak and read in English, are 21 years or older, have an existing MHAV account, and have reliable access to a desktop or laptop computer with internet access. We exclude patients living in long-term care facilities, patients with known cognitive deficits, patients with a severe visual impairment, and patients currently participating in another diabetes-related research study.

On a rolling basis, potentially eligible patients are selected from a randomly ordered list of established adult patients with diabetes from participating clinic sites and are sent a recruitment letter describing the study. In addition, we also use *My Research at Vanderbilt* to send the recruitment letter to current patient portal users who elected to allow investigators to contact them about research opportunities via email. Interested patients contact a research assistant to learn more about the study. To enroll, participants complete a web-based study eligibility screener and electronic consent form on the web via REDCap (Research Electronic Data Capture) version 5.0.8. [15].

Procedures and Randomization

A study coordinator contacts all enrolled participants to review study procedures, answer the remaining questions, and confirm eligibility criteria. The enrolled participants are sent a baseline questionnaire via REDCap. After receiving the completed baseline questionnaire, the study coordinator randomly assigns participants to 1 of 2 groups: (1) intervention or (2) usual care. The randomization sequence was generated by the research team biostatistician using a permuted block randomization scheme stratified by clinic site and participants' age group (65 years and older vs younger than 65 years) to obtain balance across treatment groups on key variables. The randomized assignment for eligible participants is accessible only to the study coordinator and biostatistician using the REDCap randomization module; the other investigators are blinded. Once a randomization assignment is finalized, participants in both arms receive an email with their treatment assignment and an explanation of how to navigate to features of MHAV specific to their treatment group. Participants are asked to reply to the email affirming that they can access MHAV and/or MDC in accordance with their group assignment. Monthly quality assurance checks are used to ensure that MDC is functioning correctly (eg, displaying data correctly) and to ensure the fidelity of the intervention.

A participant may withdraw from the study at any time by notifying the study team. In addition, participants are withdrawn from the study by the investigators if they do not complete the baseline questionnaire needed for randomization. If a participant is withdrawn from the study for any reason, they are notified, and a reason is provided.

Intervention and Control

Participants randomized to the intervention arm are provided access to a version of MHAV embedded with MDC, as described in the *Introduction* section. Participants randomized to the intervention are advised to view MDC on a desktop or laptop device because the present version of MDC is not mobile friendly. Figure 2 shows a screenshot of MDC and illustrates its features [16,17]. Participants randomized to the usual care arm have access to the currently available version of MHAV, which includes the ability for patients to review pertinent health data, review medical information about their conditions, and communicate with their health care team.

Figure 2. My Diabetes Care screenshot and features. Stars across the top fill in when the patient's glycated hemoglobin, blood pressure, cholesterol, or flu vaccine status are within goal range (ie, a value in the green zone on the infographic for each measure). Info icons provide a brief literacy-level appropriate description of each measure. Infographics display health data relative to a goal (green), caution (yellow), and warning (red) ranges. Patients Like Me indicates the average value of similar patients (ie, Vanderbilt patients with diabetes of the same gender, age group, and insulin-use status), and hovering over the icon reveals this description to the patient. Me indicates the patient's value, and hovering over the icon displays historical values. Literacy-level appropriate educational materials (hyperlinks) are paired with each measure. Message Your Doctor allows patients to send a secure message to members of their health care team. Online patient support community allows users to navigate directly to the American Diabetes Association (ADA) support community; a separate ADA account (username and password) is required. News Feeds provide newly published diabetes-related content, including recipes, discoveries, and new medications. FAQ provides answers to frequently asked questions regarding site features and navigation.
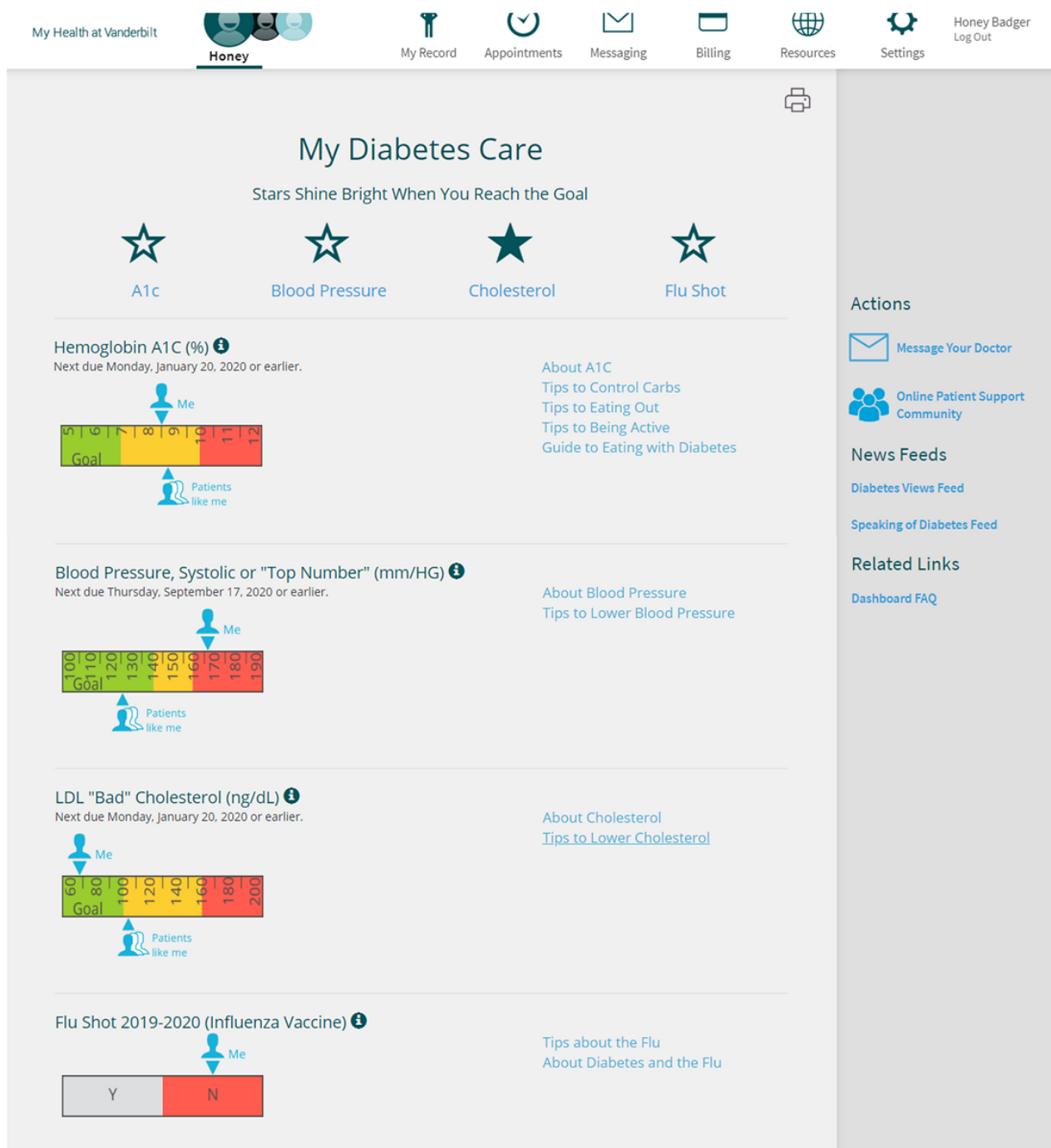
Data Collection and Measures

Enrolled participants receive 3 study questionnaires via REDCap at the associated time points (T_0-T_2): baseline questionnaire, 3-month follow-up questionnaire, and 6-month follow-up questionnaire. On the basis of pilot testing, we estimate the time to completion for the baseline questionnaire to be about 25 minutes and 20 minutes each for the 3-month and 6-month follow-up questionnaires. Participants are compensated US $40 for completing the enrollment questionnaire and US $35 each for completing the 3-month and 6-month follow-up questionnaires.

To describe the study population at baseline, we collect the following sociodemographic and clinical variables (Table 1).

Health literacy is assessed by a validated 1-item screener asking respondents to rate their confidence independently filling out medical forms [18,19]. Consistent with previous studies, participants noting any lack of confidence are classified as having limited health literacy [20,21]. eHealth literacy is assessed by the 8-item eHealth Literacy Scale (eHEALS) [22]. The eHEALS uses a 5-point Likert scale ranging from *strongly disagree* to *strongly agree*. Total scores range from 8 (worst) to 40 (best). The presence of comorbidities (ie, hypertension and hyperlipidemia) is assessed by 2 clinicians who independently review patients' problem lists and medications abstracted from the EHR, and disagreements are resolved by consensus.

Table 2 shows the primary and secondary outcomes and related measures contained within the study questionnaires and their associated time points. The same study measures are administered to all participants in both arms, except for the system use and user experience, which contain items unique to the participants' assigned condition (ie, intervention vs control).

Table 1. Sociodemographic and clinical variables collected at baseline.

Variable and units or categories	Form of collection
Age (years)	Questionnaire
<35	
35-44	
45-54	
55-64	
65-74	
75-84	
≥85	
Ethnicity	Questionnaire
Hispanic or Latino	
Non-Hispanic or Latino	
Race	Questionnaire
White	
Black or African American	
American Indian or Alaska Native	
Asian	
Native Hawaiian or Other Pacific Islander	
More than one race	
Other	
Gender	Questionnaire
Female	
Male	
Other	
Marital status	Questionnaire
Never married	
Married or partnered	
Separated or divorced	
Widowed	
Education	Questionnaire
8 grades or less	
Some high school	
High school graduate or GED[a]	
Some college or technical school	
College graduate (bachelor's degree)	
Some graduate work or school	
Graduate degree	
Employment status	Questionnaire
Working full-time: 35 hours or more a week	
Working part-time: less than 35 hours a week	
Unemployed or laid off and looking for work	
Unemployed and not looking for work	
Homemaker	

Variable and units or categories	Form of collection
In school	
Retired	
Disabled: not able to work	
Something else	
Insurance	Questionnaire
An individual plan: the member pays for the plan premium	
A group plan through an employer or union: the employer pays all or part of the plan premium	
US governmental health plan (eg, Military, CHAMPUS[b], Veterans Affairs, Medicaid, and Medicare)	
I have not had an insurance plan in the past 12 months	
Diabetes duration	Questionnaire
Years	
Health literacy	Questionnaire
Adequate	
Limited	
eHealth literacy	Questionnaire
eHealth Literacy Scale score	
Insulin status	Questionnaire
No	
Yes	
Previous diabetes self-management education	Questionnaire
No	
Yes	
Previous visit with dietician or nutritionist	Questionnaire
No	
Yes	
Comorbidities	EHR[c] abstraction
Hyperlipidemia: no or yes	
Hypertension: no or yes	
Baseline clinical data	EHR abstraction
Glycated hemoglobin (%)	
Systolic blood pressure (mm Hg)	
Diastolic blood pressure (mm Hg)	
Mean arterial pressure (mm Hg)	
Low-density lipoprotein (mg/dL)	
2019-2020 influenza vaccination status: no or yes	

[a]GED: Graduate Equivalency Degree.

[b]CHAMPUS: Civilian Health and Medical Program of the Uniformed Services.

[c]EHR: electronic health record.

Table 2. Outcome measures.

Outcomes	Measures	Variable type	Form of collection	Time points
Primary outcome				
Patient activation	Patient Activation Measure-13 (R) [23]	Continuous	Questionnaire	T_0[a], T_1[b], and T_2[c]
Secondary cognitive and behavioral outcomes				
Diabetes self-efficacy	Perceived Diabetes Self-Management Scale [24]	Continuous	Questionnaire	T_0, T_1, and T_2
Diabetes knowledge	Short Diabetes Knowledge Instrument [25]	Continuous	Questionnaire	T_0, T_1, and T_2
Diabetes self-care	Summary of Diabetes Self-Care Activities [26]	Continuous	Questionnaire	T_0, T_1, and T_2
Diabetes medication adherence	Adherence to Refills and Medications Scale for Diabetes [27]	Continuous	Questionnaire	T_0, T_1, and T_2
Diabetes distress	Problem Areas in Diabetes Scale-5 [28]	Continuous	Questionnaire	T_0, T_1, and T_2
Understanding of diabetes health measures	Unique study-specific items to assess participants' understanding of measures of diabetes health status	Categorical	Questionnaire	T_0, T_1, and T_2
Usability and satisfaction	System usability scale [29]	Continuous	Questionnaire	T_0, T_1, and T_2
System use data	- Number of MHAV[d] or MDC[e] visits - Duration of MHAV or MDC visits - Number of MDC health data-related tasks performed (eg, view most recent low-density lipoprotein value) - Number of MDC information-seeking tasks performed (eg, click links to embedded educational materials) - Number of MHAV or MDC health management–related tasks performed (eg, utilization of embedded functionality to secure message health care team) - Number of MDC social support seeking tasks performed (eg, click link to American Diabetes Association Online Community)	Continuous	System analytics (if available), self-report	T_2
User experience	Unique study-specific items to assess participants' perspectives on specific features and functionality	Categorical and qualitative	Questionnaire	T_2
Clinical endpoints	Change in: - Glycated hemoglobin - Blood pressure - Low-density lipoproteins - Flu vaccination status	Continuous	EHR[f] abstraction	T_0, T_1, and T_2

[a]T_0: baseline.

[b]T_1: 3-month follow-up.

[c]T_2: 6-month follow-up.

[d]MHAV: My Health at Vanderbilt.

[e]MDC: My Diabetes Care.

[f]EHR: electronic health record.

Outcome Measures

Patient Activation

The primary outcome measure is the change in patient activation as assessed by the Patient Activation Measure (R) (PAM) [23]. The 13-item PAM (R) survey uses a 4-point Likert scale of response options ranging from strongly disagree to strongly agree and has excellent internal consistency reliability (Cronbach α=.87). The PAM-13 (R) survey item responses result in total raw scores ranging from 13 to 52, which are converted to the linear interval scale of patient activation scores, ranging from 0 (lowest activation) to 100 (highest activation).

Diabetes Self-Efficacy

The Perceived Diabetes Self-Management Scale (PDSMS) is used to measure diabetes self-efficacy (ie, how confident participants feel about their ability to perform multiple self-management tasks) [23]. The 8-item scale is scored on a 5-point Likert scale and has excellent internal consistency reliability (Cronbach α=.83). The total PDSMS score ranges from 8 to 40, with higher scores indicating a greater confidence in managing diabetes.

Diabetes Knowledge

The Short Diabetes Knowledge Instrument (SDKI) is used to measure diabetes knowledge, including diabetes diet, hypoglycemia symptoms, foot care, and the importance of physical activity [25]. The SDKI is a 13-item scale with scores ranging from 0 to 13, representing the number of items answered correctly, and has demonstrated good internal consistency reliability (Cronbach α=.73) in a diverse sample of older adults.

Diabetes Self-care

Change in diabetes self-care is measured using the Summary of Diabetes Self-Care Activities (SDSCA) [26]. The SDSCA is an 11-item questionnaire of diabetes self-management that assesses the following 6 aspects of the diabetes self-care regimen: general diet (2 items), specific diet (2 items), exercise (2 items), blood glucose testing (2 items), foot care (2 items), and smoking (1 item). Item responses use the metric *days per week*, except for a single item about smoking status, which is a *yes* or *no* item. Each of the 6 aspects is assigned a mean score based on the number of days per week.

Diabetes Medication Adherence

Change in diabetes medication adherence is measured using the Adherence to Refills and Medications Scale-Diabetes (ARMS-D) [27]. The 11-item ARMS-D scale has excellent internal consistency reliability (Cronbach α=.86). Responses range from 1=*none of the time* to 4=*all of the time* and are summed to generate an overall score ranging from 12 (best) to 48 (worst).

Diabetes Distress

The Problem Areas in Diabetes Scale (PAID-5) is used to measure changes in diabetes distress [28]. The 5-item unidimensional scale has scores ranging from 0 to 20, with higher scores suggesting greater diabetes-related emotional distress. The PAID-5 has excellent internal consistency reliability (Cronbach α=.86) and is associated with measures of depression.

Understanding of Diabetes Health Measures

Unique study-specific items are used to measure patients' understanding of the diabetes health measures displayed within MDC. For example, patients are asked to identify the goal range for glycated hemoglobin (HbA_{1c}), low-density lipoprotein (LDL) cholesterol, and systolic blood pressure.

Satisfaction With Usability

Usability of MDC is assessed by the 10-item System Usability Scale that measures users' perceptions of ease of use, the likability of the interface, and overall satisfaction using a 5-point Likert scale (strongly disagree to strongly agree) [29]. The item scores are summed and then converted to a score ranging from 0 (worst) to 100 (best), with a score above 68 considered *above average* [30].

System Use Data

We are collecting MDC system use data, including the total number of visits, total duration, and use of embedded educational resources; secure messaging; participation in the online patient support community; and hovers over the information icon about diabetes health measures and diabetes news feeds.

User Experience

User experience is assessed by unique study-specific multiple-choice and open-ended questions that solicit participants' perspectives on specific MDC features and functionality. For example, participants are asked to identify which features, if any, helped them better understand their diabetes health data and are asked to describe any problems they encountered using MDC.

Clinical End Points

Change in the following clinical endpoints is assessed by abstracting from the EHR the closest measurement on or before T_0, T_1, and T_2 time points for each of the following measures: HbA_{1c}, blood pressure, LDL cholesterol, and flu vaccination status. For the final time point (T_2), we allow measures on or before T_2 plus 2 weeks, as these measures can be reasonably assumed to reflect the study period.

Data Analysis

Statistical Analysis Plan

The study is designed to evaluate the effects of MDC on patient activation (primary analysis) and explore the effects on other secondary cognitive and behavioral outcomes relative to the control group. We will use mixed-effects regression models to estimate potentially time-varying intervention effects while adjusting for the baseline measure of the outcome. Nonlinear associations will be modeled with regression splines. The mixed-effects model will use fixed effects for patient-level characteristics and random effects for health care provider variables, such as primary care physicians. We will provide point estimates with CIs for each follow-up and graphically depict our results. The analysis will follow a conservative intention-to-treat principle, and participants with missing values will be included along with those with complete data. Multiple imputation will be used to impute the missing values. The analysis with multiple imputation assumes missing at random (ie, the model properly handles missing data by including covariates associated with reasons for dropout). The characteristics of participants who do not complete the study or do not comply with the treatment will be compared for both conditions. Mixed-effect models will also be used to evaluate the effects of MDC on secondary outcomes. For dichotomous secondary outcomes, such as flu vaccination status, we will use mixed-effects logistic regression. Given the smaller effective size when modeling dichotomous outcomes, the model for the dichotomous outcomes will not support as many covariates as the model for continuous outcomes.

Primary Analysis

We will test the impact of MDC on patient activation compared with the control condition (Table 2). We hypothesize that participants assigned to MDC will experience greater improvements in patient activation than participants assigned to the control condition.

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Secondary Analysis

In addition, we will test the effects of MDC on other behavioral and cognitive outcomes (Table 2). Finally, we will assess whether participants assigned to MDC experience greater improvements in HbA_{1c}, blood pressure, LDL, and influenza vaccination status compared with those assigned to MHAV only.

Sample Size and Power

Assuming an up to a 20% dropout rate, approximately 240 patients (approximately 120 in each arm) are expected to complete the study. A conservative approach of a 2-sided *t* test performed at a 5% significance level would detect an effect size of 0.36 SDs for each continuous outcome with 80% power. In the context of the primary outcome PAM (R) survey and assuming a common SD of 12 points, this would be equivalent to detecting a true mean difference of 4.4 points; 4-point changes in the PAM (R) are associated with positive changes concerning particular diabetes self-care behaviors [31].

Results

Recruitment

Figure 3 shows the flowchart of the recruitment process. Recruitment began in March 2020 and ended in May 2020. Throughout the recruitment period, 4388 unique letters were sent to patients identified as potentially eligible. Separately, 2609 unique emails were sent to patients who use MHAV and previously agreed to be contacted by email about research studies for which they might be eligible. As it was not possible for the study team to cross reference the list of those who were sent letters against the list of those who were sent emails, some overlap is possible. The letters and emails generated 702 visits to the web-based REDCap eligibility screener, resulting in 576 completed screeners. Of the 576 complete screeners, 163 (28.3%) were ineligible and 413 (71.7%) were eligible. Of the 413 eligible screeners, 113 (27.4%) declined to participate and 300 (72.6%) were enrolled. We administratively withdrew 10% (30/300) of those enrolled, and the remaining 270 participants were randomized.

Figure 3. Recruitment and enrollment flowchart. MHAV: My Health At Vanderbilt; MRAV: My Research At Vanderbilt; T2DM: type 2 diabetes mellitus.
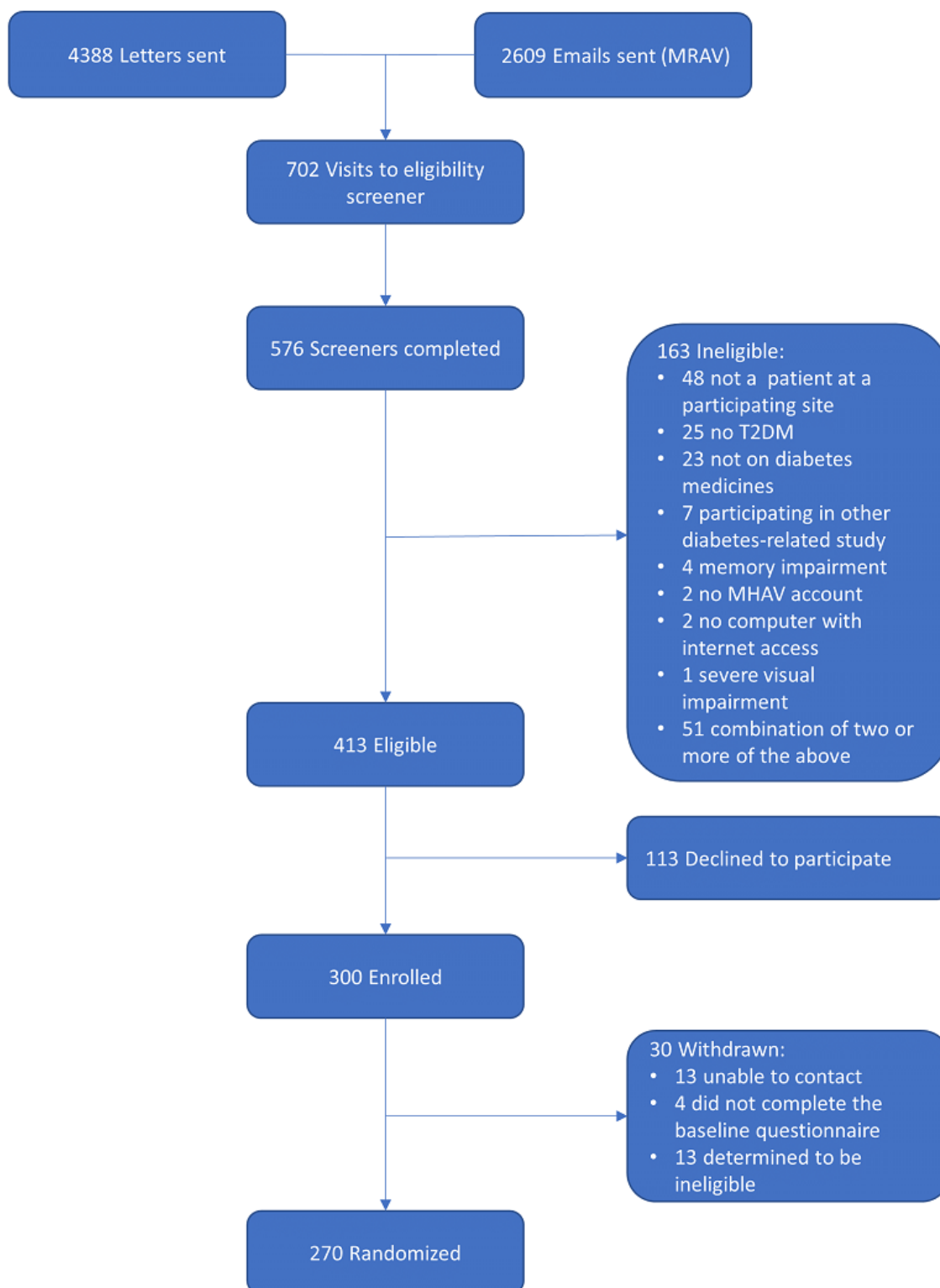
Participants

Of those randomized, most (214/267, 80.1%) were non-Hispanic White; 13.1% (35/267) were non-Hispanic Black; and 6.7% (18/267) reported being of another race, including American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, more than one race, Hispanic Black, and Hispanic White. In addition, 43.7% (118/270) reported being 65 years or older. Furthermore, 10.1% (27/268) reported educational attainment of a high school degree or less, 33.6% (90/268) had limited health literacy, and 39.6% (106/268) had only a US governmental health plan (eg, Military, Civilian Health and Medical Program of the Uniformed Services, Veterans Affairs, Medicaid, and Medicare). Approximately one-third (82/270, 30.4%) were taking insulin, the mean duration of diabetes was 12.5 (SD 8.6) years, and the mean HbA_{1c} level at baseline was

7.1 (SD 1.3). The overall clinical population with diabetes has a somewhat different demographic distribution: 66.49% (5317/7997) are non-Hispanic White, 21.83%% (1754/7997) are non-Hispanic Black, and 42.34% (3386/7997) are 65 years or older. The mean HbA_{1c} of the 7997 patients within the overall clinical population and a laboratory value in the past 12 months was 7.40. As of October 2020, we have at least 95.6% (258/270) completion among participants through the 3-month follow-up assessment.

Discussion

Principal Findings

Our study will be one of the very few RCTs to evaluate a patient-facing diabetes digital health intervention delivered via a patient portal. Although diabetes digital health interventions have great potential, their impact has been limited due to the difficulty in integrating the interventions into routine care [32]. By embedding MDC into Epic's MyChart platform with more than 127 million patient health records [33], our intervention is directly integrated into patients' health care systems and is highly scalable and sustainable. Unlike independent health apps, patient portals, by their very nature, are integrated into routine care and therefore offer greater potential for uptake and sustained use [7]. The challenge for health systems and investigators is how to make the most of patient portals to improve care.

We designed MDC to enhance and expand on existing aspects of patient portals, including access to personal health data and education, to better support diabetes self-management. Although patient portals offer easy access to personal health data, previous research suggests that complex data displays—showing many tests in small format on a single page without any indication of their clinical significance—make it difficult for patients to find and correctly interpret a particular test result [7]. MDC uses a simplified infographic to indicate normal, modestly abnormal, and more severely abnormal results and literacy-level appropriate materials to help patients better understand their diabetes health data. Thus, this research will inform how different data displays and user interface designs impact patients' ability to understand their personal health data.

Studies of other technology-enabled diabetes self-management solutions suggest additional strategies that may benefit patients [32,34]. These include analysis of patient-generated health data and tailored education and feedback [32,34]. To maximize scalability and sustainability, functionality enabling these strategies is best built directly into the EHR vendor's patient portal platform (eg, Epic's My Chart). Solutions built external to the platform may be more challenging to integrate into routine practice and run the risk of quickly becoming out of date and requiring reprogramming when vendors release platform updates. For this reason, we did not include these strategies in our intervention. However, EHR vendor solutions are emerging and may allow us to incorporate these additional patient engagement strategies into future iterations of MDC [35].

We designed MDC to be usable by the greatest number of patients, including those with limited health literacy [12].

Limited health literacy is typically associated with worse outcomes among patients with diabetes and can be a barrier to patient portal use [36,37]. Previous research has shown that patients with limited health literacy struggle to use patient portals because of complex medical terminology and a lack of literacy-level appropriate health information [20,21]. Although patient portals have the potential to worsen health inequities by further advantaging well-educated patients with greater resources, if designed and implemented appropriately, patient portals also have the potential to lower health literacy demands by ensuring that patients are presented with the health information and resources in a format that is convenient and easy to navigate and understand [38].

Our study population has a somewhat smaller proportion of racial or ethnic minorities than the overall clinical population, suggesting that additional strategies may be needed to increase adoption among these groups. Digital navigators—trained staff or volunteers who assist patients in accessing and learning how to use technology to meet their needs—have been used to increase patient portal adoption among vulnerable populations [20,39]. Smartphone use is increasingly common across different socioeconomic and racial or ethnic backgrounds, and for patients that lack broadband home internet connections, smartphones may be their only way to access the internet [40]. Thus, developing interventions suitable for mobile platforms may reduce barriers to adoption. Since the initiation of this trial, we have begun the development of a mobile-friendly version MDC that we hope will further increase its utility and accessibility.

Finally, given that racial and ethnic minorities are disproportionately affected by T2DM, future studies of MDC and other technology-delivered diabetes self-care interventions should consider using oversampling techniques, as demonstrated by Nelson et al [41,42], to recruit study populations that closely represent the overall population of patients with T2DM. Doing so will help ensure that technology-delivered diabetes self-care interventions are effective in the populations with the greatest need and inform any revisions to those interventions and/or their implementation needed to address disparities.

Limitations

This study has important limitations. It relies on self-reported measures of patient activation and several secondary outcomes that are subject to social desirability and recall bias. However, the chosen measures are validated, widely used, and accepted, offering the advantage of being brief, inexpensive, and unobtrusive compared with more objective measures. Our study is powered to examine the effects of MDC on patient activation; therefore, analyses examining the effects of other outcomes (eg, self-care behaviors and HbA_{1c}) and comparing the effects among subgroups (eg, patients with limited health literacy or poorly controlled diabetes) may be very informative but may also be underpowered. We hope that this study will serve as a pilot for a larger definitive trial evaluating the effect of MDC on clinical endpoints. Should MDC prove effective at increasing patient activation, the 6-month trial duration will not allow us to determine if the effect is temporary or sustained. A longer trial of a year or more in duration is needed to examine sustained effects. MDC is currently available only in English. This was

necessary to increase the feasibility of designing the intervention and successfully completing this initial trial. However, diabetes disproportionately affects Spanish-speaking groups, so translation into Spanish will be an important goal, if MDC should prove beneficial. Finally, although patient portal interventions offer the advantages of direct integration into routine care, scalability, and sustainability, they are subject to inequities in patient portal adoption [43] and may appeal to more activated patients [44]. However, research shows that patient portal adoption is increasing [10,45], and if designed appropriately, patient portals could reduce health disparities [38,46]. Moreover, recent research finds that patient portal users have similar levels of patient activation as nonusers, although portal users are more likely to have internet access and a higher level of education [47].

Conclusions

We expect that this study will help determine the effectiveness of MDC in increasing patient activation among patients with diabetes. Beyond this primary objective, we will also be able to examine data on secondary cognitive, behavioral, and clinical outcomes and users' perceptions of and satisfaction with the intervention. Our findings and evolving patient portal functionality will inform the continued development of the intervention to best meet users' needs and a larger trial focused on the impact of MDC on clinical endpoints.

Acknowledgments

Conflicts of Interest

None declared.

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Abbreviations

ARMS-D: Adherence to Refills and Medications Scale-Diabetes
eCCM: eHealth Enhanced Chronic Care Model
eHEALS: eHealth Literacy Scale
EHR: electronic health record
HbA$_{1c}$: glycated hemoglobin
LDL: low-density lipoprotein
MDC: My Diabetes Care
MHAV: My Health at Vanderbilt
PAID-5: Problem Areas in Diabetes Scale
PAM (R): Patient Activation Measure (R)
PDSMS: Perceived Diabetes Self-Management Scale
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SDKI: Short Diabetes Knowledge Instrument
SDSCA: Summary of Diabetes Self-Care Activities
T2DM: type 2 diabetes mellitus
VUMC: Vanderbilt University Medical Center

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Protocol

Norms and Social Network–Centric Behavior Change Intervention (Nam Nalavazhvu) for Improved Toilet Usage in Peri-Urban Communities of Tamil Nadu: Protocol for a Cluster-Randomized Controlled Trial

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Abstract

Background: Inconsistent toilet usage is a continuing challenge in India. Despite the impact of social expectations on toilet usage, few programs and studies have developed theoretically grounded norm-centric behavior change interventions to increase toilet use in low-income settings.

Objective: The objective of this paper is to detail the rationale and design of an ex ante, parallel cluster-randomized trial evaluating the impact of a demand-side, norm-centric behavior change intervention on exclusive toilet use and maintenance in peri-urban Tamil Nadu, India.

Methods: Following formative research, we developed an evidence-based norm-centric behavior change intervention called Nam Nalavazhvu (Tamil for "our well-being"). The multilevel intervention aims to improve toilet usage by shifting empirical expectations or beliefs about other relevant people's sanitation practices. It also provides action-oriented information to aid individuals to set goals and overcome barriers to own, consistently use, and maintain their toilets. This trial includes 76 wards in the Pudukkottai and Karur districts, where half were randomly assigned to receive the intervention and the remaining served as counterfactuals.

Results: We enrolled wards and conducted a baseline survey among randomly selected individuals in all 76 wards. The 1-year behavior change intervention is currently ongoing. At the endline, we will collect relevant data and compare results between study arms to determine the impacts of the Nam Nalavazhvu intervention on sanitation-related behavioral, health, and well-being outcomes and potential moderators. This study is powered to detect differences in the prevalence of exclusive toilet use between study arms. We are also conducting a process evaluation to understand the extent to which the intervention was implemented as designed, given the special pandemic context.

Conclusions: Findings from this trial will inform norm-centric behavior change strategies to improve exclusive toilet usage.

Trial Registration: ClinicalTrials.gov NCT04269824; https://www.clinicaltrials.gov/ct2/show/NCT04269824

International Registered Report Identifier (IRRID): DERR1-10.2196/24407

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Introduction

Study Rationale

Open defecation practices enable environmental contamination and contribute to poor health, well-being, and safety globally [1-3]. In the past decade, national sanitation programs, such as the Swachh Bharat Mission (SBM), have significantly increased coverage of private, shared, and public toilets to end persistent open defecation practices in India [4,5]. In addition, they have promoted exclusive use or using a toilet every time for defecation. Despite increased access to toilets, in many communities, complex sociocultural norms, along with technological and financial barriers, prevent individuals from using a toilet every time or exclusively using a toilet for defecation purposes [6-8]. Recent behavior change interventions designed to promote toilet use in rural India yielded, on average, a 5% increase in reported use amongst toilet owners, which is comparable to results generated by SBM [9-11]. Sustaining exclusive toilet use among all household members is a national priority for the current SBM 2.0, also known as the Open Defecation–Free plus scheme [12]. This is also aligned with the United Nations' Sustainable Development Goal 6.2, which calls on countries to "achieve access to adequate and equitable sanitation and hygiene for all and end open defecation" by 2030 [13].

Numerous studies have highlighted the importance of social beliefs and preferences on toilet construction and adoption [14-17]. Studies based in India found that several factors such as sociocultural inequalities, access to resources, and psychosocial determinants, such as perceived use among others in one's community, impacted toilet ownership and use [11,18-20]. Social networks were also found to be relevant: a study in rural Karnataka showed that individuals were more likely to own toilets if their social contacts owned one [21]. Following the achievements of SBM, in a context of high toilet ownership and use, perceptions of others' toilet ownership and approval might be particularly important motivators of toilet-related behavior change in India [11,19].

Previous studies that assessed psychosocial determinants of toilet use and included norm-based messaging to promote toilet use in India were primarily guided by Community-Led Total Sanitation (CLTS); the Risks, Attitudes, Norms, Abilities, and Self-regulation (RANAS) approach; or Behavior Centered Design (BCD). These approaches include norms as one driver of behavior but do not systematically evaluate and leverage specific social expectations that influence the norm [11,22-24]. It is not well understood whether the collective behavior of toilet usage is conditional on social expectations held by individuals. Social norms theory (SNT) uses a novel norms diagnostic approach to understand social expectations in distinguishing between independent or socially interdependent behaviors [25]. We based our theoretical investigation on SNT to conduct formative research as the first part of the Longitudinal

Evaluation of Norms and Network Study (LENNS). We specifically investigated whether toilet use behavior is driven by beliefs that most other people are using one (empirical expectations) or whether others think one should use it (normative expectations) [26]. By measuring social expectations and other social determinants, we determined that toilet use is socially conditional on empirical expectations in these communities (further details in following section). This allowed us to leverage specific normative components to focus our behavior change strategy.

This study protocol summarizes the rationale and methods of a cluster-randomized trial (CRT; LENNS) that aims to evaluate the impact of a multilevel, demand-side behavior change intervention package called Nam Nalavazhvu on exclusive toilet use and maintenance. Prior studies have not explored norm-based intervention techniques specifically designed to change empirical expectations of sanitation behaviors in low-income communities. Findings from this multilevel intervention can be used to adapt them for other communities to shift norms around toilet use. There is limited evidence on whether intervening upon empirical expectations of others' sanitation behaviors can lead to the emergence of normative expectations of toilet use. This type of phenomenon is theoretically plausible, and if demonstrated through this study, our findings can lead to insights to inform the design of norm-focused behavior change strategies [27,28]. Finally, our study is based in peri-urban communities, which will add to the currently limited sanitation literature regarding interventions that benefit peri-urban populations [29-31].

Specific Aims

The primary research aim of this study is to evaluate the impact of the Nam Nalavazhvu intervention on behavioral and health outcomes. The aim specifically focuses on the following: exclusive toilet usage, defined as reported use of a toilet every time for defecation among individuals aged 5 years and older (primary outcome).

Secondary aims include assessing the impact of the intervention on the following: access to improved toilets (individual or shared) for households without a toilet; maintenance of sanitation facilities for sustained use; empirical expectations, normative expectations, and other behavioral antecedents; mental well-being of respondents; and diarrheal outcomes in all household members and respiratory health in children under 5 years.

Methods

Study Setting

The study is being conducted in 76 wards in peri-urban areas of Pudukkottai and Karur districts in Tamil Nadu, India (Figure 1). The unit of randomization for this study was the ward, the smallest administrative unit of a town panchayat. According to

the 2011 Census, these are urbanizing districts, where in Pudukkottai and Karur respectively, the residents were mainly agricultural laborers (31% and 34%, respectively), workers in industries (1.3% and 1.2%, respectively), and other private businesses (16% and 43%, respectively). These districts consist primarily of Hindus (88% and 93%, respectively) and a minority of Muslims (7.1% and 5.1%, respectively). Although both districts were declared open defecation–free in October 2019, there were variations in toilet coverage and use across constituent wards, which we captured through informal conversations with officials.

Figure 1. Study sites in Karur and Pudukkottai districts of Tamil Nadu, India.
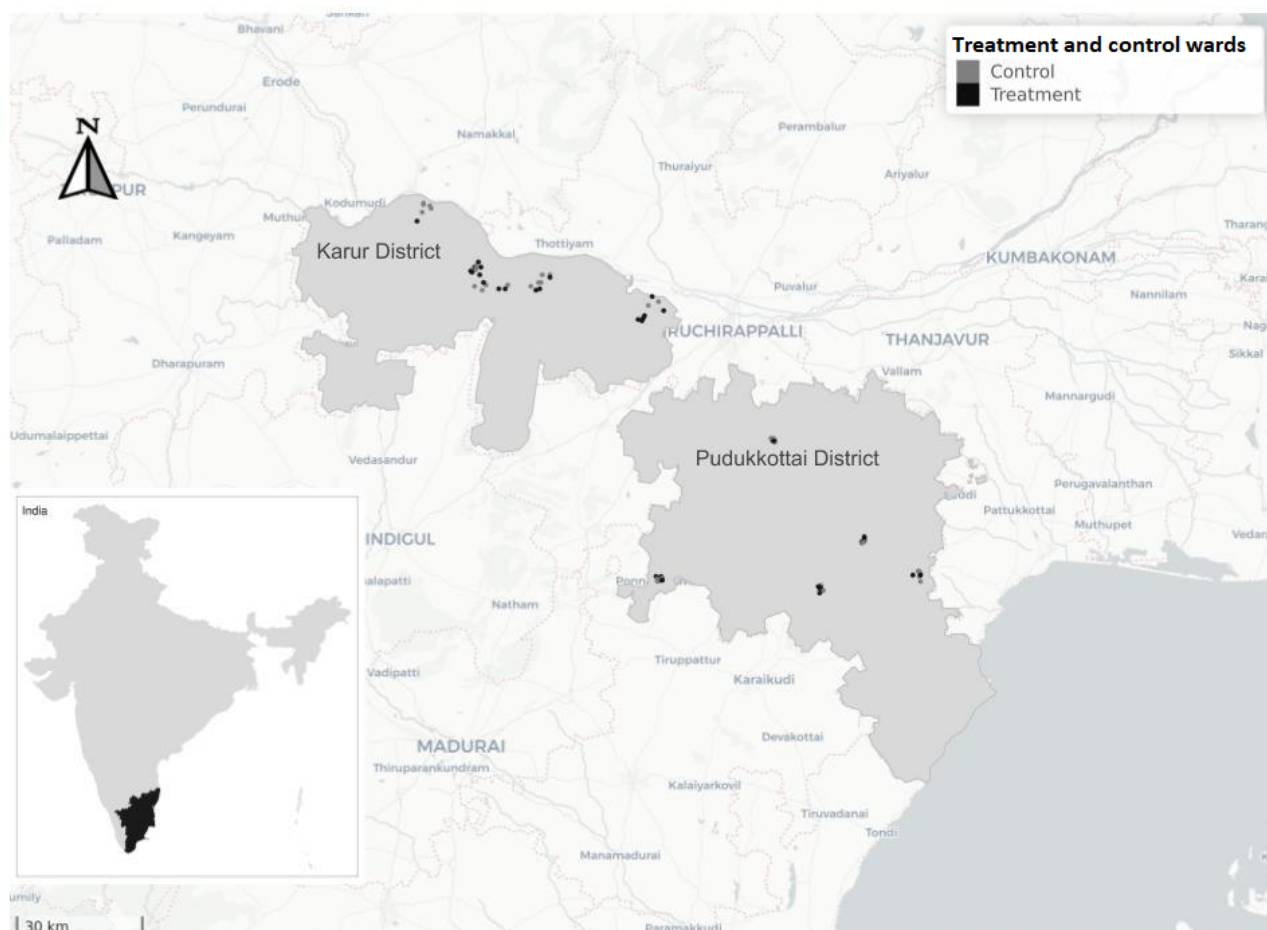
Study Design

The LENNS trial is an ex ante, parallel CRT. We will collect data relevant to our research questions in both study arms and compare results between the intervention and counterfactual arms to determine the impact of the intervention on the primary and intermediate outcomes. This study is powered to detect differences in the prevalence of exclusive toilet use between study arms.

Clusters are defined as wards within purposively selected town panchayats. Half of the clusters were randomized to receive the Nam Nalavazhvu intervention, while the other half will not receive any active intervention as part of the study. Prior to our enrollment of study participants, we created a buffer zone, minimally one ward in distance, between study clusters to minimize spillover. As this study is being conducted in a context where the Indian government is actively implementing SBM, both study arms may be subject to government-led sanitation program activities.

The Nam Nalavazhvu intervention is further detailed in the following section. We co-designed this intervention with our implementation partner, a local nongovernmental organization called Swasti. Prior to the CRT, we conducted a 3-month trial of improved practices to test, refine, and revise our behavior change intervention activities and materials among a separate population in the same study districts (Figure 2). In the CRT, the intervention will be implemented for 12 months. A baseline and 1-year follow up survey will be used to assess the impact of the intervention. We will also conduct a process evaluation to determine the extent to which the intervention was implemented as designed and identify successful pathways or barriers to the adoption of improved sanitation behaviors. Our process evaluation will assess fidelity of intervention implementation, reach, and contextual changes in community and household conditions that may facilitate improved behavioral adoption and outcomes. In addition, we will also conduct qualitative research with respondents and stakeholders to assess exposure and dose received of the intervention. Further, we aim to assess the extent of spillover in the control and the adjacent wards using mixed-method research tools.

Figure 2. Summary of overall study design, including the timeline for impact evaluation to assess the effectiveness of the Nam Nalavazhvu intervention in Tamil Nadu, India. HH: household.
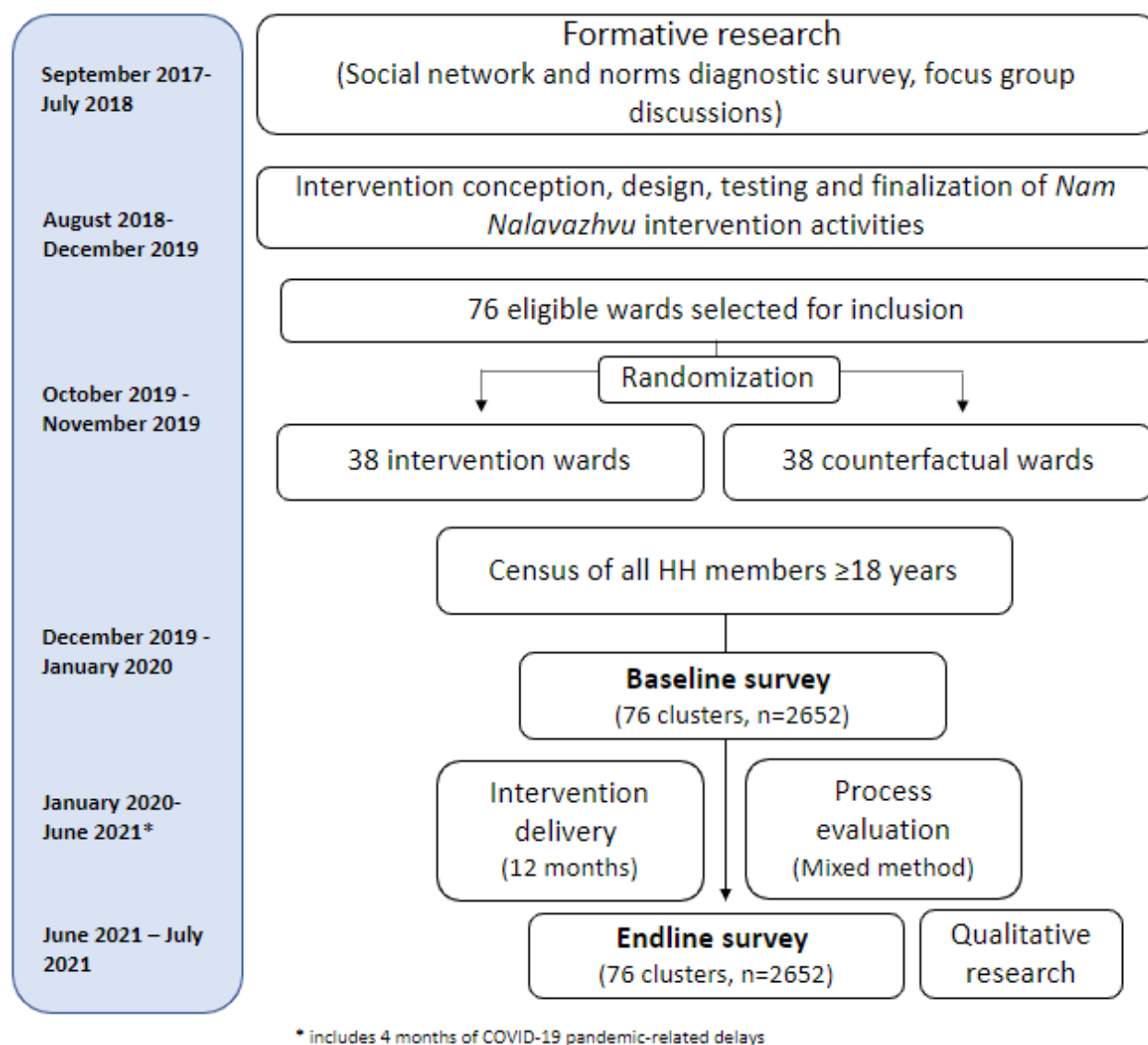
Rationale and Formative Research

The Nam Nalavazhvu intervention design leverages 2 years of mixed-method formative research which included 2 rounds of surveys with the following aims: (1) map social networks in similar communities and (2) systematically diagnose the collective behavior of toilet use with SNT. These sequential assessments were conducted concurrently in both Bihar and Tamil Nadu [26]. Specifically, the formative research comprised the following: a social network survey (n=3370) to understand the size, structure, and nature of social ties related to sanitation behaviors and ownership; 18 focus group discussions with men and women, including young unmarried women and older women to explore social and gender norms related to toilet construction and use; and a social norms survey (n=5052) to assess social beliefs, expectations, and determinants of open defecation.

As mentioned, the Nam Nalavazhvu intervention is based on the SNT, which highlights the role of social expectations and conditional preferences in guiding collective behaviors [25].

We drew on previous literature and investigated known social factors, such as preference for open defecation, perceived barriers related to toilet ownership and maintenance, and implications of social expectations of others in one's community [32,33]. We measured social beliefs, along with empirical (what others in their community do) and normative expectations (beliefs about what others should do), related to toilet usage and used the results to assess if toilet use was a socially interdependent behavior in Indian communities. Using vignettes and regression analyses, we found that empirical expectations were a strong driver of toilet use, while normative expectations were not [26]. This suggested toilet use in this context was a "descriptive norm" or an interdependent behavior where beliefs of what most other people do influence one's behavior [25]. This is consistent with other recent studies that reported empirical expectations as a significant psychosocial determinant for toilet ownership [11,15]. Based on these findings, we designed a theoretically grounded, evidence-based behavior change intervention. We will evaluate its effectiveness on the uptake of exclusive toilet use and maintenance through this randomized trial.

Theory and Evidence-Based Intervention Design

Empirical expectations can be powerful drivers of human behavior [34,35]. Norm nudging is a technique that aims to change the social expectations of an improved behavior of those around the respondent, preferably relevant social members [27]. The key assumption is that compliance is conditional or dependent on this change in expectation. Previous research to improve proenvironmental behaviors showed that telling individuals about their neighbors' electricity consumption reduced their own usage [36]. Using similar techniques, another study successfully nudged hotel guests to reuse towels during their stay [37]. Evidence also suggests that descriptive norm messages are more effective when provided through personalized normative feedback than through broadcasting [38-40].

We synthesized the insights from our norm and social network assessment in Tamil Nadu to employ a systematic, multistep process to design the Nam Nalavazhvu intervention and used a theory of change approach to do so [41]. We used problem and solution tree analysis to depict causal streams of open defecation practices, including the sanitation-related social norms that supported these practices. We used theory and evidence to articulate the mechanisms through which change and maintenance of improved behaviors may occur. Based on the specific behavioral factors, we developed an intervention-mapping matrix and identified potential intervention techniques guided by Michie et al [42]. We acknowledged that norm compliance for individuals is influenced by household, community, and contextual factors by using a socioecological framework [43]. By 2019, SBM had increased coverage of toilets and had declared most states open defecation free [4]. We leveraged this context to disseminate descriptive norms information about those with improved sanitation practices in one's community to shift empirical expectations and encourage others to conform to the norm of toilet use. We intentionally did not focus on techniques that use injunctive norms or perceived disapproval of others due to potential unintended negative consequences; to leverage personalized normative messages, we included techniques to engage community members across gender and age groups (Figure 3) [26].

Figure 3. Theory of change for the Nam Nalavazhvu behavior change intervention, Tamil Nadu, India 2020
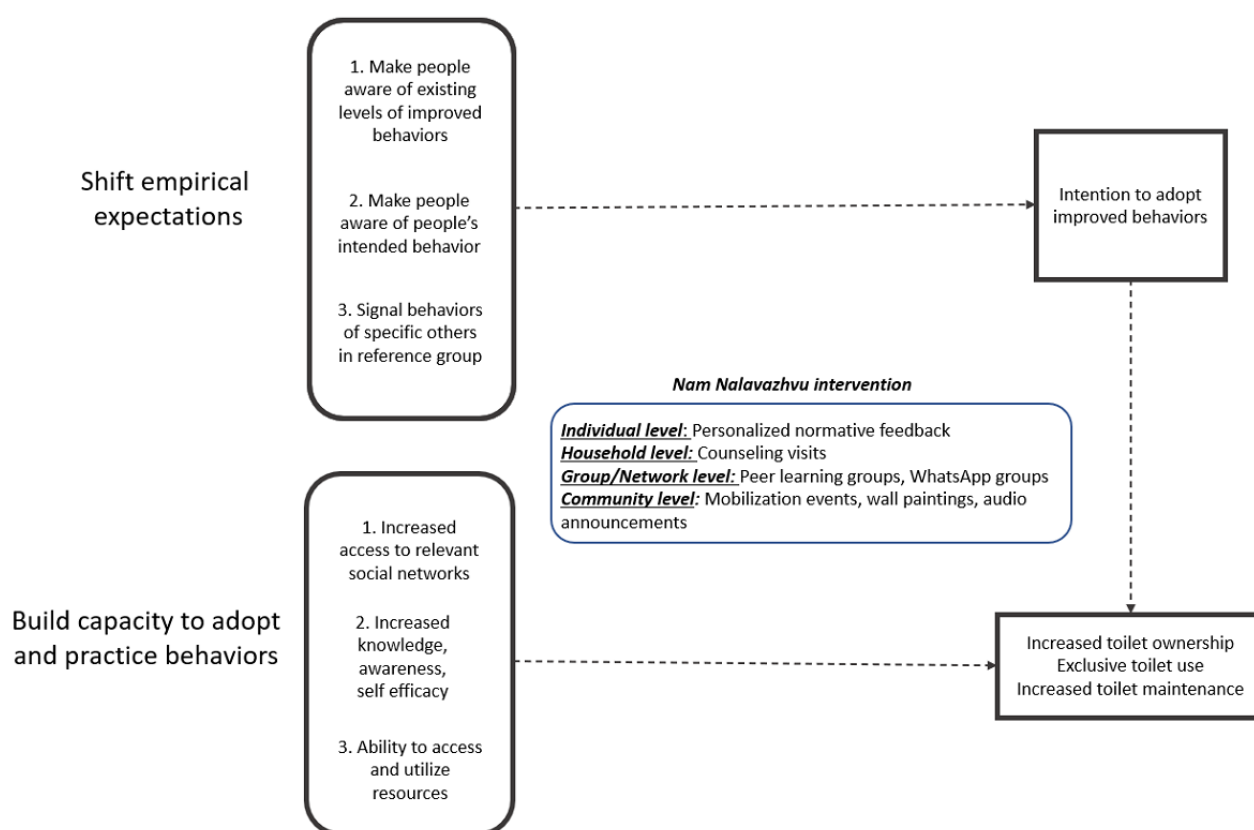
Description of Intervention

Nam Nalavazhvu means "our well-being" in Tamil and reflects a demand-side, norm-centric intervention designed to improve exclusive use of sanitation facilities for defecation purposes. Intervention activities focus on shifting empirical expectations by broadcasting improved sanitation behavior of relevant others in the community through activities at all levels and capacity building and increased action knowledge through expanded social networks and access at the group level. The program will not directly provide hardware or build toilets but actively address opportunity limitations. Details of the intervention design process as well as the theoretical and behavioral framework will be published in separate forthcoming articles.

This multilevel intervention includes activities at the individual, household, group, and ward levels (Textbox 1).

Textbox 1. Nam Nalavazhvu intervention activities for the peri-urban area, Tamil Nadu.

Ward level

- Community mobilization and public commitment events
- Mass audio broadcasting descriptive information
- Wall paintings promoting toilet ownership and use

Group level

- Peer learning sessions
- Descriptive norm messages delivered to social network members via community influencers

Household level

- Tailored counseling sessions with household members
- Visual signals of improved sanitation practices

The individual level, in concurrence with household counseling sessions

- Personalized advice, including information regarding similar others' practices

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Descriptive Information Dissemination and Capacity Building

To update empirical expectations regarding others' improved sanitation practices, we will periodically collect information about sanitation practices from all households in study clusters. We will then disseminate related descriptive norm information during community events, household visits, and via text messages from peers in social groups. Action knowledge and social connections between ward members will be increased by connecting neighbors, outreach workers, and similar individuals in the ward who have adopted improved sanitation practices through events and activities. Information about available financial schemes, sanitation markets, and masons will be provided, and the outreach workers will assist in setting goals and taking steps to make progress towards them. Details of the activities are described in the following sections.

Ward Level

Prior to the intervention delivery, ward outreach workers will meet local stakeholders to conduct a social and resource mapping to engage them, foster support for the project goals, and identify influencers who can be leveraged during the activities. Preliminary meetings will be conducted with these influencers (eg, teachers, religious leaders, self-help group coordinators) to mobilize them. Ward outreach workers will also leave their contact cards to establish communication channels.

Roving Audio Announcements

Automobiles with loudspeakers will announce the launch of the program and invite community members to group sessions and community events. The audio content will include customized jingles to promote toilet use and later disseminate ward level data regarding people's actual and intended sanitation practices.

Wall Paintings

Wall paintings (6 × 4 feet) will be used in at least four public locations per ward. Permissions will be secured from required private or government officials to paint the publicly visible wall. The motto, tagline, and norm-centric images will be painted to encourage others to "join the proud toilet owners."

Community Mobilization and Commitment Events

Participants will include influential political and community leaders to applaud exclusive toilet users and promote improved sanitation practices. Messages will highlight the change happening in their communities and the benefits of using a toilet for families, and facilitate a public commitment to exclusive toilet use. These messages will reinforce those heard by residents through other group and household activities.

Group Level

Peer Learning Session

Six to eight sex-segregated groups will be convened in each ward over 1 year to facilitate social networking between toilet users and nontoilet users. The outreach worker's supervisor will facilitate these 60-90–minute sessions. The facilitator will use social and behavior change communication materials (eg, story cards, video content) to enable norm-focused conversations and information sharing among group members on the access of sanitation markets, barrier identification, planning, and coping by discussing personal experiences, challenges, and solutions regarding target sanitation practices. Peer-to-peer knowledge sharing will be encouraged.

Social Media to Reference Networks

Influential community members who are active on social media will be recruited as volunteer promoters or advocates. We will invite them to use their social media groups to send key messages promoted by the project. The LENNS team will develop messages and monitor their deployment as per the schedule. These advocates will also use their social groups to broadcast testimonials from toilet adopters, and related community events and activities.

Household Level

Household Counseling Visits

Household counseling will allow outreach workers to acquire information about the household's potential for change. The outreach workers will communicate ward-specific toilet use of similar households to motivate change. Flipbooks and story cards will be used to engage and motivate household members. The outreach worker will counsel them on how to achieve their goals by mapping out the next steps using goal cards. These households will also be informed of their neighbors' improved practices. Ward outreach workers will focus on those lagging behind to motivate them to change, pointing out others like them who already have.

Visual Signals of Improved Practices

Improved behaviors of neighbors will be signaled using bright decals or stickers, placed in public view on the household wall. These aim to serve as a goal and a source of pride for the households who receive and display them.

During the trial of improved practices, we incorporated feedback from community members and pilot intervention recipients to ensure the feasibility, appropriateness, and acceptability of the content, and the delivery mechanism of the Nam Nalavazhvu intervention activities. Notably, we confirmed that signaling toilet ownership and use through stickers, household visits, group meetings, and testimonials were acceptable and perceived as encouraging and aspirational. We ensured that all content used positive framing and included engagements with community stakeholders to collaboratively host group and community events. We also assessed whether incentives were necessary for the influencers, and found they preferred nonmonetary compensation or incentives. We plan to recognize them at community events for their work, present them with a volunteer experience certificate, and invite them to group sessions held as a part of the intervention activities.

The implementation team is hired and managed by Swasti. Investigators at the Center for Social Norms and Behavioral Dynamics (CSNBD) at the University of Pennsylvania will provide training, technical input, and oversight to the implementation process. The main delivery agent will be ward outreach workers who are residents of the ward with a minimum of 12 years of formal education. Field supervisors will help organize and facilitate group and ward-level activities. In addition, the study will include influential members from the community to disseminate promotional and motivational messages to their social networks.

Participation in these activities will be voluntary. The audio announcements and visual cues or paintings in public spaces will be apparent during the intervention. Ward outreach workers will consider any requests to adjust the recipient's level engagement in the activities to ensure the consent and comfort of participants.

Public Involvement

As mentioned in the intervention details, members of the public will be used to disseminate promotional messages through social media, using decals, active participation in groups and community events. During the pilot phase, we also incorporated their feedback for improving intervention delivery techniques and platforms prior to the trial.

Eligibility Criteria

We randomly selected 5 town panchayats from each district. Researchers visited several wards with local Swasti officials to ensure they reflected the generalized peri-urban setting. To identify potential study wards within these town panchayats, we met local executive officers to assess ward maps. We used the following exclusion criteria: commercialized wards with few residential households, urbanized wards with known high or complete coverage of improved toilet access according to town panchayat official records, and wards which bordered two or more adjoining wards (to reduce spillover).

Our sampling frame excluded town panchayats where we piloted our interventions (n=3) or those where we did not receive permission to proceed due to political concerns (n=1).

The unit of randomization for this CRT was the ward. The demarcation of the ward was derived from the 2011 census conducted by the Ministry of Home Affairs of the Government of India [34]. Trained field teams generated ward maps to delineate the ward boundaries, confirmed it with residents, and ensured a buffer zone. We also engaged ward-level stakeholders to assist in the mapping process and gain access to communities. From the ward maps, we identified the adjoining wards, which share the borders and excluded 1 from the list of potential wards to ensure we reduced the possibility of spillover between clusters. Of the total of 153 wards considered in 10 town panchayats, we found 79 eligible wards based on our criteria. We selected a random sample of 76 wards to include in our study. These wards are more representative of residential peri-urban wards in Tamil Nadu. As the treatment arm was randomly selected, we do not expect to find systematic differences between the treatment and control arms. Following this exercise, a minimum of 1 km distance was ensured between the residential units in each cluster.

All ward residents from intervention clusters are eligible to participate in the intervention activities. For data collection, field workers surveyed randomly selected household members who were 18 years or above, planned to reside in that household continuously for the next year, and were willing and able to participate.

Selection and Assignment of Interventions

Following the baseline data collection, a coinvestigator (UD) randomly assigned the wards to counterfactual and intervention arms in a 1:1 ratio, using a computer-generated randomization sequence. The randomization was geographically pair-matched within each town panchayat (Multimedia Appendix 1). Balancing the study arms across geography will allow us to adjust for spatially clustered features or events that may be associated with our outcome. Given the nature of the intervention, the study investigators and the participants will not be masked to the intervention assignment. The data collection team will be masked to the treatment assignment.

Recruitment

Trained enumerators conducted a listing exercise to generate a sampling frame of eligible individuals within each ward. Enumerators approached the household and asked the selected individuals if they would consent to participate in the study. If the selected individual was absent or unavailable, up to three repeat visits were made to enroll them. If unsuccessful, the enumerators approached the next randomly selected individual from that cluster. Following randomization, households in intervention wards were enrolled following an oral consent process.

The individuals enrolled in qualitative studies will be purposively selected from intervention wards to address relevant research questions. Those sampled from the counterfactual wards will allow us to investigate spillover of the Nam Nalavazhvu intervention.

Sample Size

This study is powered to detect differences in the prevalence of exclusive toilet use between study arms. Measuring exclusive use is problematic due to recall and desirability bias. As a result, during our formative research phase, we asked individuals about their defecation place the last time they needed to defecate during 2 rounds of data collection conducted 8 months apart. We incorporated the correlation between these 2 measures in our sample size calculation. We powered our study at 80% based on the prevalence of reported toilet use during last defecation in peri-urban Tamil Nadu (estimated at 64.4% in 2018) and assumed a 10-percentage-point improvement as the minimum important effect [26]. To detect such a minimal effect in exclusive toilet use (given an observed intracluster correlation of 11% and correlation of last use with the one measured in the fall of 2017 of 47.5%) [26], we estimated a requirement of 76 clusters (38 clusters per arm). We require 30 individuals per cluster. Assuming 10% loss to follow-up, we will engage 34 individuals per cluster for a total of 2280 individuals. As we will collect household level toilet usage data, we will have data for more individuals beyond the actual number of respondents.

Study Outcomes and Measures

We will evaluate these outcomes at baseline and at endline in both the intervention and counterfactual clusters 1 year after the intervention implementation using verbal surveys. We will characterize sanitation facilities using standardized categorizations through direct observations.

Primary Outcome

The primary outcome will be the proportion of households where all members (18 years or older) exclusively use a toilet every time they defecate. We will combine responses to several self-reported toilet use behaviors to determine exclusive toilet use in the previous 2 days. We will also observe toilets to check for signs of use (Multimedia Appendix 2).

Secondary Outcomes

There will be 5 secondary outcomes: (1) presence and access to improved toilets will be assessed using standard questions, while spot observations of toilets will be used to assess maintenance, functionality, and recent use; (2) mental well-being will be measured using The 5-item World Health Organization Well-Being Index (WHO-5); (3) diarrheal disease for all household members will be measured using the WHO definition of three or more loose stools in a 24-hour period, with or without the presence of blood; (4) respiratory illness for children under 5 years will be measured using reported cough and/or difficulty breathing or shortness of breath according to the WHO's Integrated Management of Childhood illness; and (5) intermediate behavioral antecedents such as empirical expectations (ie, what other people do), normative expectations (ie, what other people think one should do) of prevalence of toilet ownership, exclusive use, and maintenance will be measured using tested indicators (see Multimedia Appendix 2)

Data Collection

Randomly selected individuals were enrolled for the impact evaluation. They responded to a baseline survey and will be approached to complete a 1-year follow-up survey administered by trained enumerators. The enumerators will be masked to the intervention assignment. However, given the nature of the intervention, they might observe Nam Nalavazhvu intervention products in the household during the follow-up survey.

We enrolled 34 respondents from each cluster and will attempt to reinterview them at endline. We will consider respondents lost to follow-up if any of the following occur: they refuse to participate in the follow-up survey, they relocate elsewhere outside the intervention ward, or the field team is unable to reach them after 3 attempts during data collection. We will replace respondents lost to follow-up by recruiting additional respondents from the sampling frame of the ward. We will ensure 34 respondents per ward at the endline to have adequate power to conduct cross-sectional posttest design analysis.

CSNBD researchers will work with trainers to conduct a 10-day training session prior to each survey round. The training sessions will be conducted in Tamil. Prior to the baseline survey, the instrument was administered to respondents similar to the target group to ensure comprehension. We incorporated feedback to clarify language, framing, answer choices, and administration of the survey. The survey data were collected using personal handheld devices. These electronic surveys were tested to address issues with data capture, skip patterns, and validity checks for each item in a pilot study. Quality assurance steps were taken to improve data accuracy and included regular field-level data checks and dual data capture of objective measures from a subset of households by field supervisors. Researchers from CSNBD also visited the study sites randomly to assess the situation pertaining to the survey. Weekly phone meetings were conducted with the data collection agency to ensure the quality of data.

The implementation partner will collect routine monitoring data to capture information about intervention fidelity and exposure. We will take steps to ensure that they do not involve participants enrolled in the impact evaluation to reduce participant fatigue.

We will conduct 3 rounds of qualitative data collection as part of the process documentation for this study. These will be at 3 months, 6 months, and 1 year after the start of the intervention and will assess participant response, acceptability, and the

beliefs about the improved sanitation behavior among respondents in the intervention and counterfactual groups. Trained qualitative researchers will conduct in-depth interviews and focus group discussions with purposively selected respondents in intervention clusters to assess their interaction and experience with the Nam Nalavazhvu intervention. We will use semistructured questionnaires, memos, and note-taking to record observations and will record interviews as required. Verbal consent will be taken before every data collection activity except for observations made in public spaces. Results from this qualitative investigation will be used to interpret the impact of the intervention.

Data Management

All survey data will be transmitted through secured servers and stored in password-protected folders in the Penn+Box (The University of Pennsylvania). To protect confidentiality, all subjects will be deidentified for analysis. Data will only be accessible to University of Pennsylvania faculty, staff, and data management personnel.

Statistical Analyses

We will use intention-to-treat analyses to assess the difference in specific outcomes between study arms after exposure to 1 year of the Nam Nalavazhvu intervention. For most of the outcomes, we will use a log-binomial regression model to assess prevalence ratios of postintervention sanitation-related outcomes across intervention groups. We will consider adjusting for variables that were imbalanced between the groups at baseline in adjusted models. We will also use generalized estimating equations with robust SEs to account for the clustering of observations within each cluster (ward). We will use postestimation commands to estimate and report the average marginal effects. We will not adjust P values based on multiple comparisons.

In additional analyses, we will use appropriate multivariate models to assess the impact of the intervention on secondary outcomes. Both unadjusted and adjusted effect estimates will be reported for all outcomes. Following the process evaluation findings, if fidelity or intervention quality are found to vary considerably in the trial, we will consider a per-protocol or other appropriate analysis to assess the impact of the Nam Nalavazhvu intervention on our outcomes of interest. The analyses will be conducted by the scientific team (SA, AS, UD, JK, CB) with statistical software including R (The R Project for Statistical Computing) and Stata (StataCorp).

Qualitative data will be collected until saturation is reached. We will validate key findings using triangulation of data across multiple data sources. We plan to conduct gender-stratified analyses to understand challenges to adoption of exclusive toilet usage.

Ethics and Dissemination

The ethics review board at the University of Pennsylvania (institutional review board protocol no. 833854) and the Catalyst Foundation in India reviewed and approved this research protocol. The trial is registered with ClinicalTrials.gov (NCT04269824). All amendments and protocol modifications

will be updated there. All enrolled study communities provided verbal consent to enroll in the study. Surveyed individuals provided informed consent. This consent process was conducted in the local language, Tamil. Participants will receive messages that may encourage them to improve their sanitation conditions or practices. Our assessment is that the benefits to study participation outweigh the minimal risks. Deidentified data will be used during analysis.

Research findings will be disseminated through presentations at conferences and submitted to peer-reviewed journals for open access. Our results will be shared with relevant local stakeholders through community-based meetings in participating wards through presentations made to the district and state level officials in Tamil Nadu.

Data Monitoring, Reporting Harms, and Auditing

The research team (SA, KC, AS, UD) has text message groups and weekly calls with the implementation partner to discuss progress and issues from the field, including adverse events, so that prompt action can be taken. No harm is anticipated to the intervention recipients in this study. There are no plans for a data monitoring committee or audits for this trial.

Results

This study completed its baseline survey in January 2020. Endline assessments are planned for July 2021. Results are anticipated to be published by the end of 2022.

Discussion

This study will evaluate the effectiveness of the Nam Nalavazhvu intervention, a demand-side, descriptive norm- and network-centric intervention approach that aims to shift empirical expectations on targeted sanitation behaviors. Our behavior change communication approach employs dynamic signaling (ie, dissemination of descriptive information regarding others' actual or intended improved sanitation practices) and reflects a strategy that is novel to the sanitation sector but which has been effective in changing a variety of behaviors, such as water use, drinking behavior, and energy consumption [36,44-46]. Evaluating the impact of such an approach may have widespread implications for policy and practice for sanitation programs in India and beyond if the intervention proves effective in improving sanitation behaviors via changing people's empirical expectations. Our plan to also track normative expectations will also allow us to determine whether an intervention focused on shifting of empirical expectations has spillover effects on normative expectations.

Evidence from this study will address knowledge gaps regarding the application and effectiveness of a norm-diagnostic approach in the design of behavior change strategies that intervene upon the social determinants of collective sanitation behaviors. The intervention uses outreach workers and social media users to deploy most of its messages. Understanding the transmission of messages during household visits, peer learning sessions, and text messages will inform recommendations on the feasibility and effectiveness of using these platforms for norm-centric interventions. Insights generated in this study may

generally contribute to the tools available to address descriptive norms for community-based interventions.

Limitations of this CRT include the use of wards as clusters in peri-urban communities. Although these are the smallest geographic operational units, some boundaries in specific districts were redrawn following the start of the intervention, leading to concerns about spillovers across buffer areas. Two critical country-specific incidences are impacting the implementation of the interventions. One is the highly contentious Citizens Amendment Act passed in December 2019 that led to nationwide protests in India. In our study, it led to refusals by households in predominantly Muslim wards, who resisted participating in any study that includes survey-based instruments. Secondly, the ongoing COVID-19 pandemic has led to considerable interruption in the implementation of group-level intervention activities. These aspects are being assessed through our process evaluation and will inform the interpretation of the results from this CRT.

Acknowledgments

Authors' Contributions

CB is the principal investigator for this study. She has developed the SNT and the measurements that have driven the intervention design. SA, MGD, AS, UD, and CB designed this study. CB, MGD, ET, and SA contributed substantially to the design of the multilevel behavior change intervention. SA, MGD, JK, UD, and KC contributed to the testing and implementation of the intervention. All authors contributed to the development of data collection tools. AS, UD, SA, and KC supervised the data collection. SA wrote the first draft of the manuscript. All authors reviewed, contributed to, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study wards enrolled in each town panchayat, Tamil Nadu, India, 2020.
[DOCX File , 25 KB - resprot_v10i5e24407_app1.docx]

Multimedia Appendix 2
Outcome measures.
[DOCX File , 27 KB - resprot_v10i5e24407_app2.docx]

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Abbreviations

BCD: Behavior Centered Design
CLTS: Community-Led Total Sanitation
CRT: cluster-randomized controlled trial
CSNBD: Center for Social Norms and Behavioral Dynamics
LENNS: Longitudinal Evaluation of Norms and Network Study
RANAS: Risks, Attitudes, Norms, Abilities, and Self-regulation
SBM: Swachh Bharat Mission
SNT: social norms theory
WHO-5: The 5-item World Health Organization Well-Being Index

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Protocol

Impact of Nutrition Education on the Nutrition Capacity of Caregivers and Nutrition Outcomes of Indigenous Mbororo Children in the West Region of Cameroon: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Inadequate diets and life-threatening infections have profound adverse implications for child growth, development, and survival, particularly among indigenous peoples. Evidence of the effectiveness of community-based nutrition education interventions in improving child feeding and nutrition outcomes among indigenous Mbororo population in Cameroon is scarce.

Objective: This study aims to investigate the impact of culturally tailored community-based nutrition education intervention on caregivers' knowledge, attitude, and practice regarding complementary feeding and on nutrition outcomes of indigenous Mbororo children (aged 3-59 months) in the Foumban and Galim health districts of the West Region of Cameroon.

Methods: A two-arm cluster randomized controlled trial will be conducted in the Foumban Health District and Galim Health District. The intervention and control arms will each comprise 5 clusters with 121 child–caregiver pairs. Participants in the intervention arm will be organized into 5 caregivers' peer-support platforms. A total of 12 educational sessions will be assigned to the intervention group by trained female Mbororo nutrition volunteers (n=6) and community health workers (n=6). The control arm will receive routine facility-based nutrition education. Data will be collected at 3-month and 6-month follow-up. Both descriptive statistics and multivariate logistic models will be used to estimate the effect of culturally tailored community-based nutrition education intervention (independent variable) on outcome variables (caregivers' knowledge, attitude, and practice), child growth (weight, height/length, weight for age), and morbidity status (diarrhea, cough, and fever) between both arms. Data assessors will be blinded to the group allocation. Ethical approval (reference no. 2019/1002-07/UB/SG/IRB/FHS) was obtained from the Faculty of Health Sciences Institutional Review Board at the University of Buea.

Results: Baseline data were collected in September 2019. In February 2020, 10 Mbororo communities (clusters) with 242 child–caregiver pairs were selected and allocated to the experimental and control arm in a 1:1 ratio. Community nutrition volunteers (n=6) and community health workers (n=6) were selected and trained. Data collection and analysis are ongoing, and results are not available for this manuscript.

Conclusions: The findings of this study will provide evidence on the impact of culturally tailored and health belief model–based nutrition education on behavior change as a complementary strategy for strengthening health facility–based approaches in the reduction of malnutrition burden among the study population

International Registered Report Identifier (IRRID): DERR1-10.2196/23115

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Introduction

Every year, 5.6 million children die before their fifth birthday, with 80% of these deaths occurring in sub-Saharan Africa and Asia [1]. Malnutrition accounts for more than 45% of all child deaths globally [2]. Thus, achieving the Sustainable Development Goal Target 2.2 [3] of ending all forms of malnutrition will significantly contribute to the reduction of child mortality to 25 deaths per 1000 live births in every country by 2030 [3]. Effective malnutrition reduction strategies hinge largely on reducing key underlying factors, particularly among those groups identified as high-risk according to evidence-based approaches [4].

Poor diets and life-threatening infections during childhood, such as diarrhea and pneumonia, are the immediate and major causes of childhood undernutrition in developing countries [1,5]. Low maternal socioeconomic status, inadequate nutrition capacity, limited access to health care, and poverty are important contributing factors [1]. In particular, inadequate maternal knowledge regarding exclusive breastfeeding and complementary feeding practices has been implicated in childhood undernutrition [5,6]. In Cameroon, more than half of children aged 6-23 months do not receive adequate complementary feeding, and only 33% of these children receive the minimum dietary diversity [7]. Improving mothers'/caregivers' child-feeding behavior is thus an important target and has the potential to improve child nutritional status and survival.

Community‐based programs are unique platforms for the delivery of nutrition interventions [8]. Pooled analyses show that home-based and community-based nutrition education interventions for mothers improve the nutritional status of children younger than 5 years in developing countries [9,10]. Similarly, hygiene counseling components of interventions significantly decrease diarrhea episodes and dysentery among children younger than 5 years [11]. Intervention delivery strategies, such as home visiting, conducting group meetings of caregivers and community leaders, providing education regularly, and the use of cooking demonstrations, have been shown to produce positive outcomes [9].

In Cameroon, the nutrition education for mothers is predominantly facility based. Within the context of a weak health care system, characterized by low coverage, underresourcing, and workforce shortage [12], community-based strategies are needed to complement and strengthen facility-based approaches. Further, facility-based education often fails to adequately address context-specific barriers to behavior change. Moreover, the potential for community-based nutrition education targeting the Mbororo population in Cameroon has not been adequately explored. As an ethnic minority indigenous people [13], the Mbororo reside predominantly in hard-to-reach rural settings where child malnutrition rates are disproportionately higher [7]. It is worth nothing that indigenous children experience higher nutrition-related problems than their nonindigenous counterparts worldwide [14,15]. It is against this background that this study is designed to evaluate the effect of a nutrition education intervention on caregivers' nutrition-related knowledge, attitude, and practice (KAP) and nutrition outcomes of indigenous Mbororo children younger than 5 years in the study area. The study design is informed by the health belief model and contextual realities of the target community obtained from the formative study. The study is innovative and culturally tailored to ensure acceptability and sustainability. The findings will contribute to the growing body of evidence on community-based nutrition education for behavior change as a complementary strategy for strengthening health care systems and achieving overall child health–related goals in Cameroon.

Methods

Trial Registration Status

The protocol was submitted to the Wealth Health Organization (WHO) Pan Africa Clinical Trial Registry in South Africa for review. Feedback is still being awaited. The last correspondence was on July 4, 2020.

Trial Design

As presented in Figure 1, this is a 2-arm parallel intervention study designed as a cluster randomized controlled trial. The randomization units will be clusters to prevent contamination between the experimental and control arms. A computer-generated list of 10 randomly selected clusters will be produced and placed in sealed, opaque envelopes.

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Figure 1. Flow chart showing cluster randomization and follow-up for the nutrition, water, sanitation, and hygiene (Nu-Wash) model.
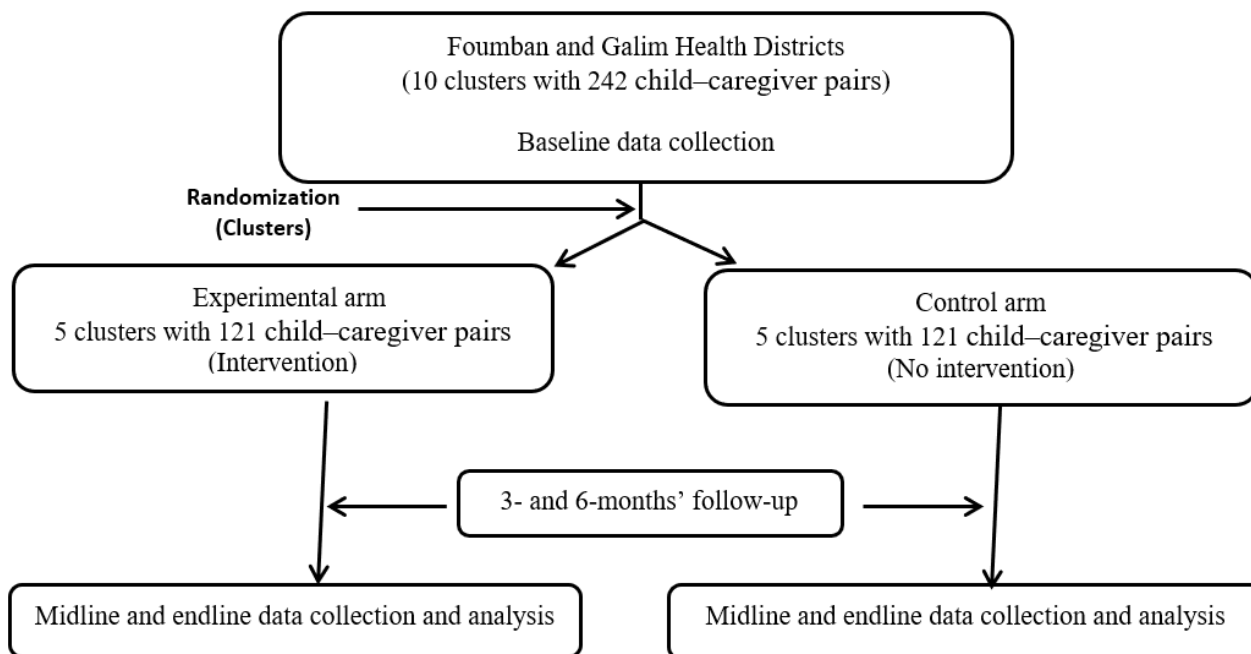
The clusters will be allocated in a 1:1 ratio in both arms. The study will be single blinded, as only the data assessors (data collectors and analysts) will be blinded to the group allocations. Within each cluster, children and caregivers meeting the inclusion criteria will be recruited for the study. Informed consent and assent will be obtained from caregivers before the intervention. Caregivers in the experimental arm will receive nutritional education under the nutrition, water, sanitation, and hygiene (Nu-WASH) model, and caregivers in the control arm will be exposed to routine nutrition education offered by health staff in the study area. Data will be collected at 3-month and 6-month follow-up.

Trial Setting

The study will be conducted in the West Region of Cameron with an estimated population of 1,785,285 inhabitants and a surface area of 13,960 km^2 [16]. The population is largely rural and relies on agro- and commercial businesses for livelihoods and income. The region is host to several cultural groupings, including the indigenous Mbororo peoples, who reside in larger communities in the Bangouraim, Bangante, Foumban, Foumbot, Kouoptamo, Galim, and Mbouda health districts of the region. Foumban Health District and Galim Health District were randomly selected for the study.

Study Participants: Inclusion and Exclusion Criteria

The study will comprise Mbororo children and their primary caregivers selected from 10 participating Mbororo communities in the Foumban Health District and Galim Health District. Participants enrolled in the study will include Mbororo households with child–caregiver pairs who participated at baseline data collection and who meet the following inclusion criteria: the children should be between 3 and 59 months of age, while their female primary caregivers should have 6 months

minimum residence status, no intention to leave before the end of the study, and have provided their verbal or written informed consent and assent to participate in the study. Mbororo households without children younger than 5 years, those who did not participate at baseline data collection, those without permanent residence, children and caregivers who become seriously sick, and caregivers who refuse to participate in the study will be excluded.

Sample Size Determination

The following formula for comparing 2 groups [17] was used for the calculation of the minimum sample size (n):

where $z_{\alpha/2} = z_{0.15/2} = 1.44$ (from z score table), $Z\beta/2 = z_{0.15/2} = 0.75$ (from z score table at 75%), $P_1 = 0.32$, $P_2 = 0.22$, $P_1 - P_2 =$ pooled prevalence (prevalence in intervention group [P1] + prevalence in control group [P2]/2):

Considering the 10% nonresponse rate, the sample size (n) was adjusted to 242.

Sampling Strategy for the Trial

A multistage sampling approach, using probability and nonprobability sampling methods, was used to select the study sites and population as illustrated in Figure 2. In the first stage, Galim Health District and Foumban Health District were selected randomly by lottery method from the 7 health districts with the highest Mbororo populations. In the second stage, 7 health areas were purposively selected, and a list of Mbororo communities (n=23) was established.

Figure 2. Flow chart of multistage sampling strategy for the intervention.
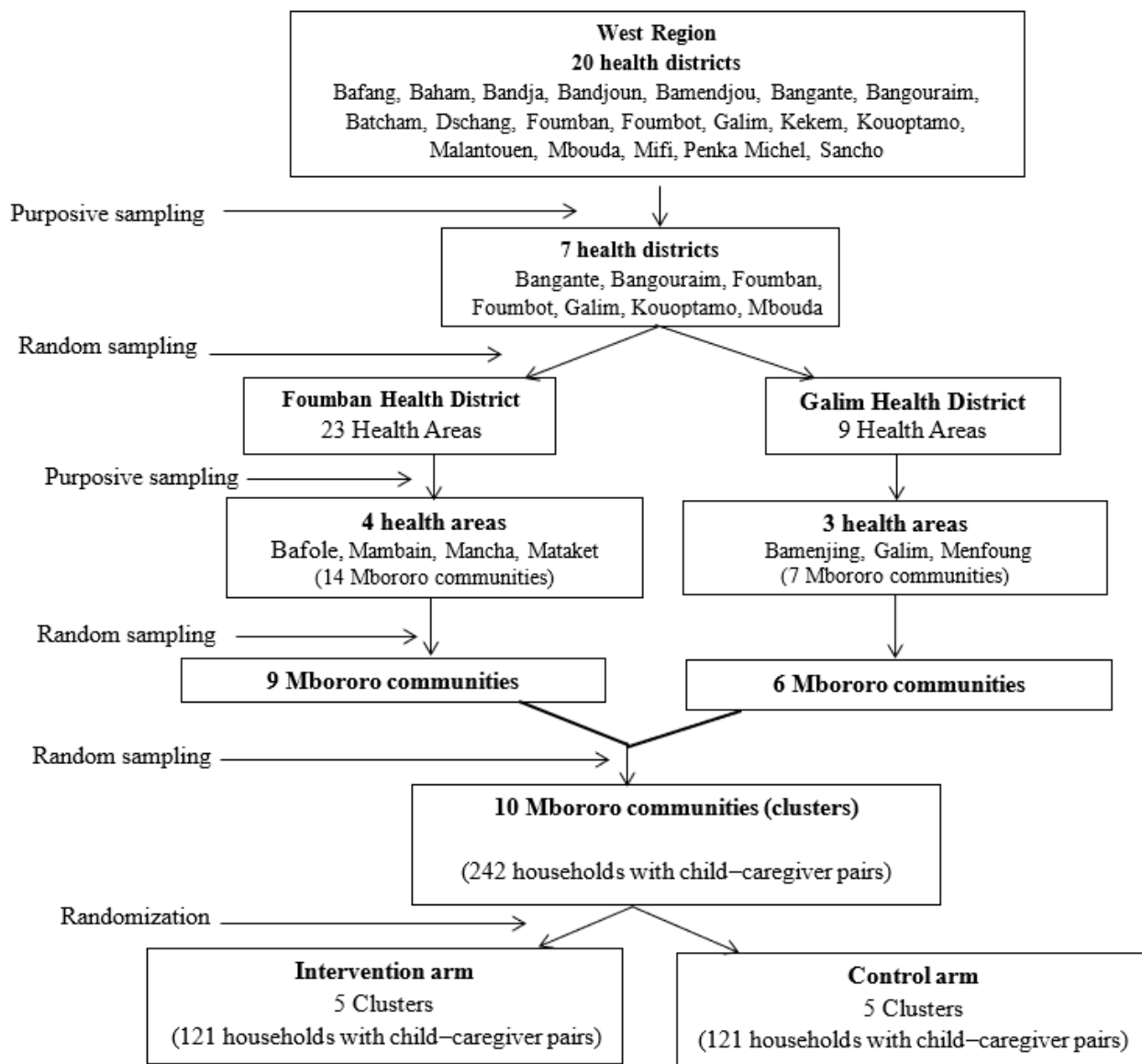
Intervention

Our Nu-WASH model comprises nutrition, and water, sanitation, and hygiene components. The nutrition component includes the following: complementary feeding, which involves the nutrition needs for young children; benefits of continuous breastfeeding for up to 24 months of child age; nutritional value of locally available plant-based and animal-based food items; dietary diversity (nutrient-rich homemade recipes); benefits and challenges of adequate complementary feeding practices; and susceptibility to, and severity of, child undernutrition. The WASH component, aimed at improving caregivers' WASH knowledge and practices, will include the following: WASH-related childhood diseases, including causes, susceptibility, and severity; water quality, including point-of-use household drinking water treatment (boiling and filtration), and safe storage; environmental sanitation, including safe collection of child feces; personal hygiene, including proper hand washing

with soap before food preparation, before child feeding, after using the toilet, after disposing of garbage, and after cleaning the baby's feces; food hygiene (preparation, covering, serving, and heating); and the perceived barriers and benefits of food hygiene.

Intervention Development

To improve on the abilities of caregivers to prevent child malnutrition, Nu-WASH will be implemented and evaluated. The target for behavior change will be caregivers assigned to the intervention arm. As illustrated in Figure 3, the intervention will be delivered through 6 logical steps: baseline data collection; the formation of caregivers' peer support groups (CPGs); the selection and training of female community nutrition volunteers (CNVs) and community health workers (CHWs); health education for caregivers through CPGs; monitoring and evaluation; and midline and postintervention data collection and analysis.

Figure 3. Summary of treatment given in the intervention and control arms. CHW: community health workers; CNV: community nutrition volunteers; Nu-WASH; nutrition, water, sanitation, and hygiene.
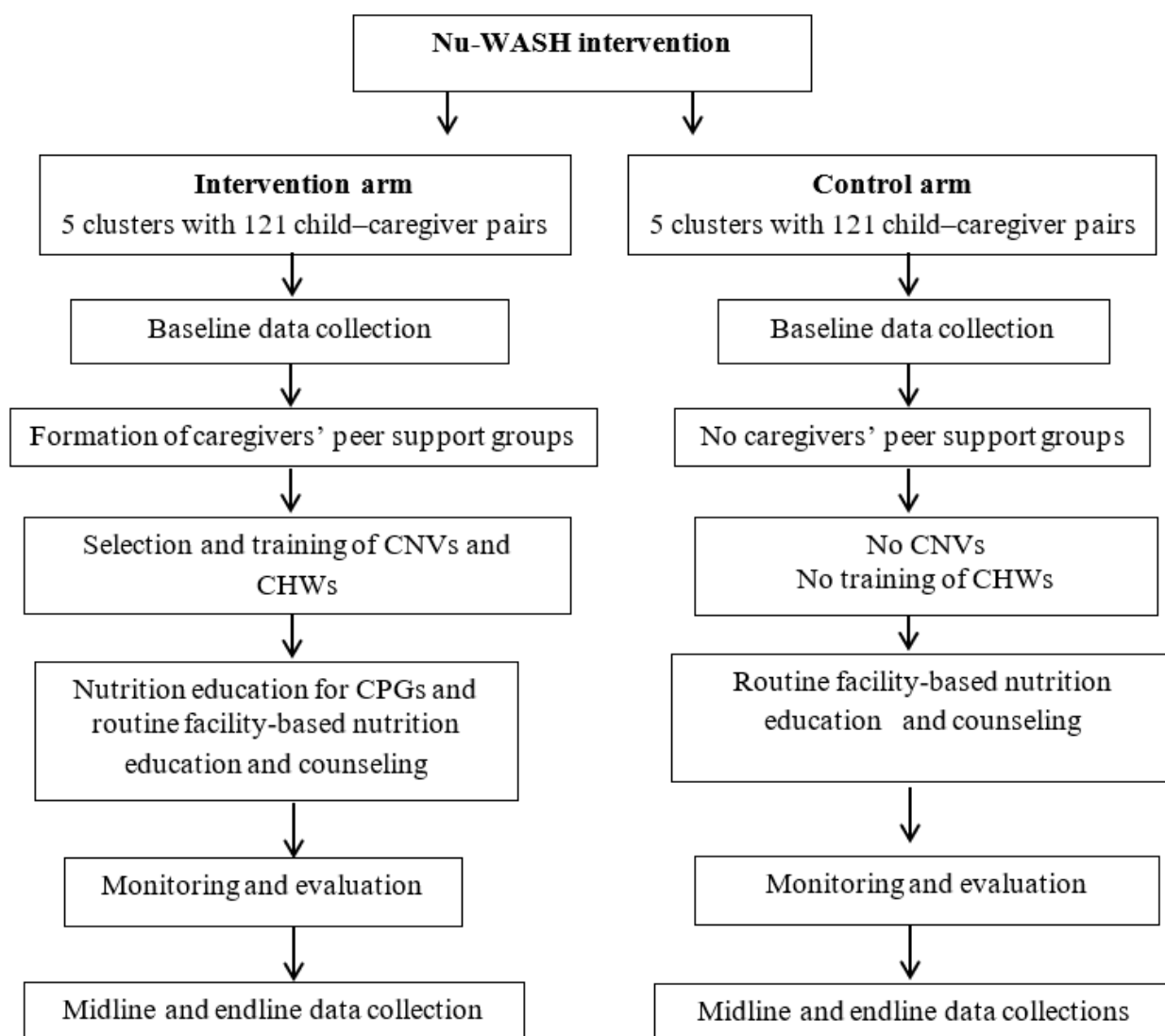
Step 1: Baseline Data Collection

A formative study was conducted from August 2019 to September in 2019 to understand the local contextual factors and to inform the experimental design. A total of 10 Mbororo communities, comprising 242 mothers/caregivers and their children (aged 3–59 months), were selected for the intervention study. Baseline data on the household, caregivers, and child variables; caregivers' nutrition-related KAP; and child anthropometric and morbidity status data were collected.

Step 2: Formation of CPGs

Caregivers in the intervention arm (n=121) were organized into 5 peer-support groups of 20 to 30 members. Each group per cluster will serve as the platform for group sessions and for interactions to enhance learning.

Step 3: Selection and Training of the CNVs and CHWs

Each participating community designated 1 Mbororo female (15 years and older) for training as a CNV. Selected CNVs and existing CHWs in the health areas were trained to lead the

nutrition education and act as resource persons for nutrition information within their communities.

Step 4: Nutrition Education for CPGs

The CPGs in the intervention arm will be exposed to Nu-WASH and routine nutrition education offered during visits to the health care facilities in the study area. Two facilitators (1 CNV and 1 CHW) will be assigned to each CPG of the intervention arm. The intervention delivery strategy will involve group sessions and individual counseling. Each CPG will be exposed to 12 sessions: 1 session every fortnight for 6 months, each lasting for 90 to 120 minutes. A participatory and interactive delivery strategy will include lectures, discussions, question-and-answer sessions, and demonstrations. Participatory cooking demonstrations using selected combinations of food items from 7 food groups will be aimed at improving self-efficacy of preparing nutrient-rich diets. Posters showing various food groups with educational messages on nutrition (cues to action) will be provided to reinforce behavior change. Caregivers facing challenges will be given personalized counseling sessions by the CNVs and CHWs. Nutrition and WASH-related perceived

barriers and benefits will be explored and discussed during the training. The control group will receive routine health facility–based nutrition and counseling offered by health care providers in the study area.

Step 5: Monitoring and Evaluation

CNVs and CHWs will visit households once monthly to monitor compliance and encourage proper child-feeding practices, treatment, and safe storage of drinking water. Data relevant to the study will be collected during each visit with the use of structured observation forms.

Step 6: Midline and Endline Data Collection and Analysis

Data will be collected from both the intervention and control arm at 3-months and 6-month follow-up with the same data collection tools, methods, and procedures as those used at baseline.

Study Objectives

Primary Objective

The primary objective will be to investigate the impact of a Nu-WASH versus facility-based nutrition education on caregivers' KAP regarding complementary feeding at baseline, 3-month follow-up, and 6-month follow-up. In the absence of a gold standard test in the measurement of KAP, composite measures will be used in this study. A composite knowledge score will be built on 4 measures based on 4 self-report questionnaire items. Knowledge will first be estimated by each measure and classified into 2 categories as adequate and

inadequate before the results of the 4 measures are finally combined into the composite knowledge score. Similarly, composite scores for attitude and practice will comprise 10 and 7 measures, respectively, as derived from corresponding numbers of self-report questionnaire items.

Secondary Objective

The secondary objective will be to compare nutrition outcomes of Mbororo children (aged 3-59 months) at baseline, 3-month follow-up, and 6-month follow-up in the control and experimental groups. Nutrition outcomes will be defined as child growth measured as length/height, weight, and weight-for-age at baseline and endline; and child morbidity status will be measured as self-reported incidence of diarrhea, fever, and cough at 2 weeks preceding baseline, and at 3-month and 6-month data collection.

Outcome Measurements

Primary Outcomes

The primary outcomes will be caregivers' nutrition-related knowledge, and attitudes and practices of caregivers as measured using self-reported items as shown in Table 1.

Secondary Outcomes

As shown in Table 1, the secondary outcomes will comprise child growth (height/length, weight, and weight-for-height), which will be measured at 6-month follow-up, and child morbidity status (diarrhea, fever, and cough 2 weeks preceding baseline), which will be self-reported.

Table 1. Primary and secondary outcome variables among study participants at baseline, 3 months, and 6 months.

Outcome measures	Scale	Type	Measure	Analysis method
Primary Outcomes				
Caregivers' knowledge	Ratio	Continuous	Change in knowledge scores	t test
Caregivers' attitudes	Ratio	Continuous	Change in attitudes scores	t test
Caregivers' practices	Ratio	Continuous	Change in practices scores	t test
Secondary Outcomes				
Child growth at 3 and 6 months				
Weight	Ratio	Continuous	Change in weight	t test
Height/Length	Ratio	Continuous	Change in height/length	t test
Weight-for-height z score	Ratio	Continuous	Change in weight-for-height	ANOVA[a]
Child morbidity at 3 and 6 months				
Diarrhea	Nominal	Categorical	% of children with diarrhea	Risk ratio
Fever	Nominal	Categorical	% of children with fever	Risk ratio
Cough	Nominal	Categorical	% of children with cough	Risk ratio

[a]ANOVA: analysis of variance.

Data Collection Tools and Procedures

Data Collection Plan

Application of baseline tools and procedures will be repeated by the field staff who participated in baseline data collection to

collect data from both arms. Before the data collection, a 1-day refresher training session will be organized for the 8 data collectors and 2 field supervisors. Recruitment of field staff was on the basis of proficiency in French, English, and Fulfulde (the dialect of the Mbororo people), familiarity with the Mbororo culture, and prior experience with surveys.

Caregivers' Interviews

Face-to-face interviews will be conducted by trained data collectors (interviewers) using pretested interviewer-administered questionnaires. The interviewer-administered questionnaires were adapted from the UNICEF (The United Nations Children's Fund) multiple indicator cluster surveys tool [18]. The adapted questionnaire was prepared in English and then translated and back-translated into French and Fulfulde. The components of the questionnaire are household and caregiver's sociodemographic characteristics, child demographic and health status characteristics, complementary feeding practices, and WASH facility and practices. Based on the health belief model constructs, the questionnaire contains 4 questions on caregiver's perception of child susceptibility to malnutrition, 4 questions on caregiver's perception of the severity of child malnutrition, 6 questions on caregiver's perception about barriers to practicing appropriate complementary feeding and WASH, 4 questions on caregiver's perceived benefits of appropriate complementary feeding and WASH practices, and 4 questions on caregiver's self-efficacy to implement recommended actions. Each interview is estimated to last between 50 to 60 minutes and will be conducted according to the time, day, venue, and language convenient to the interviewee. The interviewers will read out the questions to the respondents and complete the questionnaires accordingly.

Anthropometric Measurements

Pretested portable anthropometry tools (battery-powered digital infant and toddler weighing scales, stadiometers, measuring tape, and lying wooden boards) will be used. The weight and height/length measurements will be performed using standard procedures [19]. Lying or sitting weights for children aged 0-23 months will be measured to the nearest 0.01 kg, and standing weights for older children will be measured to the nearest 0.1 kg. The weighing scale will be calibrated to 0 before each measurement. Recumbent lengths for children aged 0-23 months will be measured to the nearest 0.1 cm with measuring tape and lying boards placed on a flat ground surface. Standing heights for older children will be measured to the nearest 0.1 cm, with the head, shoulder, buttock, and heel touching the vertical surface of the stadiometer. Measurements will be taken twice and the mean recorded.

Data Analysis Plan

Like the procedure at baseline, 1 biostatistician and 2 trained data entry clerks will be responsible for the endline data management and analysis. Data will be cross-checked for inconsistencies (outliers and extreme points) and errors and incompleteness before, during, and after manual entry into SPSS version 23 (IBM Corp). The data will be further treated for reverse coding, potential points, and outliers, as well as missing data, before being exported to SmartPLS2 for further investigation and fitting of the structural model.

Sociodemographic and child morbidity data will be analyzed and summarized using descriptive statistics. The data will be expressed as mean (SD) or median (range) for continuous variables and as a number (percentages) for categorical variables. The t test and analysis of variance for comparing group means will be used for primary and secondary outcome variables. A chi-square test will be applied to analyze the categorized variables. Child nutrition outcomes will be computed from anthropometric indices using Stata version 11 (StataCorp) and compared with the WHO 2006 growth standard median [20].

Results for group comparisons will be expressed as a risk ratio for binary outcomes, corresponding to 2-sided 95% CIs, and associated P values. P values will be adjusted to 2 decimal places with values less than .01 reported as <.01. Adjusted analyses using baseline variables will be performed using multivariate logistic regression to determine the continuing influence of key baseline characteristics on the outcomes. The Kaplan-Meier survival analysis will be used for timed variables like morbidity. Intention-to-treat analysis will be used, and the clustering effect will be considered in the analysis. All analyses will be performed at a 95% CI. The significance level will be set at a P value <.05.

Ethical Considerations

Ethical approval (reference no. 2019/1002-07/UB/SG/IRB/FHS) for the study was obtained from the Faculty of Health Sciences Institutional Review Board at the University of Buea. Administrative authorization was sought from the West Regional Delegation of Public Health. Informed verbal and signed consent and parental assent will be obtained from study participants before inclusion in the study. Participation will be voluntary with participants being able to withdraw from the study at any time. Anonymity and confidentiality will be assured and maintained.

Dissemination Plan

The results will be disseminated to internal and international audiences through publications in peer review journals, open access publications, and national and international conferences. Compensation will be provided in the form of workshops for those communities participating in the study.

Results

From the preintervention study undertaken from August 2019 to September 2019, baseline data were collected and partially analyzed to inform the design and implementation of the intervention study. In February 2020, 10 Mbororo communities with 242 child–caregiver pairs were selected for the trial, while 6 CNVs and 6 CHWs were selected and trained to lead the trial. Data collection and analysis are ongoing, and results are not available for this manuscript.

Discussion

Nu-WASH is a multicomponent health education model that will be delivered simultaneously to caregivers in the experimental arm to improve their nutrition capacity and child nutrition outcomes. To enhance its acceptability, sustainability, and cost-effectiveness, the intervention is culturally tailored for delivery in the community setting through CPGs, and led by trained female Mbororo CNVs and existing CHWs. The language of communication is predominantly Fulfulde.

Additionally, dietary diversity for young children will be based on locally available and consumed food items in various communities. It is expected that caregivers will perceive child undernutrition as an important health concern and will be motivated to practice recommended actions to bring about a positive behavioral change.

Theory-based behavioral change communication to promote healthy feeding practices is central to interventions that are aimed at improving infant and young child nutrition [8]. Our education intervention is based on the health belief model. The model posits that people will take action to prevent a negative health outcome if they regard themselves as susceptible to a condition, if they perceive a negative health outcome to be severe, and if they perceive that the benefits of adopting a particular behavior outweigh the perceived barriers they need to overcome [21]. The chances are higher if they are exposed to factors that prompt action (cues to action) and if they have the confidence to take action (self-efficacy) [21]. Based on these constructs, the intervention module is designed to enable participants to perceive malnutrition as a severe yet preventable condition that can affect their children (susceptibility). Additionally, skills acquisition will enhance their self-efficacy to overcome some perceived barriers and to take recommended action, leading to a positive behavior change. We predict that our community-led and culturally sensitive Nu-WASH intervention will improve caregivers' complementary feeding KAP and child nutritional outcomes as compared to routine health facility–based nutrition education among the study population.

Acknowledgments

Authors' Contributions

FTM and DSN conceived the study, FTM and DSN drafted the manuscript, and TOE and VSV participated in the design. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CHW: community health worker
CNV: community nutrition volunteer
CPG: caregivers' peer support group
KAP: knowledge, attitude, and practice
Nu-WASH: nutrition, water, sanitation, and hygiene
WASH: water, sanitation, and hygiene
WHO: World Health Organization
UNICEF: The United Nations Children's Fund

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Protocol

COVID-19 Rehabilitation With Herbal Medicine and Cardiorespiratory Exercise: Protocol for a Clinical Study

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Abstract

Background: Recent studies have revealed that many discharged patients with COVID-19 experience ongoing symptoms months later. Rehabilitation interventions can help address the consequences of COVID-19, including medical, physical, cognitive, and psychological problems. To our knowledge, no studies have investigated the effects of rehabilitation following discharge from hospital for patients with COVID-19.

Objective: The specific aims of this project are to investigate the effects of a 12-week exercise program on pulmonary fibrosis in patients recovering from COVID-19. A further aim will be to examine how Chinese herbal medicines as well as the gut microbiome and its metabolites regulate immune function and possibly autoimmune deficiency in the rehabilitation process.

Methods: In this triple-blinded, randomized, parallel-group, controlled clinical trial, we will recruit adult patients with COVID-19 who have been discharged from hospital in Hong Kong and are experiencing impaired lung function and pulmonary function. A total of 172 eligible patients will be randomized into four equal groups: (1) cardiorespiratory exercise plus Chinese herbal medicines group, (2) cardiorespiratory exercise only group, (3) Chinese herbal medicines only group, and (4) waiting list group (in which participants will receive Chinese herbal medicines after 24 weeks). These treatments will be administered for 12 weeks, with a 12-week follow-up period. Primary outcomes include dyspnea, fatigue, lung function, pulmonary function, blood oxygen levels, immune function, blood coagulation, and related blood biochemistry. Measurements will be recorded prior to initiating the above

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treatments and repeated at the 13th and 25th weeks of the study. The primary analysis is aimed at comparing the outcomes between groups throughout the study period with an α level of .05 (two-tailed).

Results: The trial has been approved by the university ethics committee following the Declaration of Helsinki (approval number: REC/19-20/0504) in 2020. The trial has been recruiting patients. The data collection will be completed in 24 months, from January 1, 2021, to December 31, 2022.

Conclusions: Given that COVID-19 and its sequelae would persist in human populations, important findings from this study would provide valuable insights into the mechanisms and processes of COVID-19 rehabilitation.

Trial Registration: ClinicalTrials.gov NCT04572360; https://clinicaltrials.gov/ct2/show/NCT04572360

International Registered Report Identifier (IRRID): PRR1-10.2196/25556

Introduction

In January 2020, the World Health Organization announced the outbreak of a novel coronavirus disease, called COVID-19. The COVID-19 pandemic has had devastating impacts globally, with 39,944,882 confirmed cases and 1,111,998 deaths recorded by October 20, 2020. Indeed, the number of cases of COVID-19 infection is continuously increasing with time, especially in the Americas, Europe, and Southeast Asia [1]. Although most people develop mild or uncomplicated forms of COVID-19, it has been estimated that approximately 14% of cases are associated with severe acute respiratory infection and may require hospitalization and oxygen support. Moreover, 5% of patients will require admission to an intensive care unit [2]. The COVID-19 pandemic has overwhelmed health systems worldwide. After discharge from hospital, some patients with COVID-19 continue to experience symptoms, which may last for months or even longer. These consequences include medical, physical, cognitive, and psychological problems. Although the long-term consequences are still unclear, recent studies have revealed that most patients (74%-87%) experience ongoing signs and symptoms 2-3 months after discharge from hospital, including fatigue, shortness of breath, impaired functions, and secondary mental problems [3,4]. Rehabilitation may contribute to patient recovery and is crucial in endowing patients with health improvements related to functional ability and quality of life.

For patients who have been unwell and sedentary for long periods, increased strength [5], aerobic ability [6], and exercise performance are vital to facilitate physiological [7], biochemical, psychological [8], and general recovery [9]. Considering the clinical conditions caused by prolonged immobilization and musculoskeletal deterioration, patients with COVID-19 need rehabilitation treatments following hospital discharge [10]. Exercise has direct effects on the cellular immune system; natural killer cells and T lymphocytes (T cells) become mobilized in the circulation through stress-induced shear stress and adrenergic signaling during exercise performance, providing protection and repair.

In addition to exercise intervention strategies, Chinese herbal medicines targeting gut microbiome dysbiosis have also been reported to improve immune function [11], facilitating patients'

recovery. The gut microbiome influences immune function and immune homeostasis both within the gut and systematically [12]. Chinese herbal medicines, the gut microbiome, and microbial metabolites regulate immune function and intestinal permeability involved in the pathological processes of virus-induced autoimmune diseases [11]. Restoring gut microbiome composition and its regulatory metabolites could be vital in boosting immune function and aiding recovery from COVID-19. Additionally, patients with COVID-19 experience loneliness, anxiety, depression, and decreased quality of life [13]. In summary, evidence suggests that exercise or Chinese medicines can help patients recover from virus-induced immune diseases and respiratory conditions such as pulmonary fibrosis. However, the potential beneficial individual and combined effects need further investigation.

In our proposed study, we will develop a new paradigm for the patient rehabilitation that is needed now and in the future. The specific aims of this project are (1) to investigate the effects of a 12-week programme involving cardiorespiratory exercise and Chinese herbal medicine, both singly and combined, on patients recovering from COVID-19 who exhibit pulmonary impairment and (2) to collect qualitative and quantitative data to examine the patients' loneliness, anxiety, depression, quality of life, and mental health. A further aim will be to examine how Chinese herbal medicines as well as the gut microbiome and its metabolites regulate immune function, intestinal permeability, and possibly autoimmune deficiency in the pathological recovery and rehabilitation process. The specified study objectives and hypotheses are listed below:

1. Evaluate the effects of cardiorespiratory exercise and Chinese herbal medicine, both individually and in a combination, on rehabilitation on pulmonary function among patients with COVID-19 through four intervention groups, including a cardiorespiratory exercise plus Chinese herbal medicines group, a cardiorespiratory exercise group in isolation, a Chinese herbal medicines group, and a waiting list control group (primary outcome). We hypothesize that the combination of cardiorespiratory exercise and Chinese herbal medicines will more greatly facilitate the rehabilitation of patients with COVID-19.

2. Reveal whether and how the gut microbiome plays a role in the effects of cardiorespiratory exercise and Chinese

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herbal medicines, both individually and in combination, on the rehabilitation of impaired pulmonary function. We hypothesize that the combination of cardiorespiratory exercise and Chinese herbal medicines will better modulate the gut microbiome and the related metabolites and thus better mediate the effects.

3. Assess the effects of cardiorespiratory exercise and Chinese herbal medicines on immune functions, both individually and in combination, on the rehabilitation of other relevant symptoms and signs of COVID-19. We hypothesize that the combination of cardiorespiratory exercise and Chinese herbal medicines will better modulate the immune function and thus better mediate the effects.

4. Evaluate the effects of cardiorespiratory exercise and Chinese herbal medicines, both individually and in combination, on recovery from mental health-related outcomes (loneliness, stress, anxiety, depression) and on quality of life (QoL). We hypothesize that the combination of cardiorespiratory exercise and Chinese herbal medicines will better help postdischarge patients in recovery from mental health-related outcomes and improve their QoL.

5. Assess the lasting effects of cardiorespiratory exercise and Chinese herbal medicines after a 12-week follow-up period. We hypothesize that some effects (eg, dyspnea, mental health-related outcomes, QoL) will be sustainable, while others (outcomes sensitively responded to cardiorespiratory exercise, eg, physical fitness, lung function) will partially relapse after the intervention cessation.

Methods

Study Design

The proposed study will be a triple-blinded randomized controlled trial comprising four groups: (1) a cardiorespiratory exercise plus Chinese herbal medicines group, (2) a cardiorespiratory exercise group, (3) a Chinese herbal medicines group, and (4) a waiting list group. The target population will be postdischarge adult patients recovering from COVID-19 who were diagnosed with pulmonary impairments. Recruitment will take place in Hong Kong via our International Rehabilitation Network Center for Patients With COVID-19. The proposed rehabilitation period will last for 12 weeks, with a 12-week follow-up [14]. Primary outcomes will include the clinical symptoms of pulmonary fibrosis (dyspnea, fatigue, lung function, blood oxygen levels, immune function, blood coagulation, and related blood biochemistry). Blood biochemistry will be further analyzed using unique metabolomics techniques to identify potential synergies related to immune function response to the interventions [15]. We will investigate glucose metabolism and its association with the degree of infection and prognosis. We will also profile the gut microbial metabolome to establish associations between (virus-induced) dysbiosis and the outcomes of COVID-19 infection. Pulmonary function tests will be completed using clinical spirometry, as outlined by the American Thoracic Society. Blood gas levels, immune function, and coagulation levels of the patients will be measured pre- and post-intervention in venous blood samples [16]. The trial has been registered on ClinicalTrials.gov (NCT04572360). A flow diagram of the trial is shown in Figure 1.

Figure 1. Flow diagram of the trial.
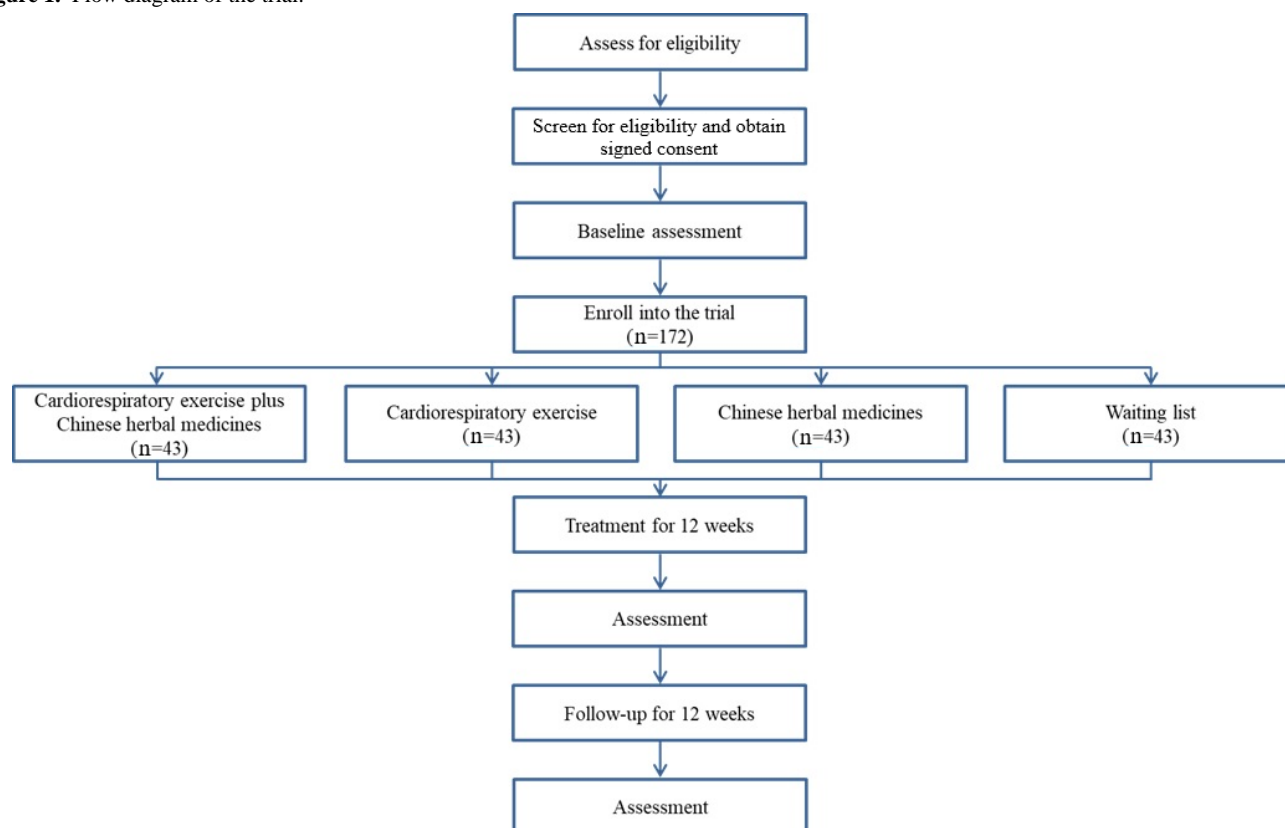
Eligibility Criteria

The target population will be adult patients with COVID-19 who have been discharged from the hospital and are still experiencing respiratory impairments. Patients will be recruited from Hong Kong. Inclusion criteria will include (1) age ≥18 years; (2) discharged from hospital for no less than 4 weeks; (3) percentage of predicted forced vital capacity (FVC) <90% or a percentage of predicted carbon monoxide diffusing capacity <90% [17]; (4) smartphone user; (5) able to communicate in Cantonese or Mandarin. Exclusion criteria will include (1) being pregnant or planning to become pregnant in the coming 6 months; (2) having acute exacerbations in the 12 weeks preceding recruitment; (3) having any contraindications for exercise (eg, physical disability, uncontrolled mental disorders, unstable heart disease, inability to perform muscle strength tests) [18]. The last two exclusion criteria will be evaluated by a physician.

Randomization and Allocation Concealment

Participants will be randomly and equally assigned to the four groups using block randomization [19]. The random allocation sequence will be computer generated by a blinded statistician outside of the research team, who will use randomly mixed block sizes of 4 and 8 and conceal the randomization procedure from the research team. The results of the allocation will be randomly coded with an identification number according to the random number table. An investigator will dispense the identification numbers according to the order of the patient's recruitment and will not be allowed to arbitrarily alter the numbering.

Blinding

One copy of the blind codes will be held by the project-responsible unit. The investigator operating the allocation of patients will not be involved in the intervention delivery, outcome measurements, or data analysis. The results of the allocation (being in the intervention or control groups) will be concealed from patients due to the waiting list control design, where patients in the control group will also receive a type of intervention and therefore will not know they are control participants. In addition, investigators assessing effects and those analyzing the data will also be blinded from the allocation.

Interventions

Cardiorespiratory Exercise Intervention

This intervention will be a 12-week progressive and individualized exercise program with a frequency of 3 sessions per week and a session duration of 60 minutes (total: 36 exercise sessions). The intervention is designed to alleviate symptoms of dyspnea, improve functional capacity, and relieve mental health problems in the short term. A further aim is to preserve physical function while improving health-related QoL in the long term. As recommended by the Official American Thoracic Society/European Respiratory Society Statement [20], 12 education sessions (30 minutes per session) will be included in and delivered together with the first exercise session in each week to motivate and empower the patients to form regular exercise habits and improve health [21,22]. A steering group will be formed to design the exercise intervention, develop relevant documentation, and monitor the implementation. Group members will include exercise experts, public health specialists, occupational therapists, doctors, and other stakeholders. Textbox 1 and Table 1 provide a summary of the intervention.

This program will be delivered using a home-based tele-exercise approach to reduce the potential to infect other individuals [24], reduce health care burden and costs for both health care providers and patients, and improve participation and retention of rehabilitation [25]. Some evidence, although not for COVID-19, has suggested that home-based pulmonary rehabilitation with minimal exercise equipment is effective and may be a viable alternative to equipment-intensive clinic-based programs [18,26]. Other studies concluded that the web-based tele-exercise approaches were as effective as conventional face-to-face interventions [27] and could enhance the reach and engagement of the rehabilitation process [21,25]. We will build and develop a web-based platform in our International Rehabilitation Network Center for Patients With COVID-19 to deliver the intervention.

Textbox 1. Description of the cardiorespiratory exercise intervention (educational session).

Educational session

- Each session will last 30 minutes and will be held before the first exercise session of each week, for a total of 12 sessions.

- The sessions will be developed mainly based on social psychological theories of intentional behavior and motivation, and aimed to improve motivation, self-regulation, and habit-formation relating to exercise [20,22,23].

- Our team members published a similar theory-based behavior change intervention in 2020 [22]. In brief, in each session, the patients will be asked about their exercise and other types of physical activity (PA), related theoretical determinants (eg, self-efficacy), and other related factors (eg, social and environmental factors). They will then receive personally tailored feedback incorporating effective behavioral change techniques (eg, goal setting) to promote motivation, solve problems, make action plans, prevent relapse, enhance self-regulation, and form healthy habits. A recap of the previous session will be added starting in the second session. Pictures, graphs, and videos will also be used where needed.

Table 1. Description of the cardiorespiratory exercise intervention (exercise session).

Content	Description
Exercise session	• 3 sessions per week for a total of 36 sessions; session duration will gradually increase from 40 to 60 minutes. • Initial face-to-face briefing will be given to enhance compliance and ensure that the patients can exercise properly. • Video feedback will be provided during each session.
Warm-up	• Warm-up will last 5-8 minutes, including both static stretching and dynamic stretching.
Aerobic training	• There will be no requirement of intensity in the initial sessions (1-2 weeks). • Exercise intensity will start from Rating 3 of the Borg Category-Ratio 0-10 Scale (Borg Dyspnea Scale) and progressively increase to Rating 6. • The training mode will be interval training in the first 4-6 weeks, followed by continuous training. • The duration will gradually increase from 10 to 30 minutes. • Effective exercises will be selected after a thorough review of the existing literature, such as walking, high knees, butt kicks, and stepping.
Resistance training	• The intensity will be one that evokes local muscular exhaustion in 6 to 12 repetitions (ie, a 6-12 repetition maximum) for major muscle groups; workload will increase when an individual can perform the current workload for 1 or 2 more repetitions than the required number in two consecutive exercise sessions [23]; there will be no requirement of intensity in the initial sessions (1-2 weeks). • The volume will be 2-4 sets, 8-12 repetitions, with 1-minute rest intervals (approximately 10 minutes). • A resistance band will be used to strengthen the muscles of either upper or lower extremities alternatively in each session. • Effective exercises will be selected after a thorough review of existing literature. Exercise examples include band bicep curl (arms), band lateral pull (arms), lateral band walk (legs), and seated banded leg extensions (legs).
Cool-down	• Cool-down will last 5-8 minutes, including static stretching and dynamic stretching.
Inspiratory muscle training	• The device used will be a POWERbreathe Classic (IMT Technologies Ltd). • The volume and intensity will be 30 breaths at 50% of maximal inspiratory pressure (approximately 5-8 minutes). • The increment of intensity will be 5% load increase each week. • Additional Inspiratory muscle training sessions will be performed without supervision according to a suggested frequency of twice daily. • Maximal inspiratory pressure will be measured with a portable hand-held mouth respiratory pressure meter (MicroRPM, CareFusion Micro Medical).

Structure of the Exercise Intervention

The intervention will include the following components: (1) a set of home-based tele-exercise sessions during which remote monitoring of vital signs will be required; (2) an individualized action plan to perform various daily physical activities; (3) educational sessions on self-management and habit formation; (4) access to a call center; (5) counselling sessions to enhance motivation to regularly engage in daily physical activities. The counseling intervention will be facilitated via a remote patient monitoring system. Patients will be equipped with an activity monitor (Mi Band 5, Xiaomi Corporation) that connects to a customized smartphone or tablet with a global system for mobile communication (GSM) connection that will receive, display, and send the data via the internet to a secure web-based server at the university. Patients will receive real-time feedback on the smartphone or tablet about their physical activity levels and their daily adjusted physical activity goals. A teleconference between the patient and the counselor will also be possible via the smartphone or tablet (using Zoom) in order to continually enhance adherence and goal achievement. Patients' daily physical activities will be acquired by the Mi Band 5 via Bluetooth technology to the smartphone or tablet; from the smartphone or tablet, data will be sent to the central server. Following the completion of the intervention, all patients will receive detailed individual feedback in relation to the outcome measures obtained via a meeting with the research team. This will comprise a question and answer session with relevant experts in their field of expertise. Patients will also receive a detailed personalized report with recommendations and information relating to the outcomes of the intervention.

The content of the exercise intervention will be developed with reference to the Official American Thoracic Society/European Respiratory Society Statement published in 2013 [20]. Each exercise session (40-60 minutes) will include a warm-up, aerobic training, resistance training, a cool-down, and inspiratory muscle training (IMT) [20,28,29]. Aerobic exercise will be arranged before resistance training, as recent evidence has shown that this order produces greater benefits than performing resistance training first [30]. Additional IMT sessions will be performed without supervision according to a suggested frequency of twice daily [20]. Before the first exercise session of each week, an additional educational session (30 minutes) will be delivered to improve motivation, self-regulation, and habit formation relating to exercise [20]. The contents of the educational sessions will be developed mainly based on social psychological theories of intentional behavior and motivation and effective behavioral change techniques (Textbox 1) [20,22]. All patients will be briefed face-to-face initially to ensure that they can undertake the intervention properly and to enhance their compliance with the intervention. In addition, they will be videotaped during the

exercise sessions, and real-time feedback will be given via the internet.

Aerobic exercise intensity will be determined using the Borg Category-Ratio 0-10 Scale (Borg CR10 Scale) modified for dyspnea, as recommended by the American College of Sports Medicine guidelines for patients with pulmonary diseases [23]. The exercise intensity will start from Rating 3 (equivalent to 53% peak work rate, ie, moderate intensity) in the first 2-4 weeks and progressively increase to Rating 6 (equivalent to 80% peak work rate, ie, vigorous intensity). Exercise intensity and session duration will be adjusted according to each patient's response and tolerance. Lighter intensities than Rating 3 may be adopted when there is a need (eg, for those with severe conditions). Patients will be given specific and standardized instructions on the ratings in advance. A pulse oximeter (Beurer PO 40, Beurer GmbH) will be used to monitor oxygen saturation in the initial exercise sessions to avoid exercise-induced oxyhemoglobin desaturation. In terms of intensity of resistance training, a practical approach to determine the appropriate intensity will be adopted, in which workloads will be set at levels that evoke local muscular exhaustion in 6 to 12 repetitions, as the one repetition maximum approach may overestimate or underestimate the optimal resistance for individuals [20,31]. Progressive target goals and detailed training plans will be set up together with each patient based on their physiological measurement results [21].

The exercise intervention will be delivered and supervised by experienced instructors. We will recruit persons who have been educated in either exercise science or rehabilitation. Each exercise session will be facilitated by two instructors dedicated to a group of 5-7 patients through the web-based platform in our International Rehabilitation Network Center for Patients With COVID-19. They will also be responsible for monitoring developments and training during the intervention.

Chinese Herbal Medicines

The Chinese herbal formula of Modified Bai He Gu Jin Tang (including Rehmanniae Radix 10 g, Rehmanniae Redix Praeparata 10 g, Ophiopogonis Radix 10 g, Lilii Bulbus 15 g, Paeoniae Radix Alba 10 g, Angelicae Sinensis Radix 10 g, Fritillariae Thunbergii Bulbus 5 g, Glycyrrhizae Radix et Rhizoma 10 g, Platycodonis Radix 15 g, and Salviae Miltiorrhizae Radix et Rhizoma 15 g) will be prescribed in granules. The rationale for the formula selection is as follows: (1) based on the syndrome differentiation, pulmonary fibrosis post–COVID-19 appears as qi-yin deficiency of the lung [32]; (2) a previous study has shown that many herbs using this formula and Salviae Miltiorrhizae Radix et Rhizoma have antifibrosis effects [33]; and (3) Bai He Gu Jin Tang has the effects of nourishing lung qi and ying deficiency [34]. Therefore, the formulation of Bai He Gu Jin Tang was modified to match the therapeutic purpose. A dose of 10 g per day (5 g, twice per day) will be ingested. Patients will dissolve a sachet of granules (5.0 g) in 200 ml of hot water twice per day after breakfast and dinner, 7 days per week, for 3 months. The entire manufacturing process will be in strict compliance with the standards of good manufacturing practice.

Waiting List Control

The waiting list control sign will be adopted to conceal the allocation results from the patients as well as to reduce selection and confounding bias and increase the participants' adherence to the study. Patients in the waiting list control group will receive no treatment in the study period (including a 12-week intervention period and a 12-week follow-up period). However, they will receive Chinese herbal medicines after the completion of the study (ie, after the third wave of measurements in the 25th week).

Outcomes

Table 2 lists a description of the outcomes and other measures, which are not exhaustive. All measurements will be recorded at baseline and repeated at the 13th and 25th weeks of the study. Patients will be assessed for risk prior to data collection. Further information from patients using appropriate data collection methodologies, including clinical symptoms, treatment history, comorbidities, physical activity, nutrition, and other potential variables, will be obtained and adjusted for during data analysis.

Table 2. Description of the outcome measures.

Measure	Outcomes
Cardiorespiratory fitness	• Six-minute walk test • Performance time test
Dyspnea	• Borg Category-Ratio 0-10 Scale (Borg Dyspnea Scale)
Body composition	• BMI • Waist circumference • Stature • Body mass • Segmental muscle mass • Anatomical circumference
Lung function test	• Forced vital capacity • Forced expiratory volume 1 • Forced expiratory volume 1/forced vital capacity • Fractional exhaled nitric oxide • DLCO[a]
Cardiopulmonary exercise test/blood gas	• VE[b] • VCO_2[c] • VO_2[d]/PCO_2[e] • PO_2[f]
Blood biochemistry tests	
Metabolic function	• Insulin
Immune function	• Coagulation • Lymphocytes • CD3 • CD4 • CD8 • CD19 • CD16+CD56 T cells
Neurological function	• BDNF[g] • Corticosterone
Cytokine profiles	• Interleukin 1 • Interleukin 6 • Tumor necrosis factor alpha
Gut microbiome	• Fecal metagenomics analysis
Glucose, fructose, and related metabolites	• UPLC-QTOF-MS[h] analysis
Metabolomics-related measurement of depression	• Metabolomics analysis of selected neurotransmitters as potential markers of depression
Quality of life and other mental health–related measures	• Self-reported scales

[a]DLCO: diffusing capacity of the lungs for carbon monoxide.

[b]VE: ventilation.

[c]VCO_2: carbon dioxide output.

[d]VO_2: oxygen uptake.

[e]PCO_2: partial pressure of carbon dioxide.

[f]PO_2: partial pressure of oxygen.

[g]BDNF: brain-derived neurotrophic factor.

[h]UPLC-QTOF-MS: ultra-performance liquid chromatography coupled with quadrupole/time-of-flight mass spectrometry,

Outcome Measures

Cardiorespiratory Fitness

Functional exercise capacity that reflects daily physical activities will be assessed using the six-minute walk test (6MWT) to assess the outcome of the intervention. This test is recommended by the American Thoracic Society to evaluate the global and integrated responses of all the systems involved during exercise, including the cardiopulmonary systems, systemic and peripheral circulation, blood, neuromuscular units, and muscle metabolism. Heart rate and blood pressure will be measured before and after exercise. The test has high test-retest reliability (intraclass correlation coefficient=0.88-0.91) [35].

Dyspnea

Dyspnea is a common exercise-induced symptom of disease and usually occurs in patients with pathophysiology that results in inefficient gas exchange and ventilator impairments. The Borg CR10 Scale (Borg Dyspnea Scale) will be used to rate the dyspnea and overall fatigue levels of the patients at the beginning and end of the 6MWT. The scale will also be used during the cardiopulmonary exercise test (CPET).

Body Composition

Segmental muscle mass and BMI (kg/m^2) will be used to assess the body composition of the patients. A bioimpedance analysis approach (InBody 770 analyzer, InBody Co, Ltd) will be used to assess the patients' segmental muscle mass. A stadiometer (Seca 284, Seca Corporation) will be used to measure stature and body mass. Anatomical circumference will be measured using a distensible measuring tape.

Lung Function

The FVC test, forced expiratory volume (FEV_1), and FEV_1/FVC ratio will be assessed to indicate the functional severity and capacity of the patients' lungs (Vmax Encore V229, VIASYS Respiratory Care Inc). Fractional exhaled nitric oxide (FeNO) will be used to assess inflammatory response to exercise and medicinal intervention (NObreath, Bedfont Scientific Ltd, England).

Cardiopulmonary Exercise

The CPET will be performed using the Vmax Encore V229. The CPET provides information concerning the level of exercise that the patient can perform without undue stress. The test results will guide the research team regarding the prescription of exercise for physical rehabilitation methodologies. It also provides quantitative evidence of the benefits of a rehabilitation program as well as information on the mechanisms involved. Improvement in exercise tolerance cannot be objectively assessed without CPET [36]. An incremental ergometry exercise test (Excalibur ergometer, Lode Ergometry), will be used to assess the responses of the cellular, cardiovascular, and ventilatory systems under precise conditions of metabolic stress. Breath by breath measurements of minute ventilation (VE), carbon dioxide output (VCO_2), O_2 uptake (VO_2), VE/VCO_2, VE/VO_2, deviation in the responses from the pulmonary to cellular respiration and arterial blood gas, partial pressure of carbon dioxide (PCO_2), and oxygen saturation as measured by pulse oximetry (SpO_2, Sentec AG), will be monitored continuously during the exercise test. Depending on the physical condition of the patients, modification of the protocols to smaller work rate increments may be warranted. Intensities and durations will be specific to each individual to facilitate measurement and data capture. Before each test, the O_2 and CO_2 analyzers of the CPET system will be calibrated using standard gases (Gas 1: O_2: 25.89%, CO_2: 0%; Gas 2: O_2: 16.44% CO_2: 3.89%), and the flow volume integration system will be was calibrated by applying a standard volume (3 L) of gas at various flow rates. Canopy studies within the Vmax software suite will be used to validate the accuracy of the gas-exchange measurement instruments that measure VO_2 and VCO_2 using the methanol burning technique. The ratio of VCO_2 to VO_2 in the combustion of methanol yields a respiratory quotient (RQ) of 0.667. We will use a 3% difference as the accuracy threshold for measured RQ (RQ range of 0.647-0.687).

Quality Assurance, Calibration, Accuracy, and Precision for the Laboratory-Based Assessment Measures

All the devices used for measurement will be calibrated according to the manufacturer's specifications. The protocols of the measurements and sources of variability will be controlled by following the standards outlined in the American Thoracic Society calibration guidelines for spirometers and gasometers. Anatomical circumference measurements will be adopted from the anthropometry procedures manual provided by the US Centers for Disease Control and Prevention [37]. Repeated tests will be performed at the same time of day in a controlled laboratory environment of constant humidity, temperature, and pressure. Patients will arrive at the laboratory at designated times for all physiological and clinical assessments. All patients will be transported to the laboratory for testing and returned home by coach. A recovery period will be observed postassessment to ensure that the participants have no negative responses to the measurements. Once the recovery period is complete, all participants will be returned home.

Blood Biochemistry

Venous blood will be drawn at 3 time points, namely at pretreatment, at posttreatment, and after the 12-week follow-up. After coagulation at room temperature for 30 minutes, the samples will be centrifuged at 3000 rpm for 20 minutes. Serum as the supernatant will be extracted and stored at –80 °C until assay. Serum levels of insulin will be assessed by a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Merck & Co). Serum will be isolated by centrifugation (1000 rpm for 30 minutes, 4 °C) and stored at –80 °C until analysis. The prothrombin time test will be used to measure blood coagulation. Venous blood will be collected by venepuncture in a tube with sodium citrate. Plasma will be isolated after centrifugation at 1000 rpm for 30 minutes at 4 °C. Thromboplastin will be added to the plasma and maintained at 37 °C for 2 minutes. Calcium chloride will be added to the mixture, and the plasma will be allowed to coagulate. The time needed for the coagulation will be recorded as the prothrombin time.

Flow cytometry for counts of main lymphocyte subpopulations (CD3, CD4, CD8, CD19, and CD16+CD56 T cells) will be performed to test immune function. Venous blood will be stored in tubes with EDTA (anticoagulant). 100 µL of blood will be stained within 24 hours of sampling by the BD Multitest 6-color TBNK reagent (BD Biosciences). The lymphocytes with the antigens CD3, CD4, CD8, CD19, and CD16+CD56, which are the main populations of lymphocytes, will be labelled by a fluorochrome-conjugated antibody in the reagent. The whole blood will be incubated in the reagent at room temperature for 30 minutes, and red blood cells will be lysed with ammonium chloride solution. Cell sorting and analysis will be performed with a BD Accuri C6 flow cytometer (BD Biosciences). Each subpopulation of lymphocytes will be expressed in absolute value and percentage of total lymphocytes.

As suggested by Hacimusalar and Eşel [38], the following markers related to emotional disturbances will be studied.

Brain-Derived Neurotrophic Factor

Serum concentration of brain-derived neurotrophic factor (BDNF) will be measured with a commercially available ELISA kit (Millipore) according to the manufacturer's instructions.

Corticosterone

Serum concentration of corticosterone will be assayed by ELISA kit (Enzo Life Sciences, Inc) according to the manufacturer's instructions.

Cytokine Profile

The serum concentrations of interleukin-1, interleukin-6, and tumor necrosis factor alpha will be assayed by multiplex cytokine analysis. A multiplex cytokine kit (20-plex, Bio-Rad Laboratories) will be used according to the manufacturer's instructions. The result will be generated by the Bio-Plex 200 suspension array system (Bio-Rad Laboratories) that is available in the University Life Science facility of Hong Kong Polytechnic University.

Gut Microbiome Test

All patients will be requested to self-sample their first morning feces by following detailed printed instructions. Collected stool samples will be immediately frozen in a home freezer (–20 ℃), then transported to our facilities in a provided freezer pack and stored at –80 ℃ for long-term use. Total DNA of 200 mg fecal samples will be extracted and purified as described [39]. The DNA concentrations and size distributions will be estimated using a NanoDrop instrument (Thermo Scientific) and agarose gel electrophoresis, respectively. The DNA one-paired-end library will be prepared using a TruSeq DNA HT Sample Prep Kit (Illumina Inc), and whole-genome shotgun sequencing of the samples will be carried out using the HiSeq 2000 platform (Illumina Inc). Low-quality reads with N bases, adapter contamination, or human DNA contamination will be filtered from the raw data, and the remaining high-quality sequences will be mapped with the published gene catalog of reference genes in the human gut microbiome [40]. Taxonomic assignment of the predicted genes and

Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis will be performed as described previously [41]. The relative abundances of phyla, genera, species, and KEGG orthologs will be calculated from the relative abundances of the respective genes. For data analysis, the quantitatively measured metabolites for each participant will be merged into the participants' clinical information through their individual sample IDs.

Mass Spectral Analysis of Glucose, Fructose, and Related Metabolites

Human serum or plasma samples will be thawed on an ice bath to minimize sample degradation. Metabolites will be extracted by adding 0.5 mL of 50% methanol (–20 °C) followed by homogenization for 3 minutes using a Bullet Blender Tissue Homogenizer (Next Advance, Inc) and centrifugation at 13,500 g for 10 minutes at 4 °C. The resulting 50 µL of supernatant will be transferred to a 1.5 mL tube and mixed with 10 µL of 200 mM 3-nitrophenylhydrazine (3-NPH) solution and 10 µL of mixed 96 mM ethylene dichloride/pyridine methanolic solution. Derivatization will be conducted by incubation at 30 °C for 1 hour before evaporation to dryness under nitrogen. 400 µL of 50% aqueous methanol will be used to resuspend the samples. The supernatants will be used for ultra-performance liquid chromatography coupled with quadrupole/time-of-flight mass spectrometry (UPLC-QTOF-MS) analysis according to previous reports with minor modifications [42,43].

Metabolomics-Related Measurement of Depression

Metabolomics Analysis

Ultra-performance liquid chromatography triple quadrupole mass spectrometry (UPLC-TQ-MS) (Xevo TQ-S system, Waters Corp) will be used to quantitatively measure the metabolites (neurotransmitters) selected as potential markers of depression. Briefly, an aliquot of 40 µl of urine or plasma will be spiked with 10 µL of internal standard (L-4-chlorophenylalanine in water, 30 µg/mL) and extracted with 200 µL of acetonitrile and methanol (9:1, v/v). The mixture will be vortexed and centrifuged. After centrifugation, the supernatant will be transferred to the sampling vials and subject to UPLC-TQ-MS analysis. The raw data generated will be processed using the TargetLynx Applications Manager Version 4.1 (Waters Corp) for targeted metabolite annotation and to obtain the calibration equations and the concentration of each metabolite in the samples.

Quality Control

Reproducible and valid results are critical for biomarker development. To achieve this, three types of quality control (QC) samples will be used in our metabolomics analysis: internal standards, test mixtures, and pooled biological samples. In addition to these QC samples, conditioning and solvent blank samples are required to obtain optimal instrument performance. Test mixtures comprise a group of commercially available standards with a mass range across the system mass range used for the study samples. These samples are analyzed at the beginning and end of each batch run to ensure that the instruments are performing within analytical specifications, such as retention time stability, peak resolution, peak signal intensity, and mass accuracy. Internal standards will be added to the test samples to monitor analytical variations during the entire sample preparation and analysis processes. The quality

assurance criteria used to monitor the internal standards include (1) coefficient of variation (CV) ≤15% within 100 injections; (2) CV ≤20% within 300 injections. The CV is defined as the ratio of the standard deviation to the mean peak signal intensity. A pooled plasma sample containing aliquots from representative participants will be used as a study QC sample for the correction of interbatch analysis. The QC samples for this project will be prepared with the test samples and injected at regular intervals, every 12 testing samples, throughout each analytical run. The purpose of using the pooled QC samples is to provide a set of data that can be used to assess overall reproducibility and to correct for potential analytical variations. To minimize the batch-to-batch and day-to-day variations, we will attempt to arrange one case and one control sample adjacent to each other in each batch and on each day of testing. (3) Data assembly: for data analysis, the quantitatively measured metabolites for each participant will be merged with the participant's clinical information through their individual sample IDs.

QoL and Other Mental Health-Related Measures (Self-Reported)

QoL will be measured using the Personal Well-being Index-Chinese Version. It is a subjective QoL measure that has been translated and validated. Anxiety will be measured using the Chinese version of the Depression Anxiety Stress Scale-21, which has been proven to have internal consistency [44,45]. The scale will discriminate between the negative emotional syndromes of depression, anxiety, and stress in Chinese populations. Only the subscales of anxiety and stress will be used. Loneliness will be measured using the Revised UCLA Loneliness Scale) [46,47]. This scale consists of 20 items and has been widely used to assess loneliness in research. General mental health will be measured using the General Health Questionnaire, which is commonly used to screen minor psychiatric symptoms [48].

Safety Observations

During the trial, each participant will receive safety monitoring. All adverse events will be forwarded to the ethics committee. They will review all documented harms during the trial and adjudicate them with regard to causality. The observations are listed below:

1. Vital signs: Body temperature, heart rate, blood pressure, and respiration (once at each follow-up visit)
2. Blood routine, urine routine, stool routine plus occult blood (once before and after treatment, respectively; twice in total)
3. Hepatic function (alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, gamma-glutamyl transferase), renal function (serum creatinine, blood urea nitrogen) (once before and after treatment, respectively; twice in total)
4. Electrocardiogram (once before and after treatment, respectively; twice in total)
5. Severity and incidence of adverse events (recorded in detail at any time)

The schedule for the enrollment, interventions, and assessment is summarized in Table 3.

Table 3. Schedule of enrollment, interventions, and assessments in the trial.

Time point	Study period (week)				
	Enrollment		Allocation	Post-allocation	Follow-up
	Washout (–3 to –1)	Run-in (–1)	0	12	12
Enrollment					
Eligibility screen	✓				
Informed consent	✓				
Randomization			✓		
Allocation			✓		
Intervention					
Cardiorespiratory exercise plus Chinese herbal medicines				✓	
Cardiorespiratory exercise				✓	
Chinese herbal medicines				✓	
Waiting list					
Assessment					
Cardiorespiratory fitness				✓	✓
Dyspnea				✓	✓
Body composition				✓	✓
Lung function test				✓	✓
Cardiopulmonary exercise test				✓	✓
Blood biochemistry tests				✓	✓
Gut microbiome				✓	✓
Glucose, fructose, and related metabolites				✓	✓
Metabolomics-related measurement of depression				✓	✓
Quality of life and other mental health-related measures				✓	✓
Safety	✓	✓	✓	✓	✓

Infectious Control

Prior to and following the testing procedures, all equipment will be subjected to rigorous disinfection methods for clinical populations as outlined by the Guidelines on Infection Control Practice in the Clinical Setting of the Department of Health [49]. Further to this, individuals involved in testing and data collection will be required to wear the necessary protective clothing and observe personal hygiene regulations as further outlined in the document [49].

Data Management and Storage

The original medical records will be kept intact by the site investigators as the original documents of the clinical trial. All researchers will receive training regarding data management. Web-based application and user sessions will be encrypted between the server and client browser through the use of industry standard secure sockets layer (SSL) certificates. The data will be entered into the electronic case report form and the database will be established before recruitment. The investigators will be responsible for verifying the accuracy of the data. Data locking will be completed by the data

management team, and the researchers will not be able to modify the data. All research documents, including paper and electronic documents, will be retained for at least 5 years after publication. All individual participant data collected during the trial will be deidentified and made available to anyone who wishes to access the data immediately following publication.

A Data and Safety Monitoring Board (DSMB) has been set up to review the protocol and the research data. The DSMB will meet regularly to review the protocol according to ethical and safety standards, monitor the safety of the trial, and monitor the authenticity and completeness of the data based on the study design. The DSMB will review the progress of the trial, determine adverse events, and have the authority to decide whether the study needs to end early.

Data Protection

All data protection and patient anonymity considerations will apply throughout the experimental and postexperimental period. All patients prior to participation will be required to complete an informed consent form, clearly outlining experimental procedures and information relating to the study. All data will

be anonymized with the unique experimental IDs provided to the patients. Data collected will be stored in a secure location under lock and key. Computer-generated information will be given specific passwords, with access granted to the principal investigator. Patients will be informed that they can withdraw from the study at any time. Prior to data collection, ethical approval will be obtained from the ethics committee. All data collection procedures, confidentiality issues, and patient integrity will be subject to methodological rigor as outlined by the data protection act.

Sample Size Calculation

Aiming to achieve a large effect size of 0.8, based on a meta-analysis of effectiveness of exercise interventions on dyspnea and exercise capacity in patients with pulmonary fibrosis diseases [28], using a significance level of 0.05, power level of 90%, and 20% drop-out rate, a sample size of 172 patients (43 per group) was preliminarily estimated for the study. The meta-analysis result was chosen because there is no similar rehabilitation program available that combines exercise and Chinese herbal medicine. Furthermore, the outcome variables in that meta-analysis are similar to our primary outcomes. Given that the effects of Chinese herbal medicine were not considered, the final sample size will be re-estimated using preliminary outcomes from the pilot study.

Statistical Analysis

A generalized linear mixed model will be used to compare between-group differences in changes of outcome variables at the 12- and 24-week periods of the study, where group and time are the two factors of interest. Mediating effects of the gut microbiome and immune function tests will be determined by fitting linear regression models for pulmonary and other outcomes, respectively. A significance level of 0.05 will be adopted (two-tailed test). Intention-to-treat procedures will be applied to the data sets obtained. Missing data will be imputed using multiple imputations with chained equations, except for those from dropouts, which will be imputed with the baseline data. Data will be scrutinized for normal distribution prior to data analysis. Sensitive analyses, such as per-protocol analysis, as-treated analysis, and analysis for complete cases, will only be performed to assess the robustness of the data analyses.

Data Sharing

All individual participant data collected during the trial will be deidentified and will be available to anyone who wishes to access the data immediately following publication.

Results

The trial was approved by the university ethics committee following the Declaration of Helsinki (REC/19-20/0504) in 2020. The trial has been recruiting patients. The data collection will be completed in 24 months, from January 01, 2021, to December 31, 2022.

Discussion

As revealed in recent studies, long-term (12 weeks or more) interval exercise can significantly improve ventilatory, central hemodynamic, and peripheral muscle capacities [50]. During the COVID-19 pandemic, home-based tele-coaching techniques, such as a smartphone and step counter, could provide a comfortable and safe environment for rehabilitation that is as effective as that of hospital-based rehabilitation [51-53].

Because of the focus on rehabilitation, using a combination of exercise and Chinese medicine, and exploring the role of the gut microbiome in a mechanistic manner, the proposed study would be the first of its kind for this type of experimental intervention. Given that COVID-19 could persist in human populations, the important findings from this study would provide valuable insights into the mechanisms and processes that are active during rehabilitation.

The proposed multiple components of the rehabilitation program will benefit patients post–COVID-19 who use the various treatment modalities in the process. The findings and implications of this study will have long-lasting positive health benefits for patients with COVID-19 and will help treat related comorbidities. The findings from the study will also provide economic comparative data relating to the development of a cost-effective model for postevent rehabilitation of patients with COVID-19.

Authors' Contributions

The exercise group is led by JSB, Y Gao, BQ, BD, and GIA. The Chinese medicines group is led by ZB, LLDZ, ZHL, and YF. The rehabilitation group is led by BWML and JSB. The systems biology group is led by WJ and BD with additional, significant contributions from JSB and ZB. The pulmonary physiology group is led by PDW. The Psychology group is led by JSB, BWML, and BQ. The epidemiology group is led by Y Gao and includes LLDZ and GIA. The data management group is led by Y Guo, YY, and Y Gao. This manuscript was drafted by Y Gao and LLDZ and reviewed by all the authors.

Conflicts of Interest

None declared.

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Abbreviations

3-NPH: 3-nitrophenylhydrazine

6MWT: six-minute walk test

BDNF: brain-derived neurotrophic factor

Borg CR10 Scale: Borg Category-Ratio 0-10 Scale

CPET: cardiopulmonary exercise test

CV: coefficient of variation

DSMB: Data and Safety Monitoring Board

ELISA: enzyme-linked immunosorbent assay

FeNO: fractional exhaled nitric oxide

FEV1: forced expiratory volume

FVC: forced vital capacity

GSM: global system for mobile communication

IMT: inspiratory muscle training

KEGG: Kyoto Encyclopedia of Genes and Genomes

PCO$_2$: partial pressure of carbon dioxide

QC: quality control

QoL: quality of life

RQ: respiratory quotient

SpO$_2$: oxygen saturation as measured by pulse oximetry

SSL: secure sockets layer

UPLC-QTOF-MS: ultra-performance liquid chromatography coupled with quadrupole/time-of-flight mass spectrometry

UPLC-TQ-MS: ultra-performance liquid chromatography triple quadrupole mass spectrometry

VCO$_2$: carbon dioxide output

VE: ventilation

VO$_2$: O$_2$ uptake

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Protocol

Effectiveness of a Two-Tier Family-Oriented Intervention in Enhancing the Family Functioning and Care Capacity of the Family Caregivers of Stroke Survivors: Protocol for a Randomized Controlled Trial

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Abstract

Background: Stroke has profound impacts on families. Often, family members, including stroke survivors and the person who takes up the role of the primary caregiver, would encounter demands on finances, rehabilitation arrangement, and even conflicts. Hence, a family-oriented intervention is expected to enable families to rebuild internal and external resources to achieve optimal rehabilitation and community reintegration.

Objective: This study aims to describe a design of a two-tier family-oriented care management intervention for enhancing the family functioning and care capacity of the caregivers of stroke survivors.

Methods: The two-tier care management intervention was guided by a standardized protocol conducted by trained professional care managers (first tier) with the support of trained volunteers (second tier), which lasted for 8-12 weeks. Participants were recruited through collaborating hospitals according to inclusion and exclusion criteria. In order to examine the effectiveness and cost-effectiveness of the two-tier care management intervention, a two-arm randomization multicenter study was designed, including an active comparison group, which was guided by a standardized protocol conducted by trained volunteers. Dyadic participants, including both stroke survivors and their primary caregivers for both groups, were invited to participate in a questionnaire survey using standardized and purposefully developed measures 3 times: before the intervention, immediately after the intervention, and 2 months after the intervention. The primary outcome was family functioning measured by the Family Role

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Performance Scale and Family Assessment Device-General Functioning Scale. The secondary outcomes included caregiving burden, depressive symptoms, care management strategies, and the incremental cost-effectiveness ratio.

Results: Recruitment began in January 2017 and was completed at the end of April 2019. Data collection was completed at the end of March 2020. As of March 2020, enrollment has been completed (n=264 stroke caregivers). A total of 200 participants completed the baseline questionnaires. We aim to publish the results by mid-2021.

Conclusions: This study successfully developed a two-tier care management protocol that aims to enhance the family functioning of the caregivers of stroke survivors. Guided by a standardized protocol, this family-oriented two-tier intervention protocol was found to be feasible among Chinese families.

Trial Registration: ClinicalTrials.gov NCT03034330; https://ichgcp.net/clinical-trials-registry/NCT03034330

International Registered Report Identifier (IRRID): RR1-10.2196/16703

Introduction

Background and Rationale

Stroke has profound impacts on families. In particular, after stroke survivors return home from discharge, they often rely on family members to meet their daily needs for care and support [1,2]. Often, family members, including stroke survivors and the person who takes up the role of the primary caregiver, would be under high stress to face the demands of supporting the activity of daily living, the instrumental activity of daily living, financial and emotional support, rehabilitation arrangement, etc. During this sudden and unexpected caregiving journey, stroke caregivers need to not only equip themselves with knowledge and skills to provide hands-on care on a daily basis but also adjust their roles and functions within the family context. The process of rehabilitation after stroke is often long and challenging, and feelings of frustration, depression, and even family conflicts are common. A study showed that stroke survivor characteristics and family conflicts surrounding recovery was associated with mental distress and physical ill health [3]. In turn, increased psychological distress and poor family function can undermine the stroke survivor's recovery and rehabilitation process [1,4,5]. Apart from the direct impact of stroke caregivers, poor recovery and rehabilitation of stroke survivors impose a significant financial burden on the health care system [6].

Stroke accounts for 30%-50% of admissions to long-term residential care homes in Hong Kong [6]. Hence, interventions targeting family dynamics are vital. Interventions focusing on primary caregivers revealed the importance of enhancing self-efficacy in reducing the burden and enhancing their well-being at the individual level [7-11]. However, as we argued above, stroke affects the entire family and not only the primary caregivers. Hence, we developed a family-oriented intervention to support families with stroke survivors. A family is the most important social unit that is expected to provide care and support when family members feel sick or ill. When a person experiences a stroke, the family as a whole is affected, and therefore, interventions that enable family functioning as a whole are required.

Research has shown that a volunteer-led community education program successfully improved stroke knowledge [12], indicating that volunteers are untapped resources that can be integrated into interventions. However, studies have shown that a professional-led intervention group produced better outcomes in preventing mood disorders among stroke patients as compared to the volunteer support group [13]. Considering that professional-led and volunteer-led interventions could have unique roles, our research team designed a two-tier care management intervention protocol. In the first tier, trained professionals focused on conducting the assessment, conducting family-oriented interventions such as work-family balance, family communication, and family conference, and assigning and supervising volunteer-led intervention sessions. In the second tier, trained volunteers focused on interventions on enhancing stroke knowledge, enabling exercise, etc. By integrating the two-tier care management intervention, professionals and volunteers could supplement each other to optimize the intervention intensity and to maximize cost-effectiveness.

In summary, our research team developed a two-tier family-oriented intervention that aims to enhance the family functioning of the caregivers of stroke survivors and it has 3 unique features. These features are (1) a family-oriented intervention that focuses on family functioning, (2) a two-tier care management approach consisting of trained professionals (first tier) and trained volunteers (second tier) purposefully designed, and (3) last but not the least, a family-oriented care management intervention, starting from needs assessment, followed by the care plan, implementation, and review.

Objectives and Hypothesis

The main objective of this 8-12-week randomized controlled trial is to investigate the effectiveness and cost-effectiveness of a two-tier family-oriented intervention in enhancing the family functioning of caregivers of stroke survivors. We hypothesized that a two-tier family-oriented intervention for caregivers of stroke survivors can enhance their family functioning and care capacity as compared to a volunteer-led control intervention.

Methods

Study Setting

This is a two-armed, multicenter, double-blind randomized controlled trial (NCT03034330). Stroke survivors and their primary caregivers (up to n=300) were included and randomized in a 1:1 allocation ratio to a two-tier family-oriented care manager–led intervention group (up to n=150) and a volunteer-led control group (up to n=150). In this study, the research team collaborated with 5 local hospitals in the Hong Kong West Cluster, New Territories East Cluster, and New Territories West Cluster and 3 nongovernmental organizations (NGOs) in the Southern, Shatin, and Tuen Mun districts with varied settings. Three on-site teams established the infrastructure to provide direct rehabilitation and support services to stroke patients. The details of the partnering NGOs are listed in Table 1.

Table 1. Details of the study sites.

District	Setting	Services
Southern	District Elderly Community Centre	Providing support services to healthy, vulnerable, and frail older adults living in the community and family caregivers
Shatin	Home Support Team of the Integrated Discharge Support Program for Elderly Patients	Providing postdischarge support services for older adult patients, such as meal delivery, household cleaning, home assessment, and modification
Tuen Mun	Community Rehabilitation Day Centre	Providing both professional and psychosocial rehabilitation services to discharged patients with stroke, neurological, or physical impairments

Ethical Approval

We obtained ethical approval from the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 16-1019), The Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (2016.679-T), and New Territories West Cluster Research Ethics Committee (NTWC/CREC/16123). The clinical trial was registered at the United States National Institutes of Health (clinicaltrials.gov; NCT03034330). Informed written consent was obtained from all participants included in the study. This study started in June 2016 and ended in March 2020.

Inclusion Criteria

All caregivers of stroke survivors identified by the NGOs or referred by the hospitals were recruited if they (1) were Cantonese-speaking adults aged 18 years or older, (2) had a family member who had a stroke (ischemic or hemorrhagic stroke) at the age of 18 years or older, (3) provided care or were with a stroke survivor for no less than 10 hours per week (including time supervising a domestic helper) after discharge from the acute hospital, and (4) reported significant caregiver burden (a score ≥6 using the four-item Zarit Caregiver Burden Interviews [14]), depressive mood (a score ≥2 using the Patient Health Questionnaire-2 [15]), or family dysfunction (a score ≥6 using 4 items selected from the Family Caregiver Conflict Scale [FCCS] for Stroke [16]). These 3 parameters were chosen because this study aims to enhance the family functioning and care capacity of stroke caregivers. The inclusion criteria for stroke survivors were (1) being a Cantonese-speaking adult aged 18 years or older, (2) having a family caregiver participating in this study, (3) being able to communicate with interventionists and interviewers, and (4) being competent to provide written informed consent.

Exclusion Criteria

Caregivers were excluded if they were diagnosed with Alzheimer disease or other types of dementia (clinically diagnosed), or were suffering from acute health conditions (eg, conditions caused by a virus, infection, injury, misuse of drugs or medication) that prevented them from providing caregiving support. As this intervention involves strong engagement and commitment from caregivers, people with cognitive impairments are not suitable for this study. Acute health conditions include cancers and other major illnesses such as stroke and a broken bone that negatively affect the caregivers' physical and mental conditions, which prevented them from providing caregiving or joining the intervention. Stroke survivors (1) who had a transient ischemic attack without a major ischemic or hemorrhagic stroke, (2) whose family caregiver refused to participate in this study, (3) who were not able to communicate with interventionists and interviewers, or (4) who were not competent to give written informed consent (eg, illiterate or with cognitive impairment) were excluded from this study.

Sample Size Calculation

We used the G*Power 3 software (Psychonomic Society, Inc) to determine the minimum sample size required for obtaining a significant medium effect size of family functioning, given α=.05 and statistical power of 0.80, with a two-sided significance of .05. While we estimated the sample size, we could only take references from similar relevant studies reported in the literature that were available. References were taken from studies using individual-based outcomes such as the readmission rate of stroke survivors [17], depressive symptoms of caregivers [18], family role performance [19], and caregiver burden [4]. We admit that this is a limitation of our study. Based on a previous study, readmission rates within 6 months after discharge were significantly lower among patients who received follow-up home visits (26%-34%) compared to those who received standard aftercare only (44%) [17]. Besides, stroke accounts for 30%-50% of admissions to long-term residential care homes in Hong Kong [6]. To the best of our knowledge, since no intervention has utilized both care managers and volunteers in providing support to stroke families, we hypothesize that our designed intervention will lower the readmission rates of stroke survivors. As per this, we hypothesized that 15% of the stroke survivors whose caregivers

were in the intervention group will be readmitted to a hospital or admitted to a residential care facility within 6 months after discharge, whereas 30% of the stroke survivors whose caregivers were in the control group will be readmitted to a hospital or admitted to a residential care facility over the same period. The resulting sample size estimate was 140 dyads per group; however, to ensure a sufficient effect size, and considering attrition, a sample size of 150 dyads per group will be used. We estimated that the attrition rate will be 25% based on the risk of second stroke occurrence within 1 year [20] as well as the fact that the previous intervention study lasted for around 6 months [17].

Screening, Randomization, and Intervention Allocation

Stroke survivors and their primary caregivers were first to be identified by physicians in the abovementioned 5 hospitals. Potential dyads were referred to the 3 NGOs using a standardized referral form developed by the research team. Stroke survivors and their primary caregivers were also identified from the pool of existing service users of the 3 NGOs. The care team consisted of trained social workers from the 3 NGOs who performed screening using a standardized screening form that comprised data on demographics, family functioning, caregiving burden, depressive symptoms, and willingness to join. Participants were recruited if they met the inclusion criteria, passed at least one threshold in the areas of family functioning, caregiving burden, or depressive symptoms, and showed a willingness to join.

After recruitment, trained social workers from the 3 NGOs notified the research team to conduct randomization. To avoid bias and to ensure an equal number in each group within each study site, group allocation was determined using computer-generated block randomization with a block size of 4 by using SPSS Statistics (version 23.0, IBM Corp). A member of the research team informed the care managers about the subject code for group allocation. The participants and researchers were blinded to the group assignment. The care managers and volunteers were not blinded to the group assignment, because they needed to know the participants' group assignment to provide interventions.

Upon randomization, trained care managers were assigned to different cases by the NGOs' internal control while 2-3 trained volunteers were assigned to the same group depending on their availability and gender. The research team was cautious about the gender of the volunteers; female caregivers may find it difficult to face many male volunteers due to traditional values, while male caregivers may be more willing to receive support from male volunteers.

Three strategies were adopted to ensure that the intervention and control groups were separated throughout the study. First, both interventions were guided by a standardized protocol conducted by the trained interventionists independently. Second, interventions were home-based, which prevented participants from meeting with each other during the intervention period. Last but not the least, the research team served as a safe guide during the monthly field visit to secure protocol compliance.

Protocol Development

The research team developed a standardized protocol consisting of 3 guidelines, that is, a Care Manager Manual (with 4 chapters), an Intervention Group Protocol for Volunteers (with 13 chapters), and a Control Group Protocol for Volunteers (with 6 chapters) to facilitate the intervention program. The research team provided training to the care managers and volunteers separately. First, we conducted a 4-day (32-hour) training session for 9 care managers (3 from each NGO) in 2016, covering the topics of the medical aspects of stroke, the intervention and assessment framework, care management, family therapy, coping with stress, problem-solving, stroke rehabilitation, and family intervention skills. Second, we provided a 5-day (40-hour) training workshop to 46 volunteers recruited by the 3 NGOs, focusing on the impact of stroke, psychoeducation, in-home exercise training, personal care techniques, counseling skills, swallowing and communications, intervention assessment, and code of practice. The number of volunteers recruited was estimated by care managers of the 3 NGOs based on the intervention protocol and resource management.

Intervention Group

Both groups followed a standardized protocol designed by the research team. The intervention group received a two-tier family-oriented care manager–led intervention consisting of a trained social worker (care manager) and trained volunteers for 2-3 months.

Control Group

The control group received a volunteer-led psychosocial education for 2-3 months. Care managers did not provide any direct intervention for the participants in the control group. Stroke survivors were not involved in the control group intervention. All participants completed a questionnaire at 3 different time points (Figure 1). A baseline assessment (T0) was conducted by care managers or volunteers before the start of the intervention. The first follow-up (T1) was conducted by a trained research assistant immediately after completion of the intervention, and the second follow-up (T2) was conducted by a trained research assistant at 2 months after completion of the intervention. Time points were chosen to better evaluate the effectiveness of the intervention and to reduce the attrition rate.

Figure 1. CONSORT flow diagram of the randomized controlled trial with 2 groups. HK: Hong Kong.
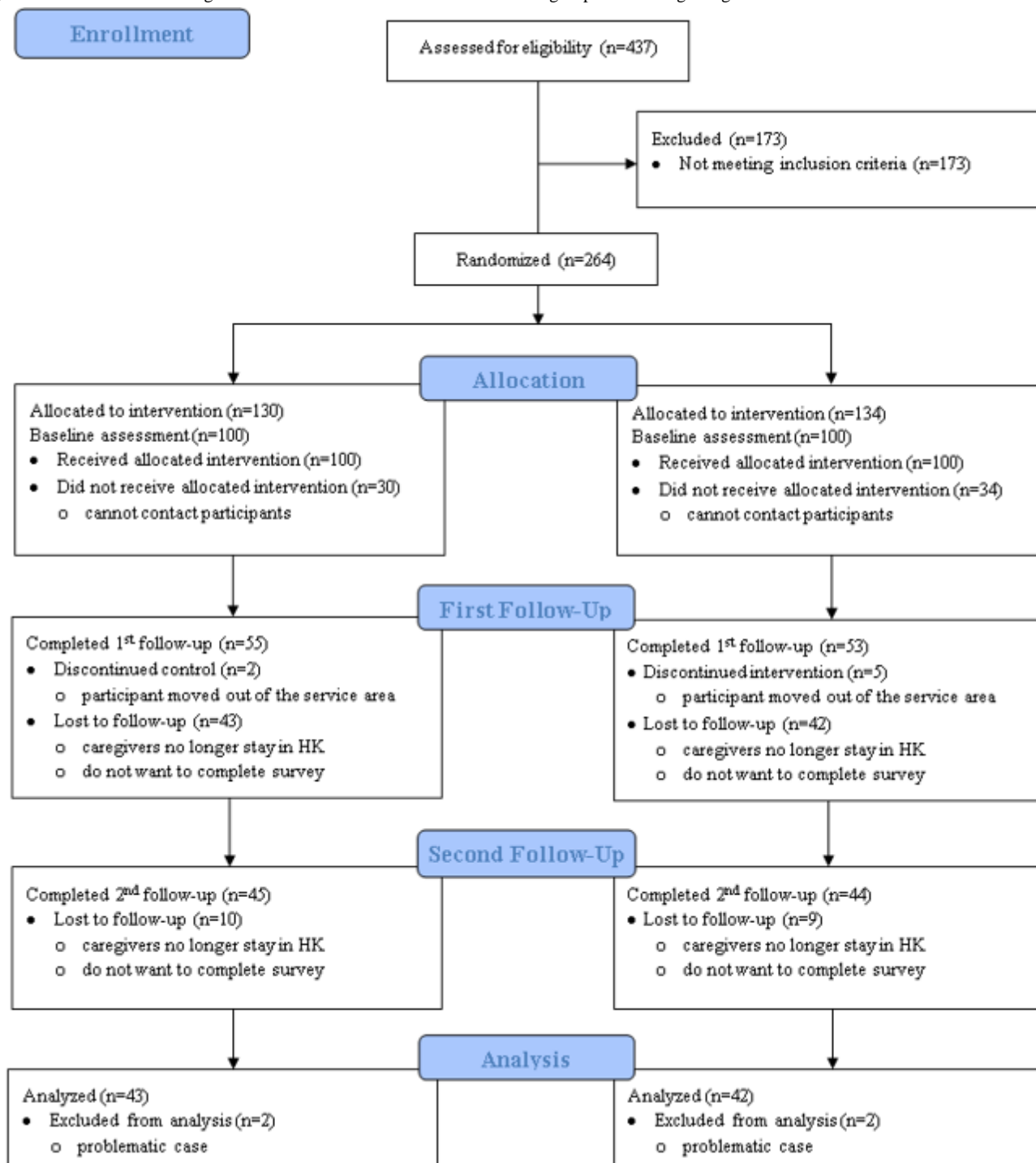
Intervention

Stroke caregiver participants in the intervention group received the following interventions.

Two-Tier Family-Oriented Care Manager–Led Intervention

The intervention was individualized and tailor-made according to the caregivers' needs assessment results. Care managers conducted an initial family needs assessment with caregivers to determine the care plan. Baseline assessments and a family genogram were used to assess caregivers' needs. Measures covered demographic information, stroke knowledge, care

management strategies, family conflicts, family functioning, social network, caregiver burden, physical and mental health, and depressive mood. The intervention lasted for 2-3 months with 6-10 weekly sessions at the homes of the caregivers or stroke survivors. Each session lasted for 60-90 minutes. The flexibility in the duration was provided based on the consideration that some participating families were more willing to share and discuss in detail, as evidenced in the pilot experiences. The research team visited each study site every 4 weeks to ensure project progress and held a full team meeting with the 3 NGOs every 12 weeks to share good practices.

The care managers determined the intensity of the intervention after the initial family needs assessment. The weekly sessions selected out of 22 choices are listed in Table 2. The trained care manager provided the first tier of the intervention, consisting of (1) the family needs assessment (session 1), (2) family support and counseling (sessions 2, 3, 4, 5, 6, and 7), (3) psychological support to caregivers (session 12), and (4) care planning and coordination (session 22). Trained volunteers, supervised by the trained care managers, form the second tier of intervention. They mainly provided in-home services, including (1) psychoeducation (sessions 13, 14, 15, 16, and 17), (2) skill-building (sessions 8, 9, 10, and 11), and (3) social support (sessions 18, 19, 20, and 21). Stroke survivors also took part in up to 4 sessions (sessions 18, 19, 20, and 21) if they agreed and were competent to take part in the intervention. However, the

participation of the stroke survivors did not affect their caregivers' involvement in the study and the intervention. Although the intervention was individualized and tailor-made, the research team provided a standardized protocol to guide the trained care managers as well as the trained volunteers in delivering the intervention. Further, the interventionists recorded the sessions conducted as well as the duration of each session in a service log. Because the collaborating NGOs provided social services or rehabilitation services to stroke survivors, rapport building between care managers and stroke families was ensured. All participating stroke families agreed on the intervention and signed consent forms. Further, care managers built a constant feedback mechanism with the participants, which can ensure participant adherence.

Table 2. Domains and themes of the intervention sessions.

Domain	Theme	Interventionist	
		Care Manager	Volunteer
Family Needs Assessment	Project orientation, family needs assessment, and goal setting	✔	
Family Support I	Family conference	✔	
Family Support II	Addressing relationship and caregiving issues of spousal caregiver	✔	
Family Support III	Addressing relationship and caregiving issues of adult-child caregiver	✔	
Family Support IV	Rediscovery of family strengths	✔	
Family Support V	Emotion management	✔	
Family Support VI	Empower stroke survivor	✔	
Skill Building I	Caregiver self-care and relaxation		✔
Skill Building II	Mastering care skills		✔
Skill Building III	Communicating with stroke survivor with communication or swallowing problems		✔
Skill Building IV	Communicating with health care professionals		✔
Skill Building V	Stress coping and problem-solving	✔	
Psychoeducation I	Understand poststroke health issues		✔
Psychoeducation II	Medication management		✔
Psychoeducation III	Home safety and emergency handling		✔
Psychoeducation IV	Promoting healthy lifestyle		✔
Psychoeducation V	Navigating community resources		✔
Social Support I	Speech training		✔
Social Support II	Cognitive stimulating activities		✔
Social Support III	In-home rehabilitation exercise		✔
Social Support IV	Family outing	✔	✔
Social Support V	Care plan and coordination	✔	

Volunteer-Led Psychoeducation (Control Group)

The control group received a standard, non–family-based psychoeducation intervention provided by trained volunteers under the supervision of trained care managers. The intervention lasted for 2 months with 4 weekly sessions held at the homes of the caregivers of stroke survivors in the first month and 2 telephone contacts made in the second month (6 contact points

in total). Each session lasted for 60-90 minutes. Care managers did not provide any direct intervention for participants in the control group. Stroke survivors were not involved in the control group intervention. Intervention in the control group consisted of 4 weekly home visits by trained volunteers who provided psychoeducation to caregivers, including (1) medication management and communication with health care professionals, (2) healthy lifestyle, (3) stroke care skills, and (4) stroke

rehabilitation knowledge. Finally, 2 telephone contacts were made by trained volunteers to educate caregivers on (1) navigating community resources, and (2) preventing recurrent stroke.

Outcomes

Primary Outcome Measures

The primary outcome revolves around the family level. The family-level outcome measures to be obtained include the Family Role Performance Scale, Care Management Strategies Scale, FCCS, and Family Assessment Device-General Functioning (FAD-GF) scale. The details of each scale are described below (Table 3).

Table 3. Outcome measures.

Outcome measures	Baseline	First follow-up	Second follow-up	Six months after second follow-up
Primary outcomes				
Family Role Performance Scale	✔	✔	✔	
Family Assessment Device-General Functioning Scale	✔	✔	✔	
Secondary outcomes				
Care Management Strategies Scale	✔	✔	✔	
Family Caregiver Conflict Scale	✔	✔	✔	
Cantonese short version of Zarit Burden Interview	✔	✔	✔	
The Patient Health Questionnaire-9 item	✔	✔	✔	
Caregiving Ambivalence Scale	✔	✔	✔	
Social care services used by stroke survivors	✔	✔	✔	
Medical care services used by stroke survivors	✔	✔	✔	
Clinical profile and service use data of stroke survivors				✔
Cost of study participation				✔

Family Role Performance Scale

The research team developed this scale to measure the frequency and ability of the family member to perform 6 major family roles, that is, advisor, emotional connector, breadwinner, caretaker, decision maker, and caregiver by using the structure developed and validated by Chen et al [19]. This scale contains 2 parts. The first part contains 6 items and asks participants how often they perform the 6 family roles. Each item is answered on a scale ranging from 0 (*never*) to 4 (*very frequently*). The second part contains 6 items and asks participants to rate their performance regarding family roles. Each item is answered on a scale ranging from 0 (*very poor*) to 4 (*very good*). The 2 parts will be scored separately.

Care Management Strategies Scale

The research team developed this scale to measure caregivers' care management strategies. The Care Management Strategies Scale consists of 18 items describing care management behaviors, including both positive and negative aspects, developed by the research team. The positive part contains 9 items and asks participants how often they perform positive care management strategies. Each item is answered on a scale ranging from 0 (*never*) to 4 (*very frequently*). The negative part contains 9 items and asks participants how often they perform negative care management strategies. Each item is answered on a scale ranging from 0 (*never*) to 4 (*very frequently*). The 2 parts

will be scored separately, and then reverse coding will be applied to the negative part to provide a composite score. A higher score indicates better management strategies.

FCCS

The FCCS consists of 15 items to assess family conflict due to stroke. Each item is answered on a scale ranging from 1 (*strongly disagree*) to 5 (*strongly agree*). It has 4 subscales, namely, communication, problem-solving, general family functioning, and perceived criticism [16].

FAD-GF Scale

The FAD-GF scale is the 12-item general functioning of the McMaster Family Assessment Device [21] to measure the family functioning of caregivers. Each item is answered on a scale ranging from 1 (*strongly agree*) to 4 (*strongly disagree*).

Secondary Outcome Measures

The secondary outcome is related mainly to the personal level. Personal-level outcome measures include the Cantonese Short Version of Zarit Burden Interview (CZBI-short), Patient Health Questionnaire-9 item (PHQ-9), and Caregiving Ambivalence Scale. The study team will also obtain service utilization records and perform a cost-effectiveness evaluation. The details of each secondary outcome measure are described above (Table 3).

CZBI-Short

The CZBI-short is a spoken Cantonese version of the 12-item ZBI to assess the burden on Chinese dementia caregivers in clinical and social care settings [22]. Each item is answered on a scale ranging from 0 (*never*) to 4 (*very frequently*).

PHQ-9

The PHQ-9 is a reliable and valid instrument for assessing depressive symptoms in the general Hong Kong population. It consists of 9 items and was developed to correspond to the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria for major depression [23]. Each item is answered on a scale ranging from 0 (*not at all*) to 4 (*nearly every day*).

Caregiving Ambivalence Scale

The Caregiving Ambivalence Scale is adapted from the Intergenerational Ambivalence Scale [24] to measure the level of ambivalence between caregivers and care recipients. The scale for caregivers consists of 6 items—3 asking the positive components and 3 asking the negative components of their relationships. Each item is answered on a scale ranging from 0 (*never*) to 4 (*very frequently*).

Service Utilization Record

The service utilization of medical and social care services by stroke survivors was obtained. Medical care services include inpatient hospital admission, specialist outpatient, accident and emergency service, and hospital rehabilitation service. Social care services include home care service, daycare service, community rehabilitation service, and residential care service (admission after study intake). The clinical profile and service use data of stroke survivors and the electronic medical records from the Hospital Authority Clinical Management System of Hong Kong will be retrieved regularly until 6 months after the completion of the second follow-up assessment.

Cost and Cost-effectiveness Evaluation

In this study, the cost of study participation, including staff cost, travel expenses, and program materials, will be calculated. The research team will use the incremental cost-effectiveness ratio as well as the additional cost incurred to bring about one additional unit of a positive outcome to evaluate cost-effectiveness.

Statistical Analysis

We will use descriptive statistics to present baseline characteristics and outcome measures, and we will transform any skewed variables and correct their skewness before inferential analysis. To assess normality, we will perform the Shapiro-Wilk test of normality as well as the normal Q-Q Plot, while we will use the Wilcoxon signed-rank test for the nonparametric test. We will also perform the chi-square or independent two-tailed *t* tests to examine the differences in the baseline characteristics between the intervention and control groups. For the primary and secondary outcomes, we will perform a multi-factor analysis of variance or general linear model to compare the differential changes in each outcome across the 3 assessment time points, that is, T0, T1, and T2

between the 2 treatment groups. This model can account for repeated measures data that are intercorrelated and that produce unbiased estimates even in the presence of the missing data, provided that the data are missing at random. Multivariate regression will be used to compare the differences in the outcomes between the 2 treatment groups and will control for the effect of potential covariates such as depressive symptoms and caregiver burden. Recruitment rate, attrition rate, and missing data will also be examined and reported. All outcome measures will be analyzed based on intention-to-treat principles. Every participant who is randomized according to the randomized treatment assignment will be included. This method of analysis preserves the prognostic balance afforded by randomization [25]. The cost of study participation, including staff cost, travel expenses, and program materials, will be expressed in Hong Kong dollars. All the statistical analyses will be performed using SPSS Statistics. All statistical tests will be two-sided with the level of significance set at .05.

Data Handling and Record Keeping

Hardcopies of the data forms will be anonymized after data entry and will be stored in a locked cabinet inside the premises at The University of Hong Kong (2/F, HKJC Building for Interdisciplinary Research). Electronic personal data will be stored in a secured server of the university. The principal investigator will be responsible for safekeeping of personal data during and after the study. The data will be used for academic and clinical research only and will be kept for up to 5 years after the first publication. This study will inform the participants that the institutional review board and ethics committee authority will have access to source data or documents related to this study directly to monitor and review the study.

Results

The clinical trial began recruiting in January 2017, and recruitment was completed at the end of April 2019. Data collection and data set construction were completed at the end of March 2020. As of March 2020, enrollment has been completed (n=264 stroke caregivers). A total of 200 participants completed the baseline questionnaires. We aim to publish the results by mid-2021. The intervention protocol is in Traditional Chinese only and is available upon request from the corresponding author.

Discussion

This is the first randomized controlled trial to investigate the effectiveness and cost-effectiveness of a two-tier family-oriented intervention that utilized trained care managers and trained volunteers to support stroke caregivers in Hong Kong. The study results will provide evidence on the feasibility, sustainability, and monetary value, and thus inform stakeholders. Stakeholders include policymakers in various government bureaus and departments such as Labor and Welfare Bureau, Social Welfare Department, and Hospital Authority; health care professionals; social work professionals, including those who provide services in the government, NGOs, as well as the private sector; semiformal caregivers such as foreign domestic helpers; stroke caregivers, stroke patients, and stroke families; and media and

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social media, on decisions in integrating this new model into the current stroke care services. This intervention attempts to fill a service gap in the current stroke care system and serves as an important basis on which future evidence-based programs supporting family caregivers of stroke survivors could be developed.

This study is not without limitations. First, the latest official statistics that we could retrieve was those of 2016 when this study began. Subsequent statistical data related to stroke patients and caregivers were not available; therefore, statistical data obtained in 2016 formed the basis of our study design. Another limitation is the potential bias and the effect of confounding, but we provided standardized training to all care managers and volunteers to minimize intervention bias.

Authors' Contributions

VWL, JYMT, and TYSL contributed to study conception and design. VWL, JYMT, GKKL, and KF were responsible for capacity building. VWL, JYMT, GKKL, CYMC, RWTK, JYF, ESLC, ACKC, EH, WWLN, FHWC, CCL, and TKK are responsible for the study implementation. All authors are responsible for the study evaluation. All authors contributed toward the drafting of the manuscript and approved the manuscript for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Demographics of the stroke caregivers and patients with stroke in the randomized controlled trial with 2 groups.
[DOCX File , 29 KB - resprot_v10i5e16703_app1.docx]

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Abbreviations

CZBI-short: Cantonese short version of Zarit Burden Interview
FAD-GF: Family Assessment Device-General Functioning
FCCS: Family Caregiver Conflict Scale
NGO: nongovernmental organization
PHQ-9: Patient Health Questionnaire-9 item

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Protocol

Promoting HIV, Hepatitis B Virus, and Hepatitis C Virus Screening Among Migrants With a Language Barrier: Protocol for the Development and Evaluation of an Electronic App (Apidé)

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Abstract

Background: Late diagnoses of HIV, hepatitis B, and hepatitis C are important public health problems that affect the population at large and migrants in particular. Missed opportunities of HIV and hepatitis screening are numerous, with language differences being a significant barrier to testing. Several studies have shown that migrants who do not speak the language of the health provider are less likely to get tested, due to health providers' reluctance to offer a test and to migrants' reluctance to accept testing.

Objective: The aim of our study is to develop a multilingual electronic tool (app) that assists health providers in offering and explaining HIV and hepatitis screenings to migrants with a language barrier and to evaluate its acceptability and impact in terms of public health.

Methods: The study will go through 3 stages: (1) concept development, (2) app development, and (3) app evaluation. A qualitative study has been undertaken to explore language barriers during health care encounters and their effect on communication, specifically when a screening test is offered. In parallel, a systematic review of the literature was conducted to have a comprehensive overlook of electronic tools designed to help health care providers communicate with migrants with a language barrier. To generate a list of items to be translated for inclusion in the app, we will conduct a focus group and Delphi survey. The development of the app will include translation and voice recording of items. The electronic development will also include 3 steps of user testing. The acceptability of the app will be evaluated using the System Usability Scale. Evaluation of the app's efficacy will consist of a stepped wedge randomized controlled trial. The study will be carried out in 16 centers that treat migrants and offer them screening tests for infectious diseases. The primary outcome is the percentage of screening tests realized. The secondary outcomes are the rate of screening proposal by health professionals, acceptance rate by migrants, number of positive cases using this app, and frequency of use of the app.

Results: The app evaluation study received a 3-year grant from the Agence Nationale de la Recherche contre le SIDA et les hépatites virales (ANRS) and from the Office Français de l'Immigration et Intégration (OFII). At the time of publication of this protocol, the initial qualitative study and systematic literature review were completed.

Conclusions: This study will develop an app that assists health providers in offering and explaining HIV and hepatitis screenings to migrants with a language barrier and measure its acceptability and effectiveness in terms of public health. When completed, this app could be distributed to numerous professionals carrying out screening with migrant populations in various health care settings.

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Introduction

There are currently around 150,000 persons living with HIV in France, and late diagnosis is an important public health problem. In addition to the individual therapeutic benefit, early diagnosis contributes, according to modeling, to primary infection prevention [1,2]. Early antiretroviral treatment initiation inhibits the multiplication of the virus, reducing the viral load and therefore the risks of future contamination. This strategy, however, requires extended screening [3,4]. Migrants (people born outside France and of non-French nationality at birth) are a population particularly at risk of the late diagnosis of HIV, as well as hepatitis B and C [5-7]. Migrants are also more prone to late diagnosis than nonmigrants [8-10]. The disproportionate risk of contracting HIV infection that migrants face in their host country is likely the result of a combination of factors, including stigma, increased risky behavior, and limited access to HIV prevention services [8]. Among the reasons for late diagnosis, the language barrier for non-French–speaking migrants might play an important role.

Research has been extensively conducted to investigate the language barrier among migrants in accessing care and prevention services and their consequences on health. Specifically, qualitative and quantitative studies carried out among different population of migrants in Australia [11], Canada [12,13], and England [14] found that lack of proficiency in English is a barrier to accessing testing for either HIV or hepatitis B or C. Those results have been confirmed in studies of health professionals caring for migrant patients in Belgium [15], England [14], and Australia [16] who state language barrier as a reason for not offering a screening test for those infectious diseases.

Beyond language proficiency issues, migrants may also face health literacy issues. The World Health Organization defines health literacy as "the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health" [17]. Health literacy can aid a person in making informed choices, reducing health risks, and improving their quality of life [18]. Thus, health literacy is important to understand to what extent the communication barrier is due to the patient's low level of health literacy in their mother tongue and to what extent it is due to the language difference.

The STRADA study (Screening strategies for infectious diseases [tuberculosis, HIV, hepatitis C, hepatitis B] in the migrant population in France) is a current, ongoing, prospective, multicenter, observational study to assess the effectiveness of a strategy for screening HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) among migrants undergoing a medical examination at the French Office for Immigration and Integration (OFII) [19]. Eligible migrants undergoing a medical examination at OFII are offered rapid screening for the 3 viruses. During the informed consent process, participants are informed that the study is voluntary and independent from the residency permit. This screening is preceded by a short risk factor questionnaire, available in 11 languages (French, English, Arabic, Mandarin Chinese, Bengali, Russian, Lingala, Portuguese, Spanish, Turkish, Haitian Creole). This screening is not mandatory, and individuals are given the option to decline or accept such testing. Migrants who are invited to participate receive information in their own language; this information indicates that they are free to refuse this test, that their refusal to participate will not change anything regarding their residency permit or their level of care (during the medical check-up or in the future), that the participation and results of the tests are kept confidential and separate from administrative papers, and that in case of a positive result, they will be able to access free treatment in France. It is made clear to the participant that a positive result is not grounds for refusing a residency permit. Throughout STRADA, we set up a study of acceptability aimed at measuring the obstacles impeding screening so as to identify strategies for achieving a better acceptance rate. A 3-minute online form is filled out by the health practitioners to report practitioners' reasons for not offering and patients' motives for refusing testing [20-22]. The results from over a year show the proposition and acceptability rates are 87.1% and 49.9%, respectively, of the patients who attended the medical check-up. Impeded communication is reported in 29.6% of the reasons health professionals are not offering screening tests, of which 93.6% are related to language barriers (see Table 1). In addition, other cited obstacles to communication include illiteracy, the presence of informal translators (which might hinder screening where sensitive and confidential information is shared), or a general lack of understanding. Among migrants who are offered screening, a majority who refuse (38.0%) said they have already been screened, although health professionals do not mention if they asked when the last screening was performed or checked thoroughly if the screening was indeed performed for the 3 diseases (HIV, HBV, HCV). Communication barriers and low health literacy might make it difficult for health professionals to investigate whether migrants need a repeat screening. Impeded communication is reported in 7.5% of the reasons migrants refuse screening when it is offered. Other reasons for refusing screening include patients do not want screening or do not see any relevance (19.2%), and 5.2% feel either not at risk or not concerned (Table 2). Those reasons might be linked to a lack of knowledge regarding HIV and hepatitis risks and necessity for regular testing, which might be overcome with clear explanations by a health professional.

Overall, communication is a major issue in the implementation of screening, and, as such, a linguistic app targeted at improving how screening is proposed to patients could potentially meet

an identified need, by reducing the language barrier on one hand and by providing motivational content to health care workers to help them explain the benefits of testing on the other hand.

Table 1. Reasons health professionals are not offering screening.

Reason stated	Responses, %
Organizational issues	36.6
Language, communication	29.6
Not known	10.8
Pregnancy	6.1
Already screened	3.9
Lack of time	3.9
Technical problems	3.6
Religious	3.2
Other	2.4

Table 2. Reasons migrants refuse screening when it is offered.

Reason stated	Responses, %
Already screened	38.0
Not interested	19.2
Not known	14.9
Language, communication	7.5
No reason given	5.8
No risk factor or not concerned	5.2
Lack of time	4.0
Other reasons	4.0
Religious	1.3

Health care professionals use multiple solutions to communicate with migrants with a language barrier: informal interpreters, formal interpreters in person or over the phone, and general translation applications. Informal interpreters are a no-cost solution that enables building a relationship of trust but represent a burden for patients who have to adjust to their availability. Informal interpreters also commit more errors with serious clinical consequences [23,24] and do not allow frank communication [25,26]. Professional interpreters provide high-quality translations that result in a better quality of care [23,27]. Medical doctors and patients are generally satisfied with professional interpreters but are limited by their availability and number of languages [26]. Professional interpreters over the phone offer the same quality of translation with greater time flexibility and more languages. However, health care professionals report less satisfaction [28,29], longer consultation times [28], and more technical problems [29] than with in-person interpreters. Although less expensive than in-person interpreters, this service still has a cost that cannot be met by various health organizations [30].

General translation applications (eg, Google Translate, Lexilogos, iTranslate) have the advantage of being free of charge and available 24/7. Some studies have tested their efficacy in the medical context with mixed results. Studies have found the quality of translation ranging from similar to professional translation [31] to incomprehensible [32] or potentially dangerous [33], depending on the specific application and language tested. The translation of languages that are widely spoken tended to be of better quality than less widespread languages. Online translation apps are not appropriate for long or complex sentences [31], for critical situations, [34], in case of emergency, or if consent is needed [35]. They are also time consuming [36], not appropriate to use with patients who cannot read, and do not allow patients to respond [30].

Besides the general translation applications mentioned earlier, some applications or electronic tools have been specifically developed to be used in medical consultations to facilitate the dialogue between health care professionals and migrants with low language proficiency. Those medical translation applications have developed different features to overcome such drawbacks. They usually consist of a list of sentences commonly used in a medical setting, translated into several languages, either by bilingual researchers or by professional translators. Those sentences are often supported by an audio recording and/or culturally adapted pictures to illustrate them. Patients can rarely give feedback on the health professional's sentences. Given the quantity and diversity of sentences that can be used in a medical setting, those applications are usually targeted to a specific

medical setting, such as patient's assessment [37]; emergency medicine [38] or anesthesia [39]; specific pathologies, such as asthma [40]; or a specific population, such as refugees [41-43]. No existing application has been developed to facilitate communication between migrants with a language barrier and health professionals regarding testing for HIV, HBV, and HCV.

The aim of the Apidé study (Electronic Application to promote screening among Migrants) is to develop and evaluate an app to assist with screening for HIV, HBV, and HCV among migrants who have low French proficiency. This will include a databank of phrases to offer, explain, and conduct a test for HIV, HBV, and HCV screening in several languages, with a voice version and pictograms, sociocultural adaptation, and adaptation to the patient's level of literacy. It will include a short evaluation questionnaire and items adapted according to the level of understanding. It will help health professionals test migrants who do not speak French and/or have a low level of health literacy. The tool will also include motivational content to improve acceptability, depending on the situation. For example, a frequent reason for migrants' refusal to screen was a lack of risk perception. The app will help overcome this objective using motivational content and explanations of the risks associated with a failure to be screened.

Methods

The study will take place in 3 parts that are detailed in the following paragraphs: development of the conceptual model, development of the app, and evaluation of the app (Figure 1). The approach we use is similar to the agile methodology for developing software, which is centered on users' satisfaction and collaboration and consists of 10 stages: communication (with potential users), requirements gathering (from the demands of users), feasibility study, system analysis (of limitations and impact), software design and coding, testing , integration (of the different modules of the software), implementation (on users' computers), operation and maintenance, and disposition [44]. In our study, the users are primarily health care workers (doctors, nurses, midwives) and other professionals involved in migrants' testing, as they will use the app for themselves and guide migrants to use it.

Figure 1. Overview of the steps in the Apidé project.
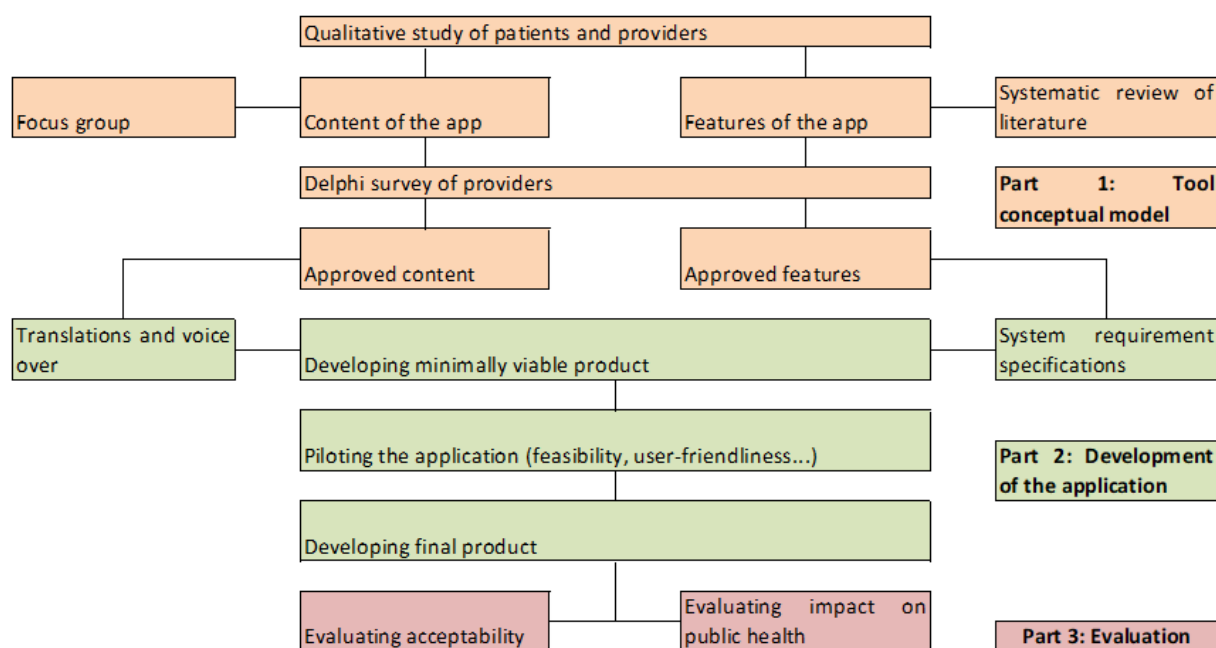
In the first part of the project, we will develop the tool's conceptual model based on a qualitative study of migrants and health care providers, a systematic review of the literature on electronic apps for migrants with a language barrier, and a focus group and modified Delphi survey with health care providers who propose screening tests to migrants. After conducting those different steps, we will have the app conceptual model, as well as language selection and a proposed layout for the app.

In the second part of the project, we will develop the app. The conceptual model will be translated by a service provider with experience in translation with cultural adaptation. All sentences will be voice-recorded in the chosen languages. The app will be developed, followed by a pilot study of the acceptability and usability of the app.

In the third part of the project, we will evaluate the acceptability and efficacy of the tool. The acceptability will be evaluated using the System Usability Scale (SUS) [45]. The efficacy of the tool will be evaluated in an epidemiological study set up in various settings where migrants go for medical consultations: OFII medical check-up, free hospital consultations (Permanences d'accès aux soins de santé [PASS]), and charity outreach that offers rapid tests. The chosen methodology is a stepped wedge randomized trial [46,47].

Qualitative Study

A qualitative study was undertaken to explore language barriers during health care encounters and their effect on communication with health care professionals, specifically in the situation when

a screening test (HIV or hepatitis) is offered. The language barriers were analyzed in relation to the cultural background of the interviewed migrants and their past screening experiences in their country of origin. Participants were all legal migrants who were present at OFII in order to undergo the obligatory routine medical visit needed to validate their residency permit. The study has been completed, and the results have been analyzed [48,49] for publication in a peer-reviewed journal. This study provides feedback from the expected user cohort on the content and features of the application.

Systematic Review of the Literature

Developing the app requires an in-depth knowledge of existing electronic tools facilitating communication between migrants and health professionals, the methods used to develop them, and available data on their acceptability and efficacy, including evidence on whether specific features or options improve the efficacy or acceptability. The objective of our systematic review of the literature is to have a comprehensive overview of electronic tools designed to help health care providers communicate with migrants who have low proficiency in the language of the country of destination or a low level of health literacy and critically synthesize evidence about the acceptability and efficacy of those electronic tools. We have written a protocol prior to starting the search, established inclusion and exclusion criteria, and evaluated the quality of selected articles. The database search, study selection, and data extraction were independently performed by 2 researchers, and the results were reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standard for reporting systematic reviews. This systematic review will help create an overview of existing apps helping to improve health communication with migrants, as well as identify the best features of the app for improving screening.

Focus Group and Delphi Survey

In order to generate a list of items and phrases to be translated and added to the electronic tool, we will use the following steps. First, we will create a list of suggested sentences used to offer, explain, and carry out a screening test. It will be informed by current guidelines on testing [50-54]. This list will be enriched by findings from the qualitative study. Then, we will conduct focus groups with health professionals. Focus groups are group interviews that include a moderator and an observer, where questions and items are being discussed in an interactive way. We will organize 2-3 focus groups of 20 individuals who have experience or expertise in testing migrants for HIV, HBV, and HCV. Unlike the qualitative study, which discussed general themes about communication with migrants with a language barrier, the focus groups will specifically discuss the text suggested by the literature to be used in the app. Health care professionals will provide suggestions for adaptation to a low level of literacy and adaptation to different cultures. Once the focus groups have been completed, their results will be used to enrich the initial list. We will also create a separate list of technical features of the app that could be incorporated. This list will be created from findings of the systematic review and will be enriched by findings from the qualitative study. The final list of items to be included in the electronic tool will be selected with a modified Delphi survey. The modified Delphi technique is a structured process that uses a series of questionnaires or "rounds" to gather information. Rounds are held until group consensus is reached [55,56]. The panel of invited participants will include a large panel of health care professionals treating migrants or conducting HIV, HBV, and HCV testing, as well as migrants' community organizations. At the end of this process, we will have a databank of phrases to be included the app.

Preparation of the App

Following those steps, we will have a validated conceptual model in the form of a pilot in French, with the content and features of the app approved (ie, a minimally viable product).

The pilot's items will be translated by a service provider with experience in translation with cultural adaptation. The choice of the languages to include in the app will be determined in the Delphi survey previously described.

Voice recordings in languages will be produced. Then, a pilot version of the electronic tool will be developed. Development of the app will be guided by system requirement specifications (SRS) that will be written by our team.

Piloting of the App

This first version will be tested in 3 stages: First, the research team will test the first version according to its intended use. The team will test all the languages and audio versions and all different combinations of sentences and different scenarios of use, as well as the technical quality of the app. All feedback, problems, and difficulties will be carefully documented and provided to the app developers.

Second, the revised app will be tested among health professionals outside real-life situations. We will invite a small but diverse sample (5-10 health professionals representing all intended categories of users) to try the app in the presence of the research team. Each session will be audio-recorded; users will be invited to navigate the app and comment aloud on its ease of use, ergonomics, and user-friendliness. All comments will be transcribed, then compiled and sent back to the developer's team for adjustments. This piloting will be performed with the Cognitive Walkthrough approach, which is a method used to evaluate the design of a user interface [57]. It is often used for the development of health care information systems and is recommended for infrequent or inexperienced users [58].

Then, the third version will be tested in real-life situation by health professionals and migrants. A large sample of health professionals will be provided with an electronic tablet or set up to use their own computer, depending on the situation. All participants will receive a demonstration of the app's functioning. Health providers will be invited to use the app during consultations with migrants and then will give specific feedback in the form of cognitive debriefing.

During the second and third steps, we will use cognitive interviews and cognitive debriefing. Cognitive interviewing is traditionally a key technique in uncovering potential problems with survey questionnaires through a process of administering

draft survey questions and then probing how subjects comprehend, recall, decide, and respond to the questions [59]. Although this technique is primarily for questionnaire development, it is also relevant for software usability testing [60]. Cognitive debriefing consists of the use of both verbal probing by the interviewer and think aloud in which the interviewer asks the respondent to verbalize whatever comes to mind as he or she answers the question [61].

Evaluation of the Acceptability

The acceptability of the electronic tool will be evaluated in a survey with the SUS questionnaire in French. The SUS is a simple, 10-item scale giving a global view of subjective assessment of usability. It was constructed from a pool of 50 potential questionnaires [45]. The original SUS instrument is composed of 10 statements that are scored on a 5-point scale of strength of agreement. Final scores for the SUS range from 0 to 100, where higher scores indicate better usability.

The advantages of the SUS compared with other similar instruments are that it is flexible enough to assess a wide range of interface technologies; the survey is relatively quick and easy to use by both study participants and administrators; the survey provides a single score on a scale that is easily understood by the wide range of people (from project managers to computer programmers) who are typically involved in the development of products and services; and the survey is nonproprietary, making it a cost-effective tool [62]. Given the diversity of potential users of the app, a large sample of potential users is necessary to evaluate its acceptability. Nielsen and Molich [63] recommend a maximum of 30 users; therefore, we aim to have a sample of 30 participants for this study. The participants will be the future users of the app; therefore, the sample of participants will consist of health professionals (doctors, nurse, midwives), volunteers, and other health care workers involved in the screening of migrants.

Evaluation of the Efficacy

Justification of Analysis

The study design for evaluating the tool will be a stepped wedge, randomized controlled trial. In this design, an intervention is launched sequentially to clusters over a number of time periods. This design is characterized by the fact that clusters are randomized for the time at which the cluster will switch from the control condition to the intervention condition. Stepped wedge designs incorporate data collection at each point (step) where a new group receives the intervention [46]. The period with no intervention is used as the control, which allows the study to take into account independent variables that might affect screening rate (such as migration changes or behavior changes brought on by the COVID-19 pandemic). This pragmatic design enables evaluations of how interventions would work in a real-world setting with limited exclusion criteria [64]. The other reason for choosing a stepped wedge cluster is ethics; it could be unethical or politically controversial to withhold an intervention that is deemed more effective than harmful to a control cluster [47]. The stepped wedge methodology is often used in public health research projects, especially in the field of HIV [47].

Setting

The study will be carried out in 16 centers taking care of and treating migrants, including the provision of screening tests: immigration centers (OFII), hospital consultations specialized for underserved persons (PASS), nonprofit organizations offering rapid tests to migrants (not exclusively), ambulatory health care professionals (general practitioners, gynecologists, midwives) with large migrant patient populations. Different regions of France will be represented.

Inclusion and Exclusion Criteria

For participating centers, the inclusion criteria are as follows. For the types of settings, OFII centers having participated in the STRADA study, PASS hospital services, medical doctors or midwives, and organizations accredited to conduct HIV and hepatitis B and C rapid tests will be used. Regarding the level of experience of the centers, we will require that they be consulting with a significant number of migrants (≥500 the previous year), experienced in offering those screening tests to migrants, and experienced in orienting patients with a positive result to an appropriate hospital service and in orienting patients to other support services if needed. Centers must also have the following resources and organization: have sufficient resources to get a phone interpreter or solution in case of a positive result and sufficient privacy to conduct a test with the assistance of an audio app.

For individual participants (migrants), the inclusion criteria are migrant status (born outside of France), over 18 years of age, having a low level of proficiency in French (not able to follow the consultation alone), not speaking another language in common with the health professional, and fluently speaking a language available in the app. The exclusion criteria are being French, speaking French, or not able to understand any of the languages available in the tool.

Intervention and Control

The control period will correspond to the typical processes of these centers for screening migrants (use of phone or in-person interpreters, informal interpreters, or not offering screening tests to migrants because of the language barrier). The intervention will be the use of the app during consultations with non-French speaking migrants to offer, explain, and carry out the screening test, with the possible help from professional interpreters if necessary.

Outcomes

The primary outcome measured is the percentage of screening tests administered. The secondary outcomes are rate of screening proposals by health professionals or associate workers, acceptance rate by migrants, number of positive cases during screening using this app, and frequency of use of the app.

Sample Size

The overall rate of screening currently carried out as part of the STRADA study in OFII centers is around 45% (average of 2 years, taking into account health professionals not offering a test and migrants refusing when the screening is offered). The primary hypothesis of this study is that the addition of the electronic screening app will increase this rate by 10%, from

45% to 55% (including an increase in the rate of screening offered by health professionals and a decrease in the refusal rate among migrants to whom screening is offered). With an alpha risk of 0.05 and a beta risk of 0.20, the total number of subjects required is 778 (ie, a workforce of 900 participants to be included to take account for missing data). Statistical comparisons will be made at the threshold of $P<.05$.

A moderate improvement was chosen because it would be a realistic but meaningful improvement, whereas a small effect size would be too small for clinical significance. Thus, our sample size will allow for the detection of moderate improvements, with ample data for subgroup analyses as well.

We will do a simple and pragmatic step wedge with 2 groups and 3 steps: first step without intervention, second starting intervention for 1 group (half of the centers), and third all centers with the intervention [65,66]. We plan to have 2 clusters with 450 participants in the OFII centers and 450 participants in the other structures (PASS, associated structures). Power and sensibility fit sample size and step wedge configuration were checked with the design effect method [67,68].

Subgroup analyses will be performed based on several variables (screening structure, level of health literacy, geographic origin of migrant, level of education, gender, age group) without adjusting the significance threshold.

Enrollment and Data Collection

At the beginning of the study, all participating investigators will have a briefing session about the aims of the study and the enrollment process and instructions. During the control period, the participants will receive a quick daily questionnaire to calculate the number of eligible patients seen in consultation and the number of patients to whom a screening test is offered and accepted (see Multimedia Appendix 1).

Statistical Analysis

We will use a mixed effects approach that allows computing effects with step wedge [69]. Mixed models will allow us to evaluate effects of treatment and covariates in one model.

Reporting the Results

The results will be published according to the validated reporting guidelines for stepped wedge randomized trials, which is the CONSORT (Consolidated Standards of Reporting Trials) guideline with the specialized extension [70]. A specialized CONSORT extension for the reporting of eHealth clinical trials has been created [71], which we will also use. We will present the 2 reporting guidelines as separate attachments.

Ethical Aspects and Possible Risks

The study will be submitted to the appropriate authorities: Comité de Protection des Personnes d'Ile de France (institutional review board) and Commission Nationale de l'Informatique et des Libertés (data protection agency). And the protocol will be registered in a clinical trials database [72].

As the study will be conducted among providers who are already experienced in conducting HIV and hepatitis B and C tests, the risks related to the testing and referral are minimal.

One potential risk is the introduction of a test to a population of patients who would not have been tested because of language barriers: patients not understanding the results of a test and having either a false sense of security or unjustified panic, receiving a positive result being distressed and the provider not able to comfort them because of language barriers, or receiving a positive result and not fully understanding the need for follow-up appointment.

To prevent and control these potential risks, we will only include centers that have sufficient resources to call for a phone interpretation service in case of a positive result or difficult communication.

Other risks specific to the use of an app to aid the communication around testing relate to confidentiality and data security. For example, there could be a lack of confidentiality if the audio version is played aloud and other people can hear from an adjacent room. It should be noted that this risk already exists for other consultations where health care professionals and migrants have a language barrier and use a phone interpreter service on a loudspeaker. There could also be a lack of data confidentiality if the sentences related to the results of the tests are recorded during the app session.

To prevent and control this risk, investigators conducting the study will be instructed to only use the app on a fixed computer or tablet securely kept (locked in a secure building) with a user password. During the development of the app, we will ensure that data security concerns are emphasized in the SRS. Sessions will be erased after a short period of time.

Results

The study has received preliminary financing from the Agence Nationale de la Recherche contre le SIDA et les hépatites virales (French Agency for Research against AIDS and viral Hepatitis [ANRS]), followed by 1 year of funding from the Office Français de l'Immigration et Intégration (French agency for migration and integration [OFII]) and then by 3-year funding, including doctoral funding from ANRS. Further funding has been requested from private sponsors and Région Ile-de-France.

At the time of publication of this protocol, the initial qualitative study and systematic literature review have been completed. The study has been completed, and the results have been analyzed [48,49,73] for publication in a peer-reviewed journal. For the qualitative study, we interviewed 33 migrants undergoing a medical check-up at OFII. Migrants reported that difficult communication with a French doctor resulted in lack of confidence and lower compliance with treatment. Migrants with a French-speaking partner were either sidelined during the medical visits, being completely dependent on translation, or their partners helped them in learning new words needed for the medical visits. For migrants who preferred translation, the preference between physically present interpreters versus interpretation by phone or the use of applications was influenced by mainly 4 factors: perceived quality of translation (interviewees were divided, with some perceiving a human interpreter with knowledge of medical jargon most accurate and

others trusting the application more), trust, intimacy, and empathy.

For the systematic review, we collected general information about the app, information about health literacy and cultural adaptation, information about the development of the app, evidence about the app's acceptability and efficacy, and information about the use of apps. We included 61 articles presenting a total of 48 applications. About one-third of the applications (16/48) were designed solely to facilitate the interaction between migrants and a health care provider during a consultation, while the remaining two-thirds (32/48) were designed to promote health among migrants with a language barrier. Overall, the applications had good levels of acceptability, while only half had their efficacy evaluated. In those evaluations, the endpoints used are mostly related to reported behavior change and knowledge improvement, which is common for evaluations of health promotion programs.

Focus groups and Delphi consensus panel for selection of the tool's content are currently underway.

Discussion

Implications of the Study

The project is well underway, with the qualitative study and systematic reviews completed. Their results will be used for the development of the app and the design of our study. The qualitative study has highlighted the necessity to have professional interpreters announce a positive result, preferably who can be reached easily. The qualitative study has also given us clues on how migrants use translation applications that can be useful for the development of our app: For example, the study found a strong desire to learn new medical terms; this possibility will be considered for the development of the app. Thanks to the systematic review, we have critically reviewed existing translation applications and noted the lessons learnt from their development and recommendations. We have compiled specific lists of features of such applications that are associated with an increased acceptability or efficacy. Those features will be suggested as options to include in our app in our Delphi survey.

If the study demonstrates an increase in screening rates and acceptability by migrants, further development may include international deployment, so as to make this app available for other countries and in other languages. Other developments might include expanding the health promotion features of the electronic tool, such as educational videos and a text messaging follow-up service for migrants who did not wish to undertake the screening immediately but were interested in a screening consultation in the future.

Strengths and Limitations

The strength of this study is that it is conducted by a research team with multidisciplinary skills, including experience in developing patient-reported outcomes (including electronic patient-reported outcomes). The team has extensive experience with working with migrants within the STRADA study [74] and has worked with many professionals working in migrants' health or HIV testing, all of whom are included in the steering committee, scientific committee, or associated committee. This study includes several methods (qualitative, quantitative, systematic literature review) and includes users in the development process.

The COVID-19 pandemic has disturbed the advancement of the study in many ways. The research team, specialized in public health and infectious diseases, has been developing research projects related to the pandemic, with a priority that has taken precedence over other existing research projects, including this study. This focus on COVID-19, as well as the postponement of recruiting new staff due to social distancing and remote working requirements and postponement of the focus groups for the same reasons, has delayed the advancement of the study. However, those short delays do not jeopardize the integrity and ultimately, the completion, of our study. In fact, better screening of infectious diseases is all the more necessary in the era of a pandemic.

Conclusion

This study will develop an electronic screening app to aid migrants who speak little or no French and measure its acceptability and effectiveness in terms of public health. At the end of this project, this app will be able to be distributed to numerous health care workers, including nonprofessionals (such as volunteers), conducting screening with migrant audiences to be used in current practice. If proven effective, the electronic tool will make testing for HIV and hepatitis B and C among migrants more readily available and more widespread and will be an asset in the fight against infectious diseases.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire for the control clusters.
[DOCX File , 15 KB - resprot_v10i5e22239_app1.docx]

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Multimedia Appendix 2
Project peer-review report 1.
[PDF File (Adobe PDF File), 143 KB - resprot_v10i5e22239_app2.pdf]

Multimedia Appendix 3
Project peer-review report 2.
[PDF File (Adobe PDF File), 171 KB - resprot_v10i5e22239_app3.pdf]

Multimedia Appendix 4
Translation of the peer-review reports.
[DOCX File , 32 KB - resprot_v10i5e22239_app4.docx]

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Abbreviations

ANRS: Agence Nationale de la Recherche contre le SIDA et les hépatites virales (French Agency for Research against AIDS and viral Hepatitis)
CONSORT: Consolidated Standards of Reporting Trials
HBV: hepatitis B virus
HCV: hepatitis C virus
OFII: Office Français de l'Immigration et Intégration
PASS: Permanences d'accès aux soins de santé
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SRS: system requirement specifications
STRADA: Stratégie de dépistage de maladies infectieuses (Tuberculose, VIH, VHC, VHB) dans la population des migrants en France (Screening strategies for infectious diseases (Tuberculosis, HIV, Hepatitis C, Hepatitis B) in migrant population in France)
SUS: System Usability Scale

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Protocol

Design and Rationale for the Deep South Interactive Voice Response System–Supported Active Lifestyle Study: Protocol for a Randomized Controlled Trial

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Abstract

Background: The rates of physical inactivity and related cancer incidence and mortality are disproportionately high in the Deep South region in the United States, a rural, medically underserved region with a large African American population compared with the rest of the nation. Given this region's lower rates of literacy and internet access, interactive voice response (IVR) system–automated telephone-based interventions have the potential to help overcome physical activity intervention barriers (literacy, internet access, costs, and transportation) but have yet to be extended to rural, underserved populations, such as in the Deep South. Thus, extensive formative research is being conducted to develop and beta test the Deep South IVR System–Supported Active Lifestyle intervention in preparation for dissemination in rural Alabama counties.

Objective: This paper aims to describe the design and rationale of an ongoing efficacy trial of the Deep South IVR System–Supported Active Lifestyle intervention.

Methods: A two-arm randomized controlled trial will be conducted to compare a 12-month physical activity intervention versus a wait-list control condition in 240 underactive adults from 6 rural Alabama counties. The Deep South IVR System–Supported Active Lifestyle intervention is based on the Social Cognitive Theory and includes IVR-automated physical activity–related phone counseling (daily in months 0-3, twice weekly in months 4-6, and weekly in months 7-12) and support from local rural county coordinators with the University of Alabama O'Neal Comprehensive Cancer Center Community Outreach and Engagement Office. The primary outcome is weekly minutes of moderate- to vigorous-intensity physical activity (7-day physical activity recall; accelerometry) at baseline, 6 months, 12 months, and 18 months. Rural Active Living Assessments will be conducted in each rural county to assess walkability, assess recreational amenities, and inform future environment and policy efforts.

Results: This study was funded in March 2019 and approved by the institutional review board of the University of Alabama at Birmingham in April 2019. As of February 2020, start-up activities (hiring and training staff and purchasing supplies) were completed. Study recruitment and assessments began in September 2020 and are ongoing. As of February 2021, a total of 43 participants have been enrolled in Dallas County, 42 in Sumter County, and 51 in Greene County.

Conclusions: IVR-supported phone counseling has great potential for addressing physical activity barriers (eg, culture, literacy, cost, or transportation) and reducing related rural health disparities in this region.

Trial Registration: ClinicalTrials.gov NCT03903874; https://clinicaltrials.gov/ct2/show/NCT03903874.

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KEYWORDS

exercise; health disparities; interactive voice response system; physical activity; rural health; telehealth

Introduction

Background

Despite the health benefits associated with physical activity, the levels of engagement in regular physical activity remain low in the United States, especially in the Deep South (ie, Alabama, Georgia, Louisiana, Mississippi, and South Carolina) [1]. Furthermore, the rates of related cancer incidence and mortality are generally higher in this underserved (rural, mostly minority) region [2] compared with the national average. Physical activity interventions are needed to address barriers related to transportation, finances, culture, and low literacy and education in the Deep South [3].

Telephone-based strategies do not require frequent clinic visits [4], literacy, or expensive technology and have led to substantial increases in physical activity in past studies [5]. However, there has been a paucity of research in this area among underserved (rural, minority) populations [6-10]. Moreover, most telephone-based interventions to date have involved counseling from health care providers or research staff [4] but can be automated with interactive voice response (IVR) systems for improved reach and reduced cost in resource-strapped rural counties.

In response, our research team developed a tailored, IVR-supported physical activity intervention for cancer risk reduction in the Deep South. The development of the Deep South Interactive Voice Response System–Supported Active Lifestyle (DIAL) intervention was guided by extensive formative research (11 focus groups with African American community health advisors and community members) [11] on physical activity intervention preferences and barriers in our target population. Results from the subsequent pilot randomized controlled trial with 63 participants supported the feasibility and acceptability of the DIAL intervention. At 12 weeks, retention (88.9%) and participant satisfaction (71.4%) were high. Furthermore, intervention participants reported greater increases in moderate-to-vigorous physical activity than control participants from baseline to 12 weeks (median change of 47.5 vs 5 min per week, respectively) and statistically significant improvements in physical activity self-regulation and social support [12]. Pilot trial findings and participant feedback guided intervention refinement (providing more accountability and encouragement) in preparation for scale-up.

Objectives

Given the promise shown in the pilot study, this study involves an amply powered randomized controlled trial (N=240) of the refined DIAL intervention in 6 rural counties in Alabama. To our knowledge, this study is the first to implement an IVR system–supported physical activity intervention in rural, mostly minority populations. The primary aim of this study is to test the efficacy of the DIAL intervention versus a wait-list control. We hypothesize that the participants receiving the DIAL intervention will report significantly greater increases in moderate-to-vigorous physical activity based on the 7-day physical activity recall (PAR) interviews and accelerometers at 6 months compared with participants randomized to a 6-month wait-list control arm.

The exploratory aims are to examine (1) changes in moderate-to-vigorous physical activity at 12 months and 18 months to assess long-term maintenance in the intervention arm and ascertain replicability of intervention effects in the wait-list control arm; (2) intervention effects on physical performance, anthropometrics, and psychosocial variables; (3) cost-effectiveness; (4) potential mediators (Social Cognitive Theory [SCT] constructs directly targeted by the intervention) and moderators (education and neighborhood and environmental features) of treatment efficacy; and (5) potential barriers to or facilitators of widespread implementation of the DIAL intervention in the rural Deep South, a region spreading across central Alabama and Mississippi that is known for both its rich black soil and high population of non-Hispanic Black individuals [13].

Methods

Recruitment and Eligibility Criteria

A total of 240 participants will be recruited from 6 rural Alabama counties (Hale, Choctaw, Greene, Marengo, Dallas, and Sumter) by local rural county coordinators from the University of Alabama (UAB) O'Neal Comprehensive Cancer Center Office of Community Outreach and Engagement (O'Neal CCC COE). The local rural county coordinators are well-respected and trusted individuals who reside in the targeted rural communities and collectively have over 50 years of experience working in their communities, implementing various community outreach and research programs.

The local rural county coordinators received training on study protocols from the DIAL program manager and the O'Neal CCC COE program director and program manager. The training included a comprehensive project overview that covered project goals with an emphasis on the county coordinators' role, participant recruitment, and data collection during assessments. Coordinators were provided with training manuals that included project protocols, assessment tools, and other forms.

Primary forms of recruitment include local newspapers and radio advertisements, study flyers, and word-of-mouth. The trial was approved by the UAB Institutional Review Board (IRB) and registered with ClinicalTrials.gov (NCT03903874). Although IRB approval was obtained for recruitment via social media, this option is yet to be used in this study. Recruitment occurs on a rolling basis, staggered by county. Approximately

40 participants will be recruited from each of the 6 counties over a 30-month period.

Potential participants are screened for eligibility via telephone by the research staff. The inclusion criteria are as follows: (1) ≥18 years of age; (2) inactive (ie, reporting less than 60 min of moderate-to-vigorous physical activity per week); and (3) residing or working in one of the participating counties. Individuals will be excluded on the basis of the following criteria: (1) presence of a medical condition that could make unsupervised physical activity unsafe (ie, history of heart disease, stroke, or orthopedic conditions that limit mobility based on the Physical Activity Readiness Questionnaire [14]); (2) plans to move from the area in the next 18 months; (3) unable to speak or read English; (4) unwilling to be randomized to either the DIAL intervention or wait-list control arm and adhere to the respective protocols; and/or (5) lack of access to a telephone.

Informational Session

Once screened for eligibility, the participants will be scheduled for an information session via Zoom (Zoom Video Communications, Inc). The program manager will provide them with an overview of study protocols, participant expectations, research staff expectations, and informed consent and then schedule baseline assessments.

Baseline Assessments

Baseline assessments occur at convenient local community locations (eg, church halls, local high schools, or county health departments). At this visit, participants will complete anthropometric measurements (ie, height, weight, and waist circumference), surveys, and the Two Minute Step Test (see the *Outcomes* section for further details). Participants will also receive an accelerometer with instructions to wear the device for 7 days and scheduled a 7-day PAR telephone interview. Figure 1 shows the study flow.

Figure 1. Study flow. DIAL: Deep South Interactive Voice Response System–Supported Active Lifestyle. IVR: interactive voice response.
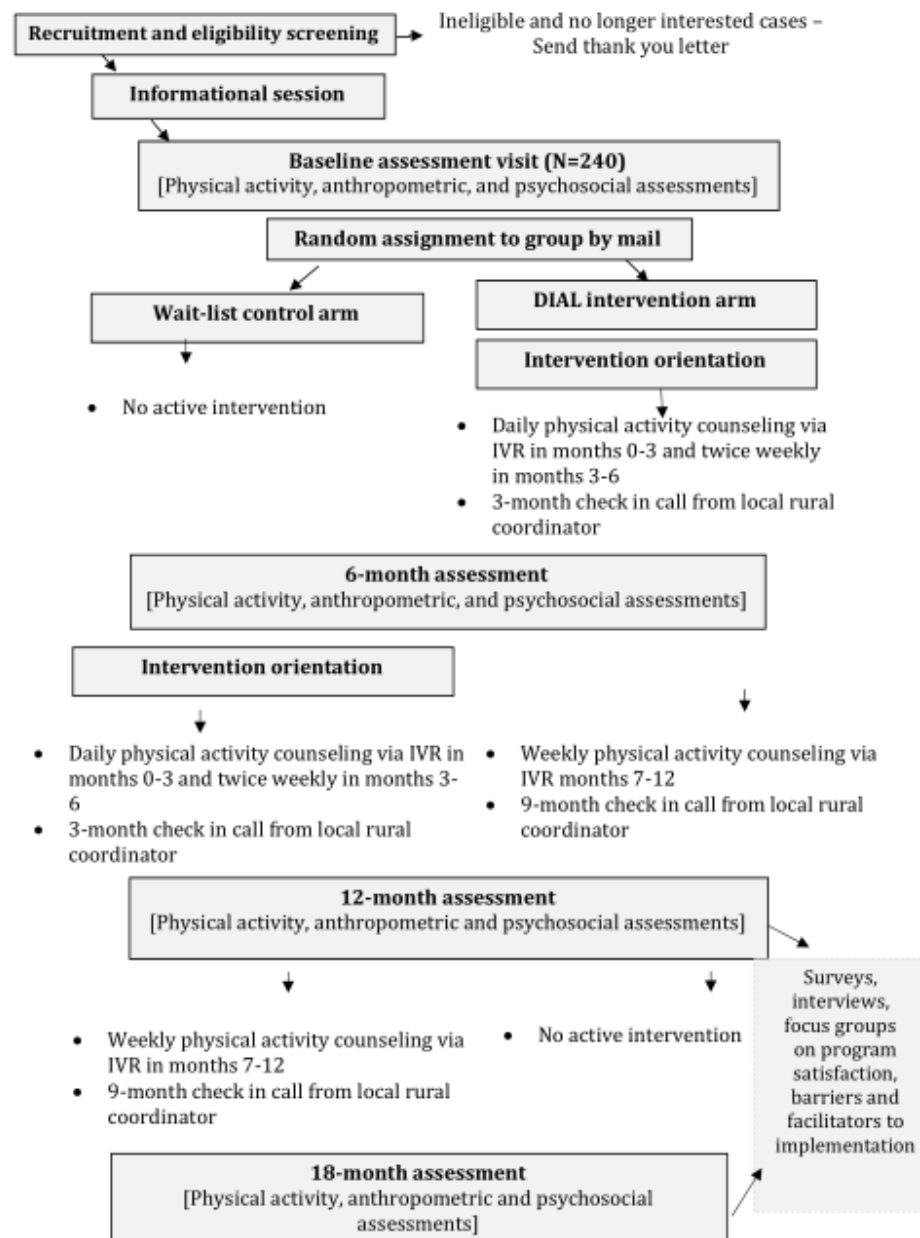
Randomization

Participants will be randomly assigned to the DIAL intervention condition after completing the baseline assessment using a stratified block randomization scheme, stratifying by county, and using a block size of 4. The randomization lists are computer generated using SAS (version 9.4). Participants will receive group assignment information via mail along with a pedometer and/or FitBit Inspire, if assigned to the DIAL intervention arm.

DIAL Orientation

During the intervention orientation, participants will be instructed to wear their physical activity tracker daily during waking hours for the next 12 months and learn how to complete the IVR system calls. Personal identification numbers are provided to confirm the identity and preserve confidentiality. IVR system calls will be scheduled per the participants' preferred time.

The staff encourage participants to gradually increase their physical activity from week to week until reaching the national guidelines of 150 minutes per week [15] of moderate-to-vigorous physical activity with an emphasis on safety and injury prevention (moderate-intensity physical activity, stretching, warming up, and cooling down).

DIAL Intervention

The 12-month DIAL intervention is based on the SCT, which posits that attitudes and beliefs, physical and social environment, and behaviors mutually influence each other [16]. Key SCT constructs (social support, self-efficacy, self-regulation, outcome expectations, and enjoyment) are targeted through the use of study-provided pedometers (Accusplit, AX2790MV), a FitBit Inspire, and individually tailored physical activity counseling calls [12].

The physical activity counseling calls are automated using the Twilio cloud communications platform and Amazon Polly for narration. Participants will complete calls daily in months 0-3, twice weekly in months 4-6, and weekly in months 7-12. There are three types of calls: physical activity tracking, goal setting, and counseling. The tracking calls allow the participant to report the number of steps and minutes of moderate-to-vigorous physical activity for the previous day. Participants set new step goals in weekly goal-setting calls and reflect on their progress. To encourage incremental increases toward 10,000 steps per day, participants will be asked if they are ready for a challenge, and if so, they will be encouraged to increase their step goal by 250 steps per day for that week. The intentionally modest number of steps was selected as it represents approximately an eighth of a mile and can be easily achieved while walking in place for the duration of the 2- to 3-minute IVR system call.

During the monthly IVR system counseling calls, participants will complete 4 brief SCT surveys (physical activity self-efficacy, enjoyment, outcome expectations, and social support) and receive individualized IVR system feedback based on their responses. Tailored algorithms focus on whether generally high or low levels of each SCT construct were described and whether these values represent improvements from the previous report. For example, for lower self-efficacy scores, participants may receive the message, "You do not sound very sure about your ability to exercise, but it's better than last time we spoke. Try squeezing in a 10 minute walk this week. Meeting this small goal will help you feel more sure that you can fit physical activity into your life."

As fresh, evolving IVR system call content will be critical for maintaining participant engagement over 12 months, libraries of rotating message options for greetings, step and moderate-to-vigorous physical activity feedback, goal setting, and SCT counseling were developed. Calls also include new physical activity tips each week on how to get more steps and physical activity benefits (eg, stronger bones and joints, toned muscles, and improved function of the heart, lungs, and other body systems) and addresses barriers (eg, lack of time, lack of support, or negative expectations). Participants will be alerted during the call when new tips are available, for example, "We have a new tip this week to encourage you as you become more active. Check it out at the end of the call!"

Participants will also receive support from their local rural county coordinator, who will call to check in on physical activity motivation and goals at months 3 and 9. Moreover, participants will receive the monthly newsletter, *The Deep South Interactive Voice Response System–Supported Active Lifestyle Intervention Dispatch*, highlighting local physical activity resources (ie, recreational facilities, walking and hiking and biking trails, and playing fields and courts) and opportunities. Also featured in the newsletter are interviews with local rural county coordinators and *selfies* of participants engaging in physical activity in their community.

Treatment Fidelity

The treatment fidelity plan is based on the National Institutes of Health Behavioral Change Consortium framework [17], which will be implemented with checklists, scripted treatment manuals, audio-recordings of participant encounters, and transcripts of sessions (eg, for intervention orientations and 3- and 9-month local rural county coordinator support calls). The staff will carefully monitor IVR system call completion via weekly generated reports and contact and/or re-engage participants who have reported medical events, nonadherence to pedometer use, and/or moderate-to-vigorous physical activity or who missed two or more scheduled calls.

To identify any *glitches* with automated physical activity–related telephone counseling, communicate these issues to programmers, and ensure appropriate feedback is being provided to the participants, 5 investigators and 6 research staff members began quality control for the IVR system regularly (daily in the first 3 months, biweekly in months 4-6, and weekly in months 7-12, similar to the intervention call schedule) in June 2020.

Wait-List Arm (Control Arm)

Participants in the wait-list control arm are encouraged to maintain their usual activity levels until completion of the 6-month assessments and then receive the same 12-month DIAL intervention. During the wait-list period, these participants will receive monthly University of Alabama at Birmingham O'Neal Comprehensive Cancer Center Office of Community Outreach and Engagement (UAB O'Neal CCC COE) newsletters and webinar invitations on cancer-related topics other than physical activity (ie, plant-based diet, healthy grocery list, mental health, developing a self-care routine, and cancer prevention).

Assessments at 6, 12, and 18 Months

At 6, 12, and 18 months, participants will repeat accelerometer protocols, 7-day PAR interviews, anthropometric assessments, Two Minute Step Tests, and psychosocial surveys. Participants will complete additional surveys and exit interviews on program satisfaction at 12 months (for the intervention arm) and 18 months (for the wait-list arm).

Outcomes

The study measures are listed in Table 1. Outcome measures will be conducted at baseline and at the 3-, 6-, 12-, and 18-month assessments.

Table 1. Deep South Interactive Voice Response System–Supported Active Lifestyle study measures.

Outcomes	Baseline	Month 3	Month 6	Month 12	Month 18
Physical activity					
7-day physical activity recall	✓[a]		✓	✓	✓
ActiGraph GT3X accelerometers	✓		✓	✓	✓
Two Minute Step Test	✓		✓	✓	✓
Potential moderators					
Anthropometrics (height, weight, or waist circumference)	✓		✓	✓	✓
Demographics	✓				
Rural Active Living Assessment (environment, walkability, or community programs)	✓				
Potential mediators					
Self-regulation scale	✓	✓	✓	✓	✓
Social support for exercise scale	✓	✓	✓	✓	✓
Outcome expectations scale	✓	✓	✓	✓	✓
Physical activity enjoyment scale	✓	✓	✓	✓	✓
Walking self-efficacy	✓	✓	✓	✓	✓
Cost-effectiveness analysis measures					
Health care use	✓		✓	✓	
EuroQol-5D[b]	✓		✓	✓	
Intervention participation questions	✓		✓	✓	
Other					
Psychosocial measures	✓		✓	✓	✓
Participant satisfaction measure				✓	✓
Stakeholder acceptability survey					✓

[a]Time point of assessment.

[b]EuroQol-5D: EuroQol- 5 Dimension.

Primary Outcomes

The main outcome is minutes per week of moderate- to vigorous-intensity physical activity. The 7-day PAR interview is administered by trained research staff, who will contact participants by telephone and ask about the amount, intensity, and types of physical activities over the past 7 days [18,19]. The 7-day PAR has demonstrated reliability, congruent validity, and internal consistency [20-28]. The instrument is sensitive to moderate changes in physical activity over time [29,30] and has been validated by telephone [22]. Moreover, these self-reported data will provide useful insights regarding the specific types of physical activities occurring in rural counties.

ActiGraph GT3X accelerometers are worn continuously for 7 days during waking (on the nondominant hip) and sleeping (on the nondominant wrist) hours at baseline and at 6, 12, and 18 months. This device measures movement, intensity of physical activity, and sleep efficiency, latency, and number of awakenings. The devices have been validated using heart rate telemetry [31] and total energy expenditure [32] and have been shown to provide valid estimates of sleep [33]. A minimum threshold of 1952 counts per minute [32,34] will be used for moderate- to vigorous-intensity physical activity with an epoch of 30 seconds. The minimum valid wear time has been set at 4 days of at least 600 minutes of wear. This objectively measured data will be used to corroborate self-reported PAR data.

Secondary Outcomes

The secondary outcomes include physical performance and anthropometrics. Physical performance is assessed with the Two Minute Step Test, in which participants step in place as fast as possible for 2 minutes while lifting the knees to a premeasured height midway between the upper tips of their patella and iliac crest when standing [35]. A score is calculated based on the number of times the right knee meets the marked height, which can be used to estimate the current level of physical function and predict future physical independence [36,37]. Anthropometric measurements include height, weight, and waist circumference. Height will be measured without shoes and with a portable stadiometer (Seca 213). Weight will be measured without shoes and in light clothing with a digital scale (Healthometer, model no: 349KLX) that is zeroed before each measurement. Waist circumference will be measured with a Gulick II tension-controlled tape measure (County Technology, Gary Mills). The tape is positioned around the natural waist,

just above the iliac crest. The measurement is recorded to the nearest 0.1 cm upon exhalation.

Psychosocial factors will also be assessed at baseline and at 6, 12, and 18 months using Patient-Reported Outcome Measurement Information System scales for anxiety, depression, fatigue, and sleep disturbance with previously demonstrated validity and reliability (α=.95, .98, .84, and .83, respectively) [38].

SCT measures will be assessed in person at the 4 assessment visits and by mail at 3 months (for mediation analyses). The measures include the 10-item self-regulation scale (α=.78) [39], 13-item social support for exercise scale (α=.61-.91) [40], 9-item outcome expectations scale (α=.89) [41], 18-item physical activity enjoyment scale with high internal consistency and test-retest reliability [42], 10-item walking self-efficacy scale (α=.82) [43], and the 12-item exercise confidence scale (α=.92) [44].

Secondary measures at baseline, 6 months, and 12 months were included in the cost-effectiveness analyses. We will use a health care utilization survey that captures information on physician and emergency room visits and hospitalizations [45]; the EuroQol-5 Dimension, which estimates utility weights to estimate quality-adjusted life years (QALYs) [46]; and a set of questions to measure time spent and expenses related to participation and time devoted to physical activity [46].

An 18-item measure adapted from similar past studies [47,48] will assess participant satisfaction with the DIAL intervention and request suggestions for program improvement at 12 and 18 months. Finally, a similar survey will be administered at 18 months to the rural county coordinators to examine stakeholders' perspectives on acceptability, barriers to and facilitators of implementation, and sustainability of the DIAL intervention in the Deep South.

The research staff will complete the three components of the Rural Active Living Assessment (RALA) for each county at baseline. This assessment consists of the street segment assessment to evaluate factors such as walkability, safety features, and terrain of individual, specific street segments; the town-wide assessment that examines community characteristics such as population, total area, and the presence of recreation activities; and finally, the program and policy assessment, which identifies community programs and policies that support physical activity [49]. These tools have been successfully used in similar past studies conducted by our research team in the Deep South [11].

Protocol Changes in Response to Feedback From Community Partners

Modifications to assessment and intervention protocols are often necessary to meet the needs of study populations and occur frequently in response to concerns and guidance from community stakeholders in this study. For example, the originally proposed 12-month wait-list control phase was reduced to 6 months due to stakeholder concerns (UAB O'Neal CCC COE, local rural county coordinators, etc) regarding withholding active intervention for so long and how this might affect participant and community engagement. In addition, we

added 3-month SCT surveys to address stakeholders' concerns and still be able to comment on potential mediators. Participant frustrations with malfunctioning pedometers and enthusiasm and desire for wristbands resulted in offering FitBit options for tracking steps.

As for assessment protocols, several instruments were cut to reduce participant burden. More specifically, short-form versions of social support and exercise and walking self-efficacy were adopted [50,51]. The Patient-Reported Outcome Measurement Information System subscales on anxiety, depression, and fatigue and exercise confidence scales were eliminated. Moreover, incentives for completing assessments were increased from the proposed amount of US $25-US $50 based on UAB O'Neal CCC COE feedback on the time spent completing surveys and incentive amounts from past studies.

Safety Precautions Related to COVID-19

In response to COVID-19, intervention and assessment protocols were substantially modified for participant and research team safety (and adherence to UAB IRB requirements). The staff are now relying solely on socially distanced recruitment strategies such as posting flyers, newspaper advertisements, emails, text messages, and telephone calls. Rather than attending in-person group information sessions to learn more about the study and complete informed consent, participants initially received a protocol overview by telephone with UAB O'Neal CCC COE county coordinators. However, these brief study descriptions were perhaps less detailed than the longer in-person information sessions and resulted in some participant confusion regarding study protocols and expectations. Thus, a compromise was reached by holding full study information sessions via Zoom (Zoom Video Communications, Inc). To further reduce face-to-face time, we will conduct the informed consent process on the web before the baseline assessments.

During the appointment reminder call and upon arriving for the baseline assessments, participants will complete COVID-19 symptoms and exposure screenings, including two survey items (ie, "Have you had any of the following symptoms in the last 14 days?" "To your knowledge, have you been in close contact with anyone diagnosed with COVID-19 in the last 14 days?"). The temperature of the participants is measured using a contact-free thermometer. If a participant has a temperature of 100.4°F or higher and/or answers *yes* to screening items, their assessment appointment will be postponed, and the participant will be asked to contact their primary care physician.

Baseline assessments still occur in convenient community locations but with social distancing and appropriate personal protective equipment. Participants will be offered masks (if needed) and hand sanitizers. Research staff will wear personal protective equipment and wipe down all surfaces and equipment with antiseptic wipes between each participant contact. Assessment stations (for surveys, anthropometric measurements, accelerometers, and scheduling) will be spaced at least 6 feet apart. Participant appointments will be carefully scheduled throughout the day to avoid crowding. Clear plastic dividers will be set up as needed at assessment stations. To reduce face-to-face assessment time, the 7-day PAR interviews will be

conducted by telephone using previously validated protocols [21].

To further reduce exposure, randomization to the DIAL intervention arm and IVR call orientation are no longer provided at local community locations but only by mail and videoconferencing. Participants will receive COVID-19 physical activity safety precaution handouts in their intervention orientation packets, which will encourage them to wear a face mask and distance themselves from others while being physically active. Moreover, we have edited any IVR system counseling messages that might be unsafe or unwise during a pandemic.

County coordinators initially planned to organize community walking groups for interested participants but are now pursuing distance-based approaches to build community support for physical activity. For example, participants are encouraged to text *selfies* of themselves being active in their community to their local rural county coordinators for a prize (ie, resistance bands, water bottles, or sweatbands) and the chance to have their selfie featured in the monthly newsletter. The wait-list control group was originally scheduled to attend in-person monthly *lunch-and-learns* with the county coordinators, but this cancer control education is now provided virtually through webinars.

RALA protocols have also been modified in response to the pandemic. The driver and observer no longer sit adjacent to another in the vehicle. These assessments are now completed in a three-row van or sports utility vehicle to allow both individuals to be positioned at least 6 feet apart for social distancing. We have also reduced the number of designated street segments to decrease the amount of time spent in the vehicle. Moreover, research team members and local rural county coordinators will carefully track the COVID-19–related changes in the available physical activity resources and programming (ie, facility hours and physical activity classes) in these rural counties while conducting RALAs and add two items on COVID-19–related physical activity changes and barriers to the 3-month surveys.

Data Management

Data were entered into databases created using the Research Electronic Data Capture System. Relational logic checks, such as out-of-range values and internal inconsistencies, will be implemented at the time of initial data entry and will then be assessed periodically to minimize and detect data entry errors. Statistical progress reports will be generated to include the following: (1) the total number of participants screened, consented, and randomized on study entry and completing each follow-up assessment and (2) a summary of demographic and baseline characteristics for comparability between randomization arms.

Sample Size Justification

Results from our previous UAB pilot study indicated an increase in minutes of moderate-to-vigorous physical activity among the DIAL intervention group compared with the control group. The SD of this measure was 90 minutes. Assuming a mean difference of 35 (SD 90) minutes in moderate-to-vigorous physical activity between the two groups from baseline to 6 months, a two-tailed two-group t test, and a significance level of 5%, we will have 80% power to detect this difference (with an effect size of 0.388) with 105 participants per arm (210 for the study). Assuming a mean change of 35 (SD 90) minutes in moderate-to-vigorous physical activity from baseline to 6 months for the intervention group, a two-tailed paired t test, and a significance level of 5%, we will have 80% power to detect this within-group change (with an effect size of 0.276) with 105 participants. Allowing for 15% attrition, we will recruit 240 participants (120 per arm).

Statistical Analyses

Analyses will be performed on an intent-to-treat basis (ie, participants will be analyzed by the arms to which they were randomized). The characteristics of the study populations will be summarized for each study arm using descriptive statistics, such as means and SD for continuous variables and frequencies and proportions for categorical variables. Unadjusted comparisons of baseline characteristics between study arms and those between participants who completed the study and those who dropped out will be performed using the two-group t test for continuous variables and the Pearson chi-square test for categorical variables. Unadjusted within-group changes (from baseline to postintervention) will be assessed using the paired t test.

The primary method of analysis for physical activity, anthropometrics, and psychosocial measures, all of which will be measured at baseline, 6 months, 12 months, and 18 months (as illustrated in Table 1), will be mixed model repeated measures analyses. Other general linear mixed model techniques may also be used. These analyses will allow us to examine changes from baseline to follow-up (within-group changes) and differences between the study groups simultaneously, while also accounting for the group-by-time interaction as well as any covariates and interactions that are of scientific interest. An appropriate covariance matrix (eg, autoregressive or unstructured) will be selected based on the final data. The Tukey-Kramer multiple comparisons test will be used to determine specific pairwise differences for statistically significant main effects. Some of these models will include the stratification variable of county and confounding variables (as covariates) such as the baseline BMI category, age, gender, and education level. Some of the models that include physical activity as the dependent variable will be adjusted for wear time. Study variables that will be analyzed using these techniques include the change in minutes of moderate-to-vigorous physical activity. Pearson correlation analysis will be performed to assess the relationship between self-reported and measured physical activity.

Distributions of the aforementioned continuous variables will be examined for normality using box plots, normal probability plots, and the Kolmogorov-Smirnov test. Variables that are determined to deviate from a normal distribution will be log-transformed before statistical testing. Nonparametric tests (eg, the Wilcoxon rank-sum test and the Wilcoxon signed-rank test) may also be used to analyze nonnormally distributed data. All statistical tests will be two-sided. All analyses will be

performed using SAS, and *P*<.05 will be deemed statistically significant.

Although a large amount of missing data is not expected for any of our study variables, a sensitivity analysis may be performed using alternative methods for handling missing data (such as multiple imputation) to assess the most appropriate approach based on the amount of missing data and effect sizes observed.

We will investigate potential mediators of the intervention effect (*social support*) using a multiple mediation approach in SPSS, in which all potential mediators are tested simultaneously, using a product of the coefficients method [52] with bootstrapped SEs (5000 samples with replacement). The interest is in estimating the path coefficients, effect sizes, and CIs rather than strict hypothesis testing.

Potential moderators and interactions will be assessed as follows. A variable will be considered a moderator if evidence exists of either qualitative or quantitative interaction with the intervention. We will use a similar analytic approach as in the primary aims; models will include the main effects of intervention (DIAL intervention vs control), the potential moderator (eg, education and neighborhood and environmental features), and the interaction between the two. Evidence of moderation exists if the coefficient of the interaction term is statistically different from zero.

Descriptive analyses of quantitative stakeholder acceptability survey items and content analyses of open-ended items from stakeholder acceptability surveys and focus group transcripts will be conducted to inform future efforts toward sustainability and large-scale dissemination in rural counties.

Cost-effectiveness Analysis

If, as hypothesized, the DIAL intervention results in significantly greater increases in moderate-to-vigorous physical activity minutes, we will conduct a within-trial cost-effectiveness analysis [53-57] to determine if the DIAL intervention is cost-effective compared with no active intervention. Perspectives will be those of the health care sector, participants, and society. The time frame will be 6 months. We will estimate the DIAL implementation costs and participants' medical and other costs that may be affected. Effectiveness will be measured by the change in moderate-to-vigorous physical activity minutes and QALY.

Implementation costs will include start-up and ongoing costs necessary to implement the DIAL intervention in other settings and will not include costs of intervention development and research activities (eg, consent process). Start-up costs will include time spent on training by trainers and intervention personnel, materials, space, and other supplies needed. To identify and value the DIAL intervention's ongoing costs, we will develop process maps with intervention staff to identify all key processes (eg, supervision and orienting the participants to the IVR system, preparing, and IVR system tracking and maintenance) and the personnel involved in those processes, and develop a time tracking system to record the time spent in the identified processes. To reduce burden, this system will be used in random weeks by each intervention staff member.

County coordinators will also complete time studies to estimate their time. Over the course of the study, we will select 1 week per month randomly for each intervention staff member. Data will then be annualized and combined with hourly wages and fringe benefits of the personnel to value annual personnel costs per activity. Costs of workbooks, handouts and other materials, phone and IVR system, office space, shipping, and others will be tracked and valued using project records or current market prices. Implementation cost data will be summed overall and by intervention-related categories, for example, IVR tracking and maintenance or feedback reporting. We will calculate the average DIAL intervention cost per participant and per minute moderate-to-vigorous physical activity increase.

The implementation costs of participants will include participation time costs, which will be captured with our surveys at baseline, 6 months, and 12 months. Survey questions will ask participants about the time spent reviewing intervention materials and calling into the IVR system and completing surveys and other intervention activities. These activities will also be tracked using the IVR system user data. Time costs will be valued using hourly wages and fringes based on average age and gender groups [58].

As improving physical activity has effects on well-being and potentially health care use, in the cost-effectiveness analysis, we will estimate medical costs for the DIAL intervention participants and control participants. At baseline, 6 months, and 12 months, we will use a health care utilization survey to capture information on physician and emergency room visits and hospitalizations [45]. To calculate medical costs, we will combine self-reported health care use and associated time and out-of-pocket costs and third-party payer unit costs. We will measure the cost of time spent exercising using the self-report 7-day PAR data and accelerometer data. All time costs will be valued using hourly wages and fringes based on average age and gender groups [58].

Medical and other costs will be added to the implementation costs. Incremental cost-effectiveness ratios (ICERs) will be calculated as the average net cost per minute of moderate-to-vigorous physical activity. In a previous study, physical activity interventions had ICERs of US $0.05-US $0.15 per moderate-to-vigorous physical activity minute [59,60]. We will also calculate the ICERs per QALY gained. QALYs will be calculated over a 6-month follow-up period using utility weights derived from the EuroQol-5D [46]. To determine if the DIAL intervention is cost-effective compared with no active intervention, ICERs will be compared with the commonly used threshold of US $50,000-US $100,000 per QALY [61].

To examine uncertainty, we will sample the replacement costs and outcomes from the two trial arms and calculate the mean costs and outcomes for each bootstrap sample, repeating the procedure 1000 times. Differences in costs and outcomes between the two groups from each sample will be plotted in a cost-effectiveness plane [61,62]. ICERs will be obtained for each sample, and confidence limits around the ICER will be obtained by taking the values at the 5th and 95th percentile of the distribution. Analyses will be repeated to examine the uncertainty around data inputs, such as hourly wages or medical

care costs. In addition, we will construct an acceptability curve by considering the proportion of bootstrap replications for which the ICER falls below the possible thresholds of cost per QALY [63].

Results

Start-up activities (staff hiring and training, ordering supplies, and equipment) have been completed. Although the suspension of nonessential research activities at UAB in March 2020 due to COVID-19 delayed the start of the clinical trial, this time was used to refine intervention and assessment protocols to address new health and safety concerns and further beta test and improve the automated telephone counseling system. Participant recruitment and data collection began in September 2020 and is ongoing. In Dallas County, 43 participants completed baseline assessments at the local Young Men's Christian Association in September 2020, and all participants have been randomized to the study arm. In addition, all 43 Dallas County participants have completed their 3-month surveys. In Sumter County, 42 participants completed baseline assessments at a local community center in November 2020. Moreover, 51 participants completed baseline assessments in Greene County at a local high school in early February 2021. Baseline assessments for the next county (Marengo) are projected to begin mid-March 2021, followed by 3-month surveys in Sumter County, and 6-month assessments in Dallas County.

Discussion

Principal Findings

This study will test the efficacy of the DIAL intervention versus a wait-list control condition for increasing physical activity in the Deep South region of the United States, an area with high rates of physical inactivity and related cancer disparities. To our knowledge, this is the first study to implement an IVR system–supported physical activity intervention for underserved (minority, rural) populations. Past IVR-based physical activity interventions were conducted in largely White and well-educated [6] populations. Some studies relied on unidirectional IVR system calls (ie, system-initiated) [7,8], whereas others involved bidirectional IVR system calls [6,9] (system and participant initiated), as in this study. Promising findings, for example, increases in physical activity [6,8], increases in muscle strength, improvements in balance [7], and decreases in one-mile walk time [9], bode well for the success of the current efforts. Past physical activity–related IVR system–based studies [6-9] were grounded in evidence-based behavioral science theory (ie, SCT and/or Transtheoretical Model) and were found to be effective for increasing physical activity. Some past studies involved a short intervention duration (ie, 12 weeks) [8,9]. Studies conducted over longer periods (ie, 12 months) found relative maintenance of physical activity over the course of the intervention [6,7]. This study will extend this line of research to an at-risk sample of rural, mostly minority adults in the Deep South and extend the follow-up to 18 months.

As for limitations, at 12 months, we will not be able to compare the DIAL intervention arm to a true control arm. As previously mentioned, a 12-month wait-list was proposed but stakeholders felt that the 12-month waiting period was too long and could consequently result in a lack of interest in the study, reduced engagement, and/or drop out among wait-list control participants. Finally, we had to reduce our survey battery and used short-form versions in response to concerns regarding participant burden. Despite the established validity of these measures, using the short versions could result in potentially less validation through assessments of these psychosocial constructs.

The strengths of the ongoing study include the randomized controlled design, hybrid (ie, efficacy combined with implementation outcomes), multilevel intervention, evidence-based theoretical framework, collection of built environment data, and assessment of barriers to and facilitators of future broader dissemination and implementation of the DIAL program with rural county coordinators and UAB O'Neal CCC COE. Another key strength is the use of high-reach, low-cost, technology-supported strategies for addressing rural health disparities. Tracking intervention costs will allow us to comment further on the cost-effectiveness of this approach. We will assess physical activity objectively using accelerometers as opposed to relying solely on subjective, self-reported data, unlike previous studies [6,8,9]. Other areas in which this work moves the field forward include (1) assessing long-term outcomes (12-18 months) and (2) determining the effectiveness and convenience of scheduled calls made by the out-DIAL program (as opposed to solely participant-initiated calls).

Conclusions and Clinical Implications

The findings from this study will help establish the efficacy of IVR system–supported physical activity promotion strategies for underserved rural regions. Moreover, these findings have implications for health care providers and public health practice for physical activity promotion when barriers such as distance, transportation, and lack of staff hinder face-to-face visits and interaction. Future directions include (1) working with stakeholders to address identified barriers to implementation and sustainability in rural counties, (2) pursuing further large-scale dissemination of the DIAL intervention, and (3) addressing built environment concerns in the rural communities through policy advocacy and implementation, based on RALA findings.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review by the Center for Scientific Review Special Emphasis Panel.
[[DOCX File , 28 KB](#) - [resprot_v10i5e29245_app1.docx](#)]

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Abbreviations

DIAL: Deep South Interactive Voice Response System–Supported Active Lifestyle
ICER: incremental cost-effectiveness ratio
IRB: Institutional Review Board
IVR: interactive voice response
PAR: physical activity recall
QALY: quality-adjusted life year
RALA: Rural Active Living Assessment
SCT: Social Cognitive Theory

UAB O'Neal CCC COE: University of Alabama at Birmingham O'Neal Comprehensive Cancer Center Office of Community Outreach and Engagement

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<u>Protocol</u>

Effectiveness of an Integrated Care Package for Refugee Mothers and Children: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Thousands of Rohingya refugee mothers at the world's largest refugee camp located in Bangladesh are at risk of poor mental health. Accordingly, their children are also vulnerable to delayed cognitive and physical development.

Objective: The aim of this study is to evaluate the effectiveness of an integrated care package in reducing the prevalence of developmental delays among children aged 1 year and improving their mothers' mental health status.

Methods: This is a parallel, two-arm, single-blind, cluster randomized controlled trial (cRCT). A total of 704 mother-child dyads residing at the Kutupalong refugee camp in Cox's Bazar, Bangladesh, will be recruited from 22 clusters with 32 mother-child dyads per cluster. In the intervention arm, an integrated early childhood development and maternal mental health package will be delivered every quarter to mothers of newborns by trained community health workers until the child is 1 year old. Our primary outcome is a reduction in the prevalence of two or more childhood developmental delays of infants aged 1 year compared to the usual treatment. The secondary outcomes include reduced stunting among children and the prevalence of maternal depression. We will also assess the cost-effectiveness of the integrated intervention, and will further explore the intervention's acceptability and feasibility.

Results: At the time of submission, the study was at the stage of endpoint assessment. The data analysis started in December 2020, and the results are expected to be published after the first quarter of 2021.

Conclusions: This study will address the burden of childhood developmental delays and poor maternal mental health in a low-resource setting. If proven effective, the delivery of the intervention through community health workers will ensure the proposed intervention's sustainability.

Trial Registration: ISRCTN Registry ISRCTN10892553; https://www.isrctn.com/ISRCTN10892553

International Registered Report Identifier (IRRID): DERR1-10.2196/25047

Introduction

Rohingya refugees settled in Bangladesh are one of the largest groups of refugees in the world [1]. Cumulatively, by 2019, approximately 911,566 Rohingya refugees settled in both refugee camps designated by the government as Forcibly Displaced Myanmar Nationals [2]. Among the camp residents, 52% are women, 23% of whom are within reproductive age [3].

These refugees residing in the camps live in drastic situations and suffer from hunger, poverty, lack of safety, and appropriate access to health services [3]. The mental health status of Rohingya refugee women has been reported to be poor, which could be due to prolonged exposure to violence, trauma, and stress of living under terrible circumstances [4]. Maternal mental health is a crucial factor in ensuring healthy child development [5]. However, women who have experienced a traumatic event in their lives, as is the case for refugees, are at higher risk of postpartum depression, which can impact the growth and nutrition [6] and development of their child [7], as childhood development is mediated by mothers' responsive feeding and caregiving skills. Moreover, prolonged exposure to psychosocial risks such as maternal depression, violence, and lack of stimulation can profoundly affect children's health and cognitive development under the age of 2 years [8]. Studies have shown that at least 2% of the total refugees who are children (approximately 17,200) aged less than 1 year [9] are at risk of delayed development at the refugee camps.

Health care barriers faced by refugees continue to increase the risk of delayed child development and poor mental health for women [10]. Only 10 hospitals currently serve refugee settlements with an allocation ratio of 1 per 130,000 people. The health care systems are overburdened, short-staffed, and lack the necessary resources and infrastructure to provide adequate care, and have been reported to show significant gaps in treatment available for mental health and child development care. These health care challenges indicate the need to evaluate a service delivery model for early child development that will help support the health care providers with effective, scalable, and cost-effective alternatives to promote the child development and maternal mental health of refugees [11]. Integrated childhood development care within maternal, neonatal, and child health services has already proven to be effective in preventing developmental delays for children 2 years of age in a similar context [12,13].

To address the challenges highlighted above, this study has the objectives to: (1) evaluate the effectiveness of an integrated care package in reducing the prevalence of two or more developmental delays among infants aged 1 year and improving childhood stunting compared to the usual treatment, (2) evaluate the effectiveness of the integrated care package in reducing maternal depression, (3) explore the cost-effectiveness of the integrated care package in reducing childhood developmental delays, and (4) perform a mixed method process evaluation study to explore the acceptability and feasibility of the intervention for both the providers and participants.

Methods

Study Design, Settings, and Participants

We will use a parallel arm, single-blind, cluster randomized controlled trial (cRCT) design [14] to evaluate the integrated and contextualized package's effectiveness in reducing childhood developmental delays compared to the usual treatment.

The study will be performed in the Kutapalong Rohingya refugee camp located in Cox's Bazar, Bangladesh, selected

based on its size and distance from the district city and ease of communication. The Kutupalong refugee settlement is a cluster of 20 camps, most of which are adjacent to each other. Each camp has definite boundaries and segments called "blocks." Two blocks are combined to form a cluster for randomization in this study.

The research participants will be 704 mother-child dyads recruited from the 22 clusters in the Kutupalong refugee camp. The inclusion criteria for mother-child pairs are that the child should be less than or equal to 6 weeks old, live with their biological mother, had a gestational period of at least 36 weeks, and weighed at least 2.5 kilograms at birth. Children with congenital abnormalities and mothers that have to move out of the area during the study period will be excluded from the trial. Participation of mother-child dyads in the study will be required for 12 months.

Procedures

Randomization and Masking

To minimize the risk of contamination between research participants, the randomization unit will be a cluster comprising two blocks. Blocks are geographical areas with defined boundaries in refugee camps. A sampling frame of eligible blocks within camps in the study site will be drawn before randomization using the population data and live birth record rates. Eligible clusters will be randomized before the recruitment of research participants from each cluster. The clusters taking part in the study will be randomized to the intervention or control arm by an independent statistician on a 1:1 allocation ratio. SAS PROC PLAN will be used to generate the randomization sequence code.

Given the nature of the intervention, it will be impossible to blind participants to the treatment allocation status. However, the assessment team, principal investigators, and the trial statistician will be blind to clusters' allocation status.

Sample Size Calculations

For a two-sided hypothesis test with 22 clusters randomized at a 1:1 allocation ratio, and assuming an effect size of 0.35 with outcome proportions ranging from 34% to 20% for child development and from 30% to 15% for maternal depression, with 80% power, .05 significance, an intracluster correlation coefficient of 0.12, and accounting for 10% attrition, we will need 704 mother-child dyads (ie, 352 in each group), with 32 participants from each cluster on average. Findings from evidence synthesis indicate that early child development interventions usually yield small effect sizes [15], ranging from 0.2 to 0.4, per the Cohen criteria for effect sizes [16].

Package of Care in Intervention and Control Arms

The care package will be delivered by the community health workers (CHWs) identified from the selected clusters. CHWs having at least 10 years of formal education and willing to contribute to the community will be preferred for collecting data and delivering the intervention.

For standardization of research results, the control arm will be strengthened by providing a 2-day training to CHWs on

recruitment of the mother-child dyads, administration of outcome measures, record-keeping, log maintenance, compliance, and communication. They will also be trained on taking anthropometric measurements to record the children's height, weight, and mid-upper arm circumference (MUAC) every quarter. These inputs will be the same for the control and intervention arms.

In addition to the procedures mentioned above, CHWs in the intervention arm will be provided an additional 2 days of training on delivering the intervention to mothers. They will be trained on using necessary counseling skills while interacting with the mothers, such as empathy, rapport-building, trust, sympathy, privacy, mindfulness, and suggestion. They will also learn how to deliver counseling sessions to participants using a pictorial training flipbook with educative messages.

The integrated care package delivered in the intervention arm has been adapted and contextualized in consultation with international early childhood development and mental health experts. A logic model describing the intervention mechanism is presented in Figure 1.

Figure 1. Logic model for intervention mechanism. CHW: community health worker; ECD: early childhood development; ASQ-3: Ages and Stages Questionnaire third edition; PHQ-9: Patient Health Questionnaire-9.
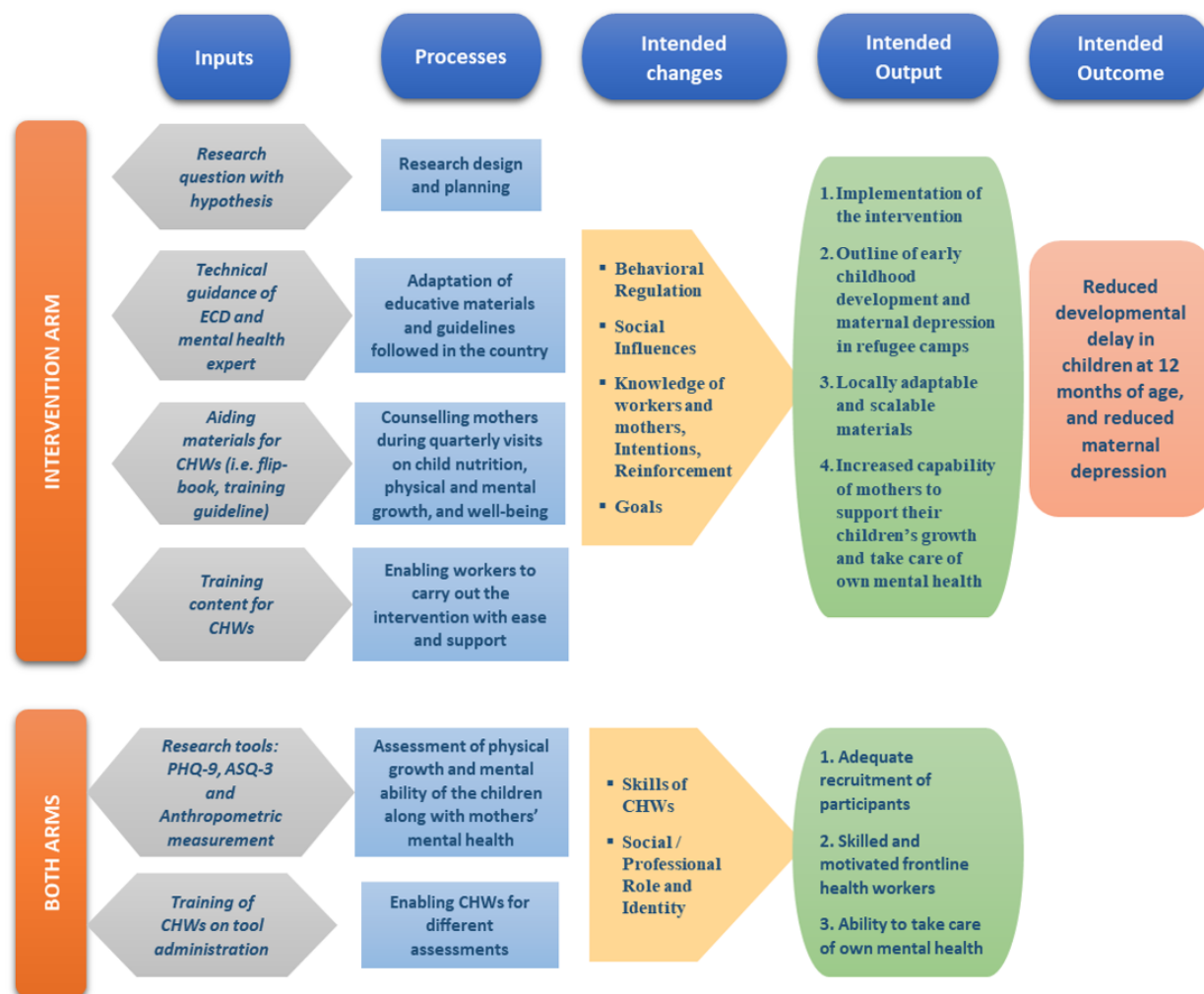
A total of four counseling sessions will be delivered to mother-child dyads by CHWs in the intervention arm to promote early child development and maternal mental health. The counseling sessions will focus on the child's cognitive and physical development, and the mother's mental health based on a few key messages (see Table 1). The counseling contents are developed in consultation with technical experts, supported by a pictorial flipbook that has been modified according to the local context and translated into Burmese to be consistent in delivering the messages. The flipbook pictures are self-explanatory, and the CHWs will explain each of the pictures regardless of the mother's ability to read the text of the flipbook. Each session will take at least 10-15 minutes.

Table 1. Key counseling messages and their delivery time for the intervention arm according to child age.

Theme	Key messages to the mother
First quarter: 0-6 weeks old	
Nutrition	Frequent and exclusive breastfeeding, avoiding intake of other food items, and timely immunization are essential to the child's health
Mental ability	Ensure your presence and attention toward the child by caressing, talking, and looking at them with affection and a smile
Physical ability	To improve the child's physical ability, encourage the movement of their body parts
Mother's health	Eating full meals thrice a day, using iodized salt, and taking rest are essential to the mother and child's health
Second quarter: 3 months old	
Mental ability	Play with the child and make them aware of different parts of the face, sounds, and colors
Physical ability	Increase the movement of different body parts of the child for the development of their physical health
Third quarter: 6 months old	
Nutrition	Roti, rice, curry, and other food items at home (eg, kheer, mashed fruits) are important components of a child's soft food
Diet	After cooking properly with necessary ingredients, smash them and prepare soft food for your child
Protecting health	Clean/wash utensils, regularly wash your hands, and cover food to prevent the child from becoming ill
Mental ability	Encourage the child to pronounce words, identify facial parts, be with other children of the same age group, and find hidden items
Physical ability	Encourage the child to use different body parts for improved physical ability
Fourth quarter: 9 months old	
Mental ability	Encourage the child to participate in daily activities/identify items/follow instructions/find hidden items
Physical ability	Encourage the child to use different body parts for improved physical ability
Maternal mental health	Make a routine to pray, share your emotions with a trustworthy person, and make time for yourself and your mental well-being

Data Collection and Outcomes

Our primary outcome is the reduction in the prevalence of two or more childhood developmental delays of infants aged 1 year compared to the usual treatment, which will be measured by the Ages and Stages Questionnaire (ASQ) 3rd edition [17]. The ASQ is a brief, valid, and reliable measure of childhood development that is widely used to assess childhood developmental difficulties [18]. The ASQ has also been widely used in lower-middle-income countries and has been reported to be culturally valid [19,20]. It has 30 items and consists of 5 subscales to measure communication skills, fine motor, gross motor, problem-solving, and personal-social skills.

Secondary outcomes include stunting and maternal depression. Children's anthropometric data on height, weight, and MUAC will be collected as part of the delivery process by the CHWs every quarter.

Patient Health Questionnaire-9 (PHQ-9) will be used to measure maternal depression at the endpoint of the study by the trained external assessors. The PHQ-9 has 9 items, which are rated on a 3-point Likert scale of 0 (not at all) to 3 (nearly every day) [21,22].

Project Evaluation

The trial flow is given in Figure 2. The project implementation will be evaluated to understand the scalability and sustainability of the intervention. We will use the following evaluation methods: (1) process evaluation and (2) economic evaluation.

Figure 2. Trial flow. ECD: early childhood development; ASQ-3: Ages and Stages Questionnaire third edition; PHQ-9: Patient Health Questionnaire 9.
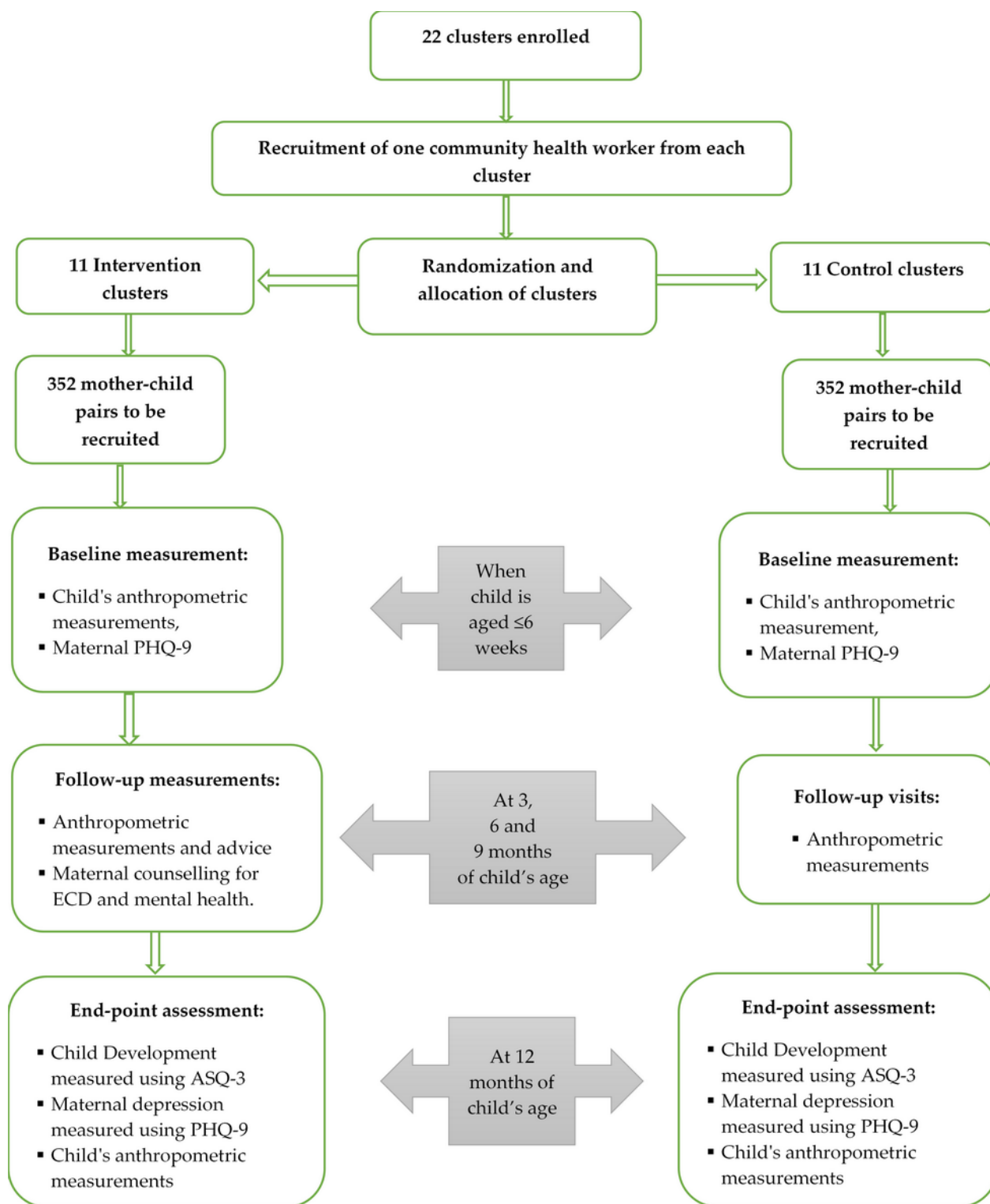
In process evaluation, the trial will be followed by a mixed methods approach following the Medical Research Council guideline [23]. Quantitative data on the trial's implementation will be extracted from the study records. Simultaneously, the qualitative data will be collected via in-depth interviews with participants and providers to explore the intervention's acceptability and feasibility.

An exploratory economic evaluation will be performed to assess the integrated early childhood development and maternal mental health program's cost-effectiveness in refugee camps. Project budgets and expenditure reports will be used to estimate the costs of the intervention, followed by calculating the incremental cost-effectiveness ratio using World Health Organization guidelines [24].

Statistical Analysis

The findings of the study will be reported following CONSORT guidelines for cRCTs [14]. The data will be entered regularly after receiving the paper forms from the field, and then checked for missing data before the next visit scheduled in the clusters, allowing researchers to communicate with the CHWs to address such issues. Furthermore, we will follow the recommended methods for treating missing data per the guidelines of the outcome measures being used. Finally, we will analyze data using intention-to-treat analysis that handles any missing data at the endpoint. Descriptive statistics will be calculated for outcome variables and baseline characteristics of participants according to treatment arm to ensure the comparability of all outcomes across arms. Adjusted analysis and subgroup analysis will be based on covariates determined at baseline.

Data will be analyzed using cluster trials with relatively few clusters in each arm in IBM SPSS Statistics version 23. Crude analysis to estimate cluster-level proportions will be used for categorical outcomes. An independent sample t test to calculate the absolute difference in outcome proportions between the two study arms at the endpoint will be calculated with 95% CIs and significance values. For continuous outcomes, cluster-level outcome values based on the mean outcome scores in each cluster will be calculated, and an independent t test will be used to estimate the treatment effect as the mean difference in the cluster level outcome values between the two arms (control and intervention) at the endpoint, with associated 95% CIs and P values. A two-stage method will be used to adjust for confounding variables using a logistic regression model for individual-level outcome data. We will then calculate the covariate-adjusted difference residuals for each cluster by calculating the mean difference between observed and predicted outcomes. Independent t tests will be used to estimate the covariate-adjusted treatment effect as the risk difference in the cluster-level difference residuals between the two arms, with associated 95% CI and P values. No interim analysis of outcomes is planned.

Ethical Approval

Ethical approval for the study has been obtained from two government bodies in the country: (1) Bangladesh Medical Research Council for research under reference number BMRC/NREC/2016-2019/843 and (2) Refugee, Rehabilitation and Repatriation Commission for project implementation under reference number ShoTraProKa/RHU/ARK Foundation/13/2019/589.

Results

During the submission of this paper, the study was at the stage of endpoint assessment. The analysis of data obtained from the field started in December 2020, and we expect to publish the study results after the first quarter of 2021.

Discussion

The aim of this study is to address the health and economic burden of childhood developmental delays and maternal mental health by delivering a community-based integrated care package in Bangladesh's refugee camps. Intervention delivery by the community health care volunteers will ensure the proposed intervention's sustainability if proven useful in the context. To the authors' knowledge, this study is the first to test an integrated care package for early childhood development and maternal mental health in refugee camps.

The intervention and its components were designed in consultation with international experts, collaborators, and primary health care specialists in Bangladesh. However, some anticipated challenges in implementing the intervention can be anticipated. First, retention of the project's CHWs might be a challenge, as they continuously look for better income opportunities. In that case, repeated search of CHWs may be needed for clusters, and additional refresher training sessions may need to be organized. Second, the language barrier between the field coordinators and the CHWs may result in communication gaps, affecting intervention delivery; a translation expert might be used to address this challenge. Third, mothers of the intervention arm will be more familiar with the child's development activities, creating recall bias during the endpoint assessment of a child's development at 12 months. This issue may be addressed by performing on-site observations. The qualitative aspect of the process will help us to better understand the participants' and providers' challenges during implementation.

The study results will be used to achieve impact by being embedded within the country's health care system. Stakeholders at different levels will be engaged for the maximum impact of maternal mental health on childhood development. Moreover, general practitioners in emergency settings such as those working inside the refugee camps, set up by different national and international organizations, can adapt and integrate the approach with their "First 1000 Days" health interventions for better health outcomes of both mothers and children. Upon success, a similar intervention can be replicated in the host community with the help of the existing health workforce.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Canadian Institute of Health Research.
[PDF File (Adobe PDF File), 85 KB - resprot_v10i5e25047_app1.pdf]

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Abbreviations

ASQ: Ages and Stages Questionnaire
CHW: community health worker
cRCT: cluster randomized control trial
MUAC: mid-upper arm circumference
PHQ-9: Patient Health Questionnaire 9

Protocol

Interrupting Sitting Time in Postmenopausal Women: Protocol for the Rise for Health Randomized Controlled Trial

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Abstract

Background: Many older adults spend the majority of their waking hours sitting, which increases their risk of chronic diseases. Given the challenges that many older adults face when engaging in moderate-to-vigorous physical activity, understanding the health benefits of decreasing sitting time and increasing the number of sit-to-stand transitions is needed to address this growing public health concern.

Objective: The aim of this 3-arm randomized controlled trial is to investigate how changes in sitting time and brief sit-to-stand transitions impact biomarkers of healthy aging and physical, emotional, and cognitive functioning compared with a healthy attention control arm.

Methods: Sedentary and postmenopausal women (N=405) will be recruited and randomly assigned to 1 of the 3 study conditions for 3 months: healthy living attention control (Healthy Living), reduce sitting time (Reduce Sitting), and increase sit-to-stand transitions (Increase Transitions). Assessments conducted at baseline and 3 months included fasting blood draw, blood pressure, anthropometric measurements, physical functioning, cognitive testing, and 7 days of a thigh-worn accelerometer (activPAL) and a hip-worn accelerometer (ActiGraph). Blood-based biomarkers of healthy aging included those associated with glycemic control (glycated hemoglobin, fasting plasma insulin and glucose, and homeostatic model assessment of insulin resistance).

Results: Recruitment began in May 2018. The intervention is ongoing, with data collection expected to continue through the end of 2022.

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Conclusions: The Rise for Health study is designed to test whether 2 different approaches to interrupting sitting time can improve healthy aging in postmenopausal women. Results from this study may inform the development of sedentary behavior guidelines and interventions to reduce sitting time in older adults.

Trial Registration: ClinicalTrials.gov NCT03473145; https://clinicaltrials.gov/ct2/show/NCT03473145

International Registered Report Identifier (IRRID): DERR1-10.2196/28684

Introduction

Background

Many older adults find it challenging to engage in health-enhancing physical activity (PA) and can spend up to 11 hours a day sitting [1]. Greater amounts of sedentary time, including time spent sitting and lack of PA, are associated with an increased risk of type 2 diabetes; all-cause mortality; cardiovascular disease; higher insulin; hypertension; and, specifically in older adults, poorer physical functioning [2-11]. Older women, in particular, are at an increased risk of chronic diseases and disabilities [3]. Furthermore, older women require more health care than other segments of the population and account for approximately 14% of all outpatient physician visits and 22% of hospitalizations, although they represent only 7% of the US population [12]. With the high use of health care, feasible behavior change interventions are needed to improve health and physical function.

Despite decades of public health efforts to encourage a minimum of 30 minutes per day of moderate-to-vigorous physical activity (MVPA), which has many positive health effects in older adults [13], only 3% to 6% of older adults meet public health guidelines for MVPA [14,15]. Although there have been some successful PA interventions for older adults (eg, Lifestyle Independence for Elders [16]), social and environmental conditions, functional challenges, and disease factors may limit the capacity of many older adults to engage in MVPA [17]. One promising alternative strategy to improve health is to interrupt sitting behaviors. This may be a more viable behavior change goal for many older adults because it does not involve high-intensity or high-impact activity and can be done anywhere and at any time. It is also possible that intervening on sitting behaviors, for example, by reducing the time spent sitting or increasing sit-to-stand transitions, could be the first step toward a more active lifestyle [18]. Changing sedentary behavior by reducing the time spent sitting has yielded favorable changes in blood pressure, glucose control, insulin sensitivity, and waist circumference [19]. Data from randomized controlled trials (RCTs) are needed to determine if changes in sedentary time lead to health improvements in older adults outside of worksite settings.

Several feasibility studies have indicated that time spent being sedentary can be reduced in older adults by 30-60 minutes per day [20-24]. Existing studies with older adults generally have small sample sizes, poor methodological quality, and relatively short durations [25]. The majority of previous studies have focused on reducing sitting time and, therefore, have not found appreciable improvements in sit-to-stand transitions. However, sit-to-stand transitions have been shown to increase postural blood flow and positively impact insulin and homeostatic model assessment of insulin resistance (HOMA-IR) [8,26-29]. There is a need to better understand how changing these distinct aspects of sedentary time, sitting less and transitioning more, may impact biological, physical, cognitive, and emotional health.

Objectives

The Rise for Health trial seeks to address gaps in the literature and is based on a pilot study conducted by our team. In a 2-week study, older adults were randomized to either reducing their sitting time or increasing their sit-to-stand transitions [21]. This preliminary study found that those in the reducing sitting arm decreased their sitting by 130 minutes without changing their sit-to-stand transitions, and participants in the increasing sit-to-stand transition arm increased their transitions by about 13 per day but did not change their sitting time [21]. These findings highlight the distinct nature of these 2 aspects of sedentary time and the need to understand how changing each affects health. Rise for Health builds on the findings of this study by conducting a fully powered 3-month intervention. The ultimate goal of Rise to Health is to determine whether reducing the overall time spent sitting or increasing brief sit-to-stand transitions, as measured with a thigh-worn accelerometer (activPAL; PAL Technologies), results in changes in health outcomes, including glucose control, blood pressure, and physical and cognitive function, in older, overweight women.

Methods

Overview

Rise for Health is a 3-arm RCT of 2 interventions that address changing sitting in overweight, postmenopausal women over a 3-month period, compared with an attention control condition. This study is one of the three projects within the National Institute on Aging Program Grant named *Sedentary Time and Aging Mortality and Physical Function* (STAR). The program grant proposes a paradigm shift away from energy expenditure as the primary mechanism for improving health outcomes to investigate potentially feasible behaviors such as brief sit-to-stand transitions that expend little energy but engage muscles, improve postural blood flow, and may impact physical functioning in older adults. The STAR program includes 3 projects and 2 cores for studying postmenopausal women at risk of chronic diseases. In addition to the RCT described here (project 2), STAR includes a 3-condition randomized crossover

laboratory trial of strategies to interrupt sitting time (n=78; project 1) and a study that optimizes new computational techniques for objectively measuring sedentary behavior to apply to existing prospective hip-worn accelerometer data from the Objective Physical Activity and Cardiovascular Disease Health in Older Women (OPACH) cohort of the Women Health Initiative (N>6000, project 3). All projects are investigating the consequences of sitting and brief sit-to-stand transitions on the mechanisms of healthy aging, including glucose regulation and endothelial functioning. The STAR program will provide a comprehensive evidence base that can inform public health guidelines on sitting behaviors and healthy aging.

Study Objectives

Rise for Health will examine 3-month changes in biomarkers of healthy aging and physical, emotional, and cognitive functioning across a 3-arm randomized trial: (1) healthy living attention control (Healthy Living), (2) reduce sitting time (Reduce Sitting), and (3) increase sit-to-stand transitions (Increase Transitions). The study aims to enroll 405 postmenopausal women into the 3-month trial. The primary aim is to compare changes in glucoregulatory biomarkers (fasting plasma insulin and glucose, HbA_{1c}, and HOMA-IR) and blood pressure over 3 months for the 2 intervention arms compared with the attention control condition. We hypothesize that, compared with those allocated to the attention control arm, participants in the 2 intervention arms will have greater improvements in glycemic control and blood pressure. In addition, we will evaluate the dose-response effects of sitting behavior changes on glucoregulatory biomarkers and blood pressure. We hypothesize that greater improvements in the target behavior will be associated with greater improvements in glucoregulatory biomarkers and blood pressure. The secondary aims of the study are to examine the effects of the intervention on physical, emotional, and cognitive functioning. This project will also explore (1) the modifying effects of age on the relationship between the 3 conditions and primary and secondary outcomes, (2) the psychosocial and mediators and moderators of changes in sitting behaviors, and (3) the differences in outcomes between the 2 sitting interruption intervention arms. The purpose of this paper is to describe the study protocol of Rise for Health, a 3-arm randomized trial, to assess ways of interrupting sitting in postmenopausal women.

The institutional review board of the University California San Diego (UC San Diego) approved all study procedures, and all participants will provide written informed consent. Study recruitment, participant safety, and progress are reviewed semiannually by an external independent data safety monitoring board appointed by the National Institutes of Health (NIH).

Participants

Eligibility

To be eligible, participants must be female and meet the following inclusion criteria: currently 55 years or older; sit for more than 7 hours on a majority of device-measured days, as assessed by activPAL (as given in the *Screening Visit* section); do 70 or fewer sit-to-stand transitions on a majority of device-measured days, as assessed by activPAL; no health

conditions that would inhibit standing; able to read and write fluently in English; postmenopausal, defined as no menstrual period in the last 12 months; BMI≥25 kg/m^2 and <45 kg/m^2; able to walk, stand, and perform sit-to-stand transitions without a high risk of falling, determined by the Short Physical Performance Battery (SPPB); and able to travel to study visits. Exclusion criteria include the use of insulin, uncontrolled diabetes defined as HbA_{1c}>10%, uncontrolled blood pressure defined as systolic blood pressure>180 or diastolic blood pressure>110, and participation in another research study or program that would impact the outcomes of this study.

Recruitment and Screening

The primary methods of recruitment are contacting UC San Diego patients identified through electronic health records and contacting women in San Diego through marketing lists. Women are mailed a letter and a flyer to explain the study. Prospective participants are informed that the study staff would contact them or they could call to opt out. Additional recruitment methods include advertisements on social media platforms, such as Facebook and Instagram, flyers and listserv postings, and ResearchMatch [30].

Trained recruiters describe the study activities and conduct phone eligibility screening with potential participants. After phone screening, eligible women are scheduled for an in-person screening visit at UC San Diego.

Screening Visit

At the initial visit, study requirements are reviewed and signed informed consent is obtained. Next, participants complete a medical history questionnaire and self-report their current medication and supplement use to confirm they do not have a medical condition that would inhibit standing or sit-to-stand transitions and do not use insulin. Measurements of height, weight, and blood pressure are taken to screen for BMI and blood pressure. Hip and waist circumference measurements are also recorded. Participants perform SPPB to assess physical functioning and the ability to safely stand and perform sit-to-stand transitions. If all the preliminary screening criteria are met, participants complete a battery of cognitive tests and questionnaires on self-reported demographics and PA. Participants are given an activPAL, a thigh-worn accelerometer that objectively measures sitting time and number of sit-to-stand transitions, and an ActiGraph GT3X+ (ActiGraph, LLC) accelerometer, a waist-worn device that objectively measures minutes of PA. Participants are shown how to attach activPAL using waterproof Tegaderm dressing so that it does not have to be removed, and replacement waterproof dressing is provided. Participants are asked to wear these devices for 24 hours continuously, except they are asked to remove the ActiGraph GT3X+ accelerometer before bathing or swimming for the next 7 days.

Baseline Visit

Participants return to the clinic after at least seven days of wearing the two devices. Data from activPAL are screened for sitting time (more than 7 hours on a majority of measured days) and sit-to-stand transitions (70 or fewer transitions per day on a majority of measured days) to confirm eligibility. Participants

provide fasting blood samples via a finger prick to screen for HbA_{1c}. Those who pass these final eligibility criteria then have a venous blood draw taken by a certified phlebotomist and complete additional questionnaires. Participants receive a total of US $35 for completing baseline measures. After all baseline assessments are complete, the participants are then randomized.

Randomization is stratified by BMI (overweight vs obese) and employment status (full-time vs nonfull-time employment). A computerized randomization scheme was created using the STAR program grant Biostatistics Core, using a random number generator. A stratified permuted block design is used in this study. After randomization, the participants review the expectations and requirements of their study group assignment (details given in the *3-Month Intervention* section). Data collectors and the principal investigator are blinded to the study group assignment.

3-Month Final Visit

Before their final visit, participants are mailed the accelerometer and activPAL and asked to wear both devices continuously for 7 days before the visit. At this visit, participants repeat the same measures collected at the screening and baseline visits, including blood draw, anthropometric measures, battery of cognitive tests, SPPB, and questionnaires. Participants receive up to US $110 for completing the final measures.

3-Month Intervention (Rise for Health)

Reduce Sitting and Increase Sit-to-Stand Transitions

The primary goal of the respective intervention arms is to interrupt the current sitting patterns by targeting 2 specific behavior changes: reducing the amount of time spent sitting (Reduce Sitting) or by increasing the number of sit-to-stand transitions each day (Increase Transitions). Both interventions, Reduce Sitting and Increase Transitions, use habit formation [31-34], social cognitive theory [35], and motivational interviewing techniques to support behavior change. See Figure S1 in Multimedia Appendix 1 for the outline of the intervention topics and schedule of activities.

Health Coaching Sessions for Reduce Sitting and Increase Transitions

Participants in both intervention arms receive 5 in-person, individual coaching sessions (weeks 1, 2, 3, 4, and 8) and 2 individual phone coaching sessions (weeks 6 and 11) over the course of the 12-week program. Participants are asked to wear activPAL on their thigh continuously for the first 4 weeks of the study and then again during weeks 7 and 8 to help with self-monitoring, goal setting, and personalized feedback.

During the first 60-minute in-person session, the health coach provides an overview of the intervention and gives participants a binder of printed educational materials and safety tips, printed action plan forms, and tracking logs. First, participants are asked to share their motivation to join the study. Next, they review reasons for sitting, dangers of prolonged sitting, and benefits of breaking up sitting. Tips for safely reducing sitting or

increasing sit-to-stand transitions based on group assignments are reviewed. The health coach models the target behavior by having participants in the Reduce Sitting arm practice standing for up for 5 minutes in the middle of the session, and participants in the Increase Transitions arm perform 3 brief sit-to-stand transitions in a row, holding each for 5 seconds, twice during the session. Participants are then given a wrist-worn activity band that is programmed to prompt sitting breaks based on group assignment (refer to the *Toolbox* section). Participants are shown graphs from activPAL data, either of time spent sitting or sit-to-stand transitions, depending on the group assignment (Figures 1 and 2). The health coach and participants use the graphs to (1) review a typical day and identify times during the day when participants may be able to take sitting breaks or perform sit-to-stand transitions, (2) set behavior change goals for the next week, and (3) create a specific action plan. Participants complete an action plan by identifying the specific strategy, location, days of the week, time of day, and tailored goals for the participant (number of minutes to reduce sitting by or number of transitions to complete). Participants brainstorm potential obstacles to following the action plan and solutions for overcoming each obstacle. Using motivational interviewing techniques, confidence is assessed and supported using a 0 (very low confidence) to 10 (very high confidence) scale (*ruler*). To further support behavior change, participants are provided with several tools they can choose to use. As people vary in their preferences and needs, a toolbox approach allows participants to select tools they want to try (refer to the *Toolbox* section). At the end of the session, participants are given an activPAL to wear for the next 7 days and bring in the following week so that they can review their behavior with their health coach. If the participant provides consent, the health coach sessions are audio recorded for quality checks and training.

At each subsequent coaching session, the health coach starts by assessing the adverse events that may have occurred since the last session. The health coach and the participant then model the respective behavior, gradually increasing the number of minutes of standing or number of transitions each week until week 4, when standing time may be up to 10 minutes and the number of transitions at the beginning of the session may be 5. The health coach reviews any key topics from the previous session before introducing the new behavior change topic (Figure S1 in Multimedia Appendix 1). When worn, the previous week's daily activPAL data are reviewed using daily graphs of data (Figures 1 and 2), as described above for week 1. Graphs of weekly data are shown to discuss progress toward the target behavior (Figures 3 and 4). At each session, the health coach supports the updating of personalized goals and action plans. There is a second break to model the target behavior before completing the action plan. Discussions on barriers and solutions and the confidence to meet the goal are addressed. Weeks 2, 3, 4, and 8 sessions are carried out in person and last approximately 60 minutes each. Weeks 6 and 11 sessions are carried out over the phone and last approximately 30 minutes each. Participants are given activPAL to wear in weeks 1, 2, 3, 4, 8, and 9.
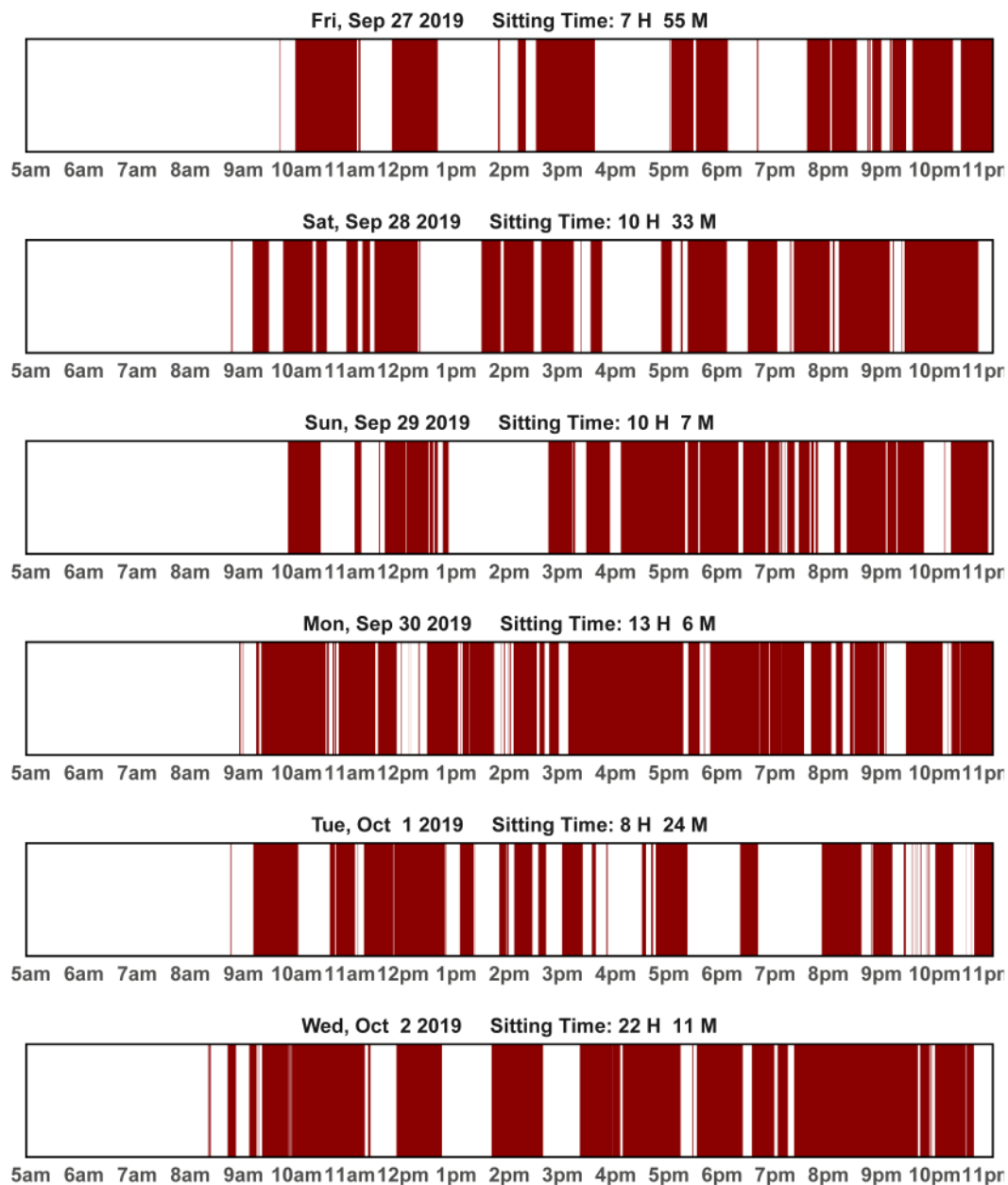
Figure 1. Sample feedback graph for the Reduce Sitting group: day-level activPAL data; red indicates where sitting occurred.
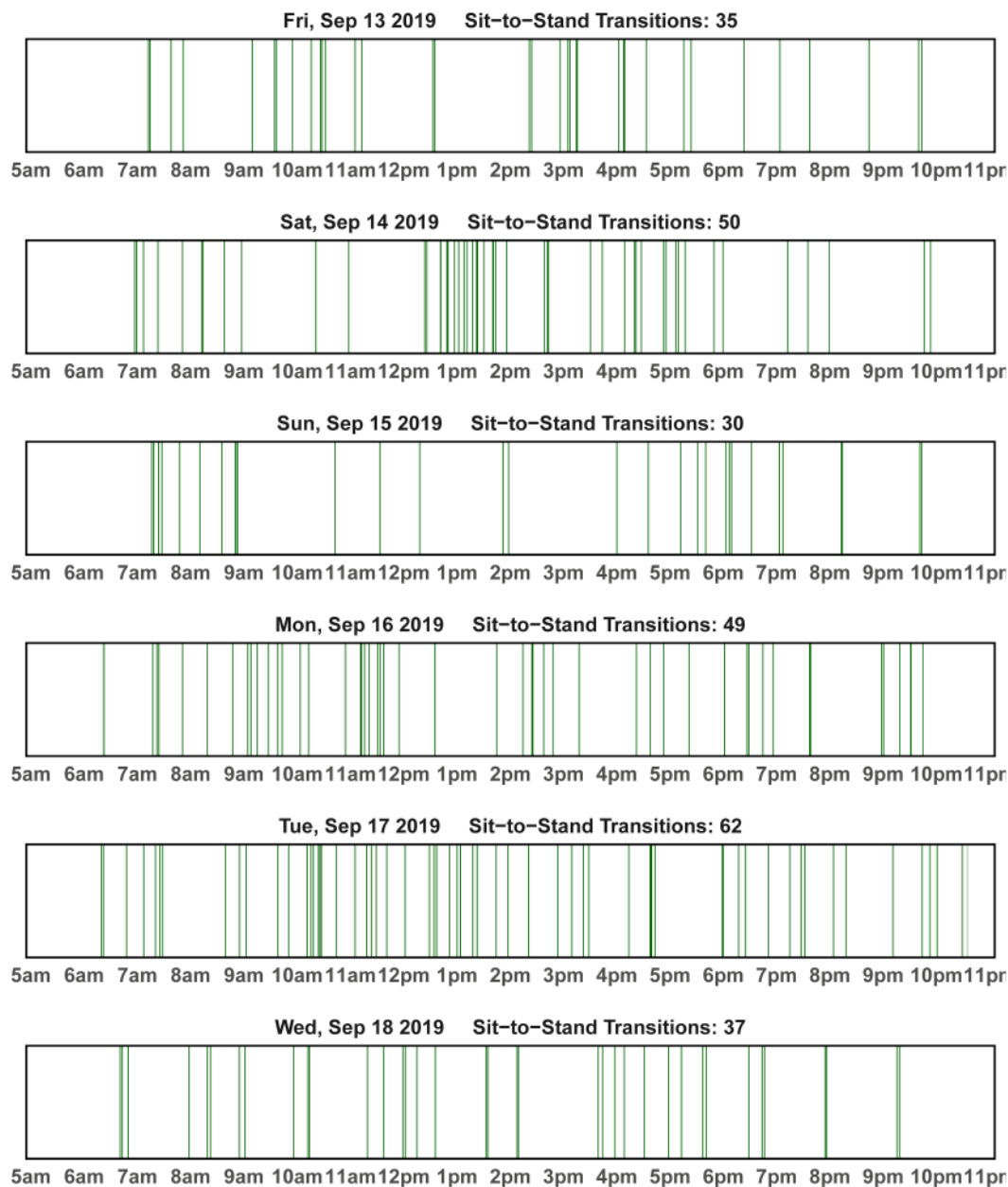
Figure 2. Sample feedback graph for sit-to-stand transitions: day-level activPAL data; green indicates where a sit-to-stand transition occurred.

Figure 3. Sample feedback graph during intervention for the Reduce Sitting group: week-level activPAL data; average sitting time.

Table 1: Weekly Average on Sitting Time

| Time	Type	sitTime
Week 1	Sitting Time	12.05
Week 2	Sitting Time	9.65
Week 3	Sitting Time	8.61
Week 4	Sitting Time	8.70

Weekly Average on Sitting Time
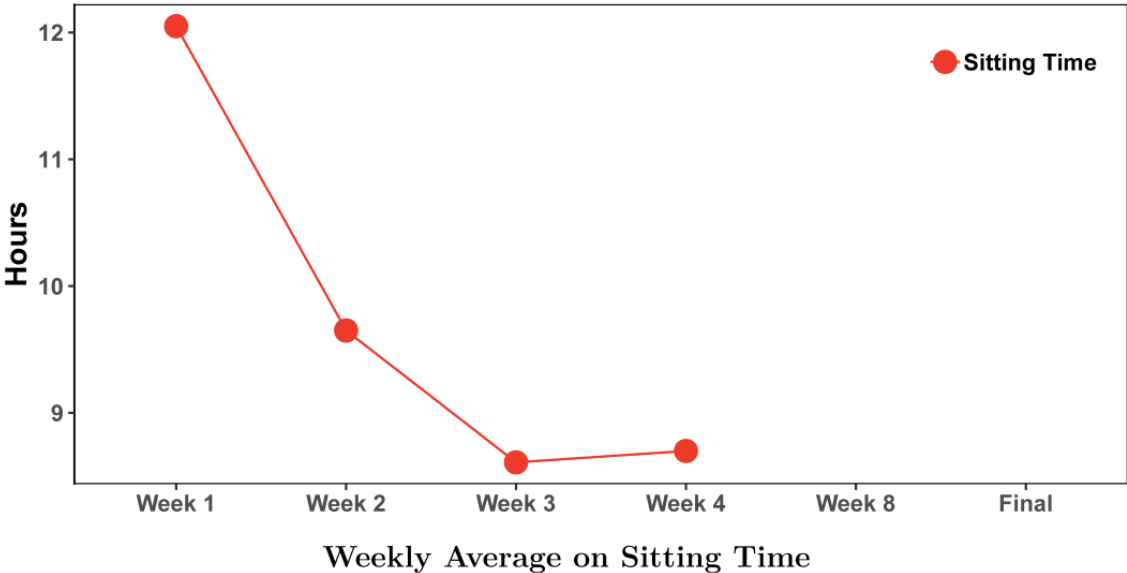
Figure 4. Sample feedback graph during intervention for Sit-to-Stand Transition Group: week-level activPAL data; average sit-to-stand transitions.

Table 1: Weekly Average on Sit-to-Stand Transitions

Week	Transitions
Wk1	43.83
Wk2	63.17
Wk3	84.50
Wk4	98.25

Weekly Average on Sit-to-Stand Transitions
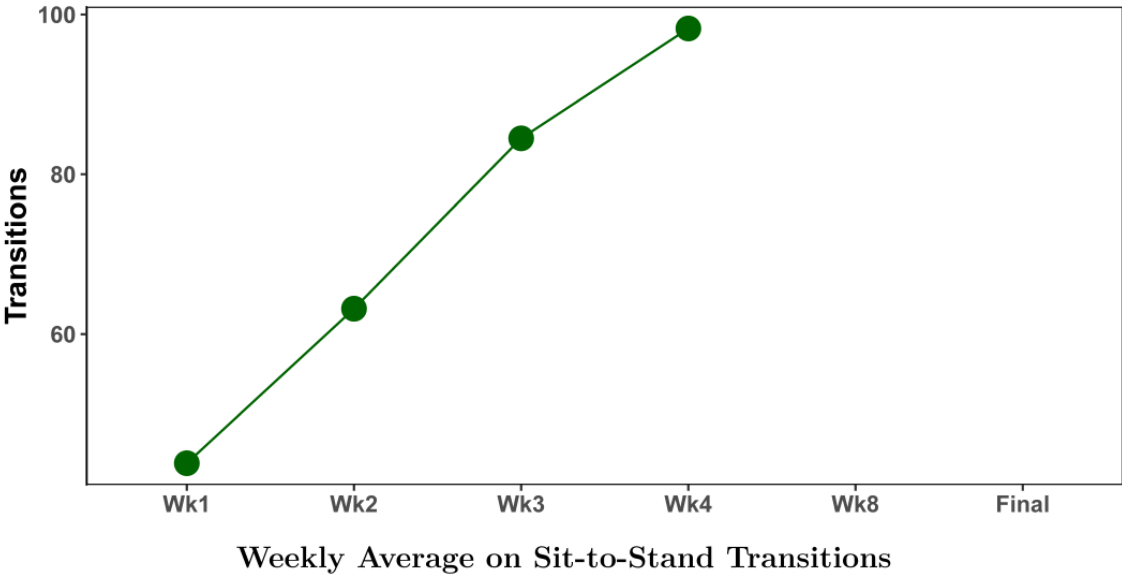
Intervention Toolbox

Participants are provided with a toolbox of options to help with their personalized behavior goals. Participants can choose different tools at each in-person session and can keep tools for the duration of the study or trade them in for new tools as desired. All participants are encouraged to use a wrist-worn device (eg, Watchminder) that provides reminders to engage in the behavior. The wrist-worn device is programmed to vibrate and display the message *Rise Up* periodically from 8 AM to 9 PM every day; however, participants have the option to change these times to match their personalized action plan. For participants in the Reduce Sitting arm, the reminder is set to once an hour. For participants in the Increase Transitions arm, the reminder is set to every 20 minutes. Other tools offered to help prompt behavior change include lists of computers, tablets, and phone apps that prompt sitting breaks; egg timers; and visual reminders (cue cards and a study-branded bracelet). Participants in the Reduce Sitting arm have the option of a standing desk to use at home or work starting in week 2, and participants in the Increase Transitions arm have the option of a tally counter to count transitions throughout the day.

Healthy Living

Participants in the healthy living attention control (Healthy Living) condition receive an equal number of contacts as those in the 2 intervention arms. The first session (week 1) is delivered in-person, whereas the remaining sessions (weeks 2, 3, 4, 6, 8, and 11) are delivered over the phone. During the first session, the health coach provides an overview of the study group and gives the participant a folder that includes information, worksheets, and resources on various healthy aging topics that may be discussed throughout the study. A new healthy aging topic is discussed at each session, with sleep and aging as the first topic. For all future phone sessions (weeks 2, 3, 4, 6, 8, and 11), the participant chooses which healthy aging topic to discuss. Example topics include safe driving, stress reduction, and healthy bones (Figure S1 in Multimedia Appendix 1). At each session, the health coach first provides an introduction to the selected topic. The health coach then reviews the learning objectives for the session, provides additional information about the health topic, and prompts the participant to complete the topic's worksheet. The health coach and participant then set the goal of the participant's choice related to the topic for that session and develop a related action plan. Using motivational interviewing techniques, confidence is assessed and supported using a 0-10 ruler question. At the end of each session, the health coach summarizes the session and confirms the date and time of the next session. The initial in-person session lasts 60 minutes, and subsequent phone sessions last 30 minutes.

COVID-19 Considerations

Owing to the COVID-19 pandemic, temporary pauses in enrollment of new study participants and in-person sessions occurred and may continue to occur consistent with UC San Diego research policies and San Diego County health orders. To minimize data loss during the pause of in-person visits, enrolled participants whose final 3-month assessment visits are scheduled during office closures will be asked to complete measures remotely. For remote measures, the participants are mailed an automated blood pressure machine and a measuring tape. A Zoom videoconferencing session is scheduled to obtain the blood pressure, waist and hip circumferences, balance tests, chair raises (as part of the SPPB), and NIH Toolbox measures (oral symbol digit test and the list sorting working memory test) using the NIH Toolbox recommendations for remote delivery [36]. Participants are mailed activPAL and ActiGraph to objectively measure sedentary time and sit-to-stand transitions per protocol on the due date. Survey measures through REDCap (Research Electronic Data Capture) [37-39] are emailed to participants on the due date. Participants are offered extended phone coaching with continued behavior change support until they are able to complete a blood draw either via mobile phlebotomy that goes to their home or upon our ability to conduct in-person assessments. Additional measures of anxiety (PROMIS Bank v.10–Anxiety and Cognitive and Affective Mindfulness Scale–Revised) have been added to better understand how anxiety and stress during this period relate to behavior change.

The study protocols may continue to shift to support remote delivery and to respond to the changing requirements related to the COVID-19 pandemic to maintain safety for participants and study staff.

Measures and Outcomes

Primary Outcomes

Glucose Regulation and Blood Pressure

The primary outcomes are glucose regulation and blood pressure assessed at baseline and at 3 months. Glucose regulation will be assessed by fasting plasma insulin and glucose, HbA_{1c}, and HOMA-IR. Fasting blood (45 mL) is collected in EDTA and Li-Heparin vacutainers. Frozen processed samples will be stored in locked freezers at −80 C. Plasma and whole blood samples will be used for glucose and HbA_{1c} assays, and all analyses will include normalization and quality control standards. HbA_{1c} is measured in whole blood in real time (DCA Vantage, Siemens). After blood sample collection is complete, fasting plasma glucose will be measured using the standard glucose oxidase method (YSI Bioanalyzer) and fasting plasma insulin will be measured using an immunoassay kit (Meso Scale Discovery, catalog #K151BZC). Standard curve samples and quality control replicates (minimum of 2 per plate) will be run on each assay plate. Linear dilution and spike-in controls will also be included in each assay run. Additional aliquots of samples will be stored at −80 °C should repeat analyses be required and for future ancillary analyses. Blood pressure is measured using the Dinamap or Accutor 7 or Dinamap V100 blood pressure monitor after participants have rested while seated for at least 5 minutes. Measures are taken at least three times, and the mean of the second and third readings will be calculated.

Objective Measure of Sitting Time and Sit-to-Stand Transitions

Measures used to examine the dose-response effects of behavioral changes on glucoregulatory biomarkers and blood pressure are activPAL and ActiGraph GT3X+. For 7 days before the baseline and 7 days before the 3-month final visit,

participants are asked to wear the 2 devices for 24 hours a day. activPAL is a small and lightweight accelerometer worn on the anterior aspect of the thigh that produces a signal related to thigh inclination, which is used to estimate the time spent in different body postures (sitting and standing) and the number of sit-to-stand transitions [40]. activPAL has demonstrated good reliability and validity [41-43]. activPAL data will be downloaded using activPAL Professional Research Edition software package using the 15-second Epoch. To filter nighttime sleeping, participants are asked to keep a sleep log each night they wear the activPAL. ActiGraph GT3X+ is a small device attached to a belt, positioned over the right hip. The ActiGraph collects data on 3 axes at 30 Hz to estimate the minutes spent in sedentary, light, moderate, and vigorous activity using calibration thresholds. ActiGraph has been validated against heart rate telemetry [44] and total energy expenditure [45,46]. Nonwear time will be classified using Choi algorithm with 90 consecutive zero counts on the x-axis [47]. We will use the newly validated OPACH cut points to assess moderate PA [48]. In addition, data will be provided to the Biostatistics Core and project 3 for further analysis of bouts, time of day, and clustering with sleep and to validate the machine-learned algorithms.

Secondary Outcomes

Secondary outcomes focus on physical, emotional, and cognitive function and will be measured at baseline and at 3 months. Objective lower extremity functioning will be measured using the SPPB to measure balance, gait speed (4 meters course), and chair stand [49]. Self-report physical functioning will be measured using 6 items from the Activities of Daily Living Survey, which focuses on the ability to perform basic tasks of everyday life, such as eating, bathing, or dressing with or without assistance [50,51]. Physical and emotional functioning will be measured using the Physical Functioning Survey [52]. It comprises 36 items that assess 8 health concepts: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy or fatigue, pain, and general health perceptions. Physical Functioning Survey has been found to be reliable, valid, and responsive for a variety of medical diagnoses. Depressive symptoms will be measured using the validated 10-item Center for Epidemiologic Studies Depression Scale short form [53]. These outcome measures were selected for consistency with the outcome measures used in the cohort for project 3 of the STAR program.

Objective cognitive functioning will be measured using the Dimensional Change Card Sort, List Sorting Working Memory, and Oral Symbol Digit from the NIH Toolkit [54,55]. These tests assess executive function, memory, and processing speed, respectively. These 3 tests take about 17 minutes to administer via an iPad (Apple Inc) app and have been validated and normed in individuals aged 3-85 years [54,55]. Self-report cognitive functioning is assessed using the 8-item Cognitive Function Questionnaire from the Patient-Reported Outcomes Measurement Information System (PROMIS) [56].

Additional Measures

As psychosocial factors may mediate and moderate sedentary behavior changes, these domains are also measured. Self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep are measured using the NIH PROMIS Sleep Disturbance 8a Short Form [57]. Self-reported barriers and benefits related to sitting are assessed on a 9-item, 5-point Likert scale assessing the mental and physical factors that affect their ability to sit adapted from a scale for PA [58]. Participants are asked to rate their confidence in performing the targeted sedentary behaviors (sitting reduction and increase in sit-to-stand transitions) on a 2-item confidence scale, which is modeled after a PA self-efficacy scale [59]. Self-reported PA is measured at baseline using the Community Healthy Activities Model Program for Seniors Physical Activity Questionnaire for Older Adults, which asks about weekly frequency and duration of a variety of lifestyle physical activities that are meaningful and appropriate for older adults [60]. Community Healthy Activities Model Program for Seniors was selected for measurement consistency across all the STAR projects. Anxiety will be assessed using the NIH PROMIS computer-adaptive version of their anxiety measure [61]. Cognitive and Affective Mindfulness Scale–Revised is a 12-item measure that captures mindful approaches to thoughts and feelings [62]. Pain will be measured using the PROMIS pain interference NIH PROMIS pain interference and intensity short forms and modified items recommended by the NIH Task Force for Research Standards for Chronic Low Back Pain [63,64]. Additional measures that were adapted from validated measures to specifically address sedentary behavior include the Self-Report Behavioral Automaticity Index [65] and habits and perceptions [66]. A complete list of measures is given in Textbox 1.

Textbox 1. Rise for Health study measures. Measures are collected at baseline and at 3 months except where noted.

Primary outcomes

- Glucose regulation biomarkers

  - Glucose, insulin, and HbA_{1c} measurements. Glucose and insulin will be assessed individually and in combination to measure insulin sensitivity

- Blood pressure

  - Mean of the second and third readings of 3 measures

Objective sedentary and physical activity

- Sedentary behavior

  - 7-day, 24-hour, thigh-worn activPAL

- Physical activity

  - 7-day, 24-hour, hip-worn ActiGraph GT3X+

Secondary outcomes

- Physical function—objective

  - Short Physical Performance Battery (balance, gait speed, and chair stands) [49]

- Physical function—self-report

  - Activities of Daily Living [50] and Medical Outcome Study 36-item short form health survey [52]

- Depressive symptoms

  - Centers for Epidemiologic Studies Depression Scale short form [53]

- Cognitive function—objective

  - National Institutes of Health (NIH) Toolbox Cognition Tests: Dimensional Change Card Sort, List Sorting, and Oral Symbol Digit [54,55]

- Cognitive function—self-report

  - Patient-Reported Outcomes Measurement Information System (PROMIS) Cognitive Function Measure [56]

Other relevant measures

- Height and weight

  - Digital scale and stadiometer (height baseline only)

- Waist and hip circumference

  - Assessed in centimeters

- Demographics (baseline only)

  - Age, education, income, race, and marital status with standard surveys

- Medical history—self-report

  - Medical history, recent medical history, and medications

- Psychosocial measures

  - NIH PROMIS Anxiety [61], Cognitive and Affective Mindfulness Scale–Revised [62], benefits and barriers [58], self-efficacy [59], Self-Report Behavioral Automaticity Index [65], habits, and perceptions [66]

- Physical activity—self-report

  - Community Healthy Activities Model Program for Seniors Physical Activity Questionnaire for Older Adults (baseline only) [60]

- Sleep—self-report

- NIH PROMIS Sleep Disturbance 8a Short Form [57]

- Pain—self-report

  - NIH PROMIS Pain Interference and Pain Intensity Short Form [63,64]

Statistical Analysis and Sample Size Considerations

We aim to recruit 405 participants for the study to ensure 80% power to detect meaningful improvements in glucose regulation after accounting for a 10% dropout or missing data (eg, unassayable sample) rate. Given the multiple correlated biomarker outcomes, we will create a composite outcome derived as a sum of z-scores of the (possibly transformed) markers. A few previous interventions aimed at decreasing sedentary time in adults or increasing standing observed effect sizes between 0.39 and 0.49 on fasting insulin. Thus, we based sample size estimates on an assumed effect size of 0.4 at 3 months. We set the significance level α=.025 for 2 comparisons (each of the sitting interruption interventions compared with the control). Under these assumptions, we would need 121 subjects per arm, based on a 2-sided (2-tailed), 2-sample *t* test to detect an effect size of 0.4 with 80% power between the 2 sitting interruption arms compared with the control arm. To translate these effect sizes to biomarker values, we used preliminary data from our OPACH study of approximately 6000 postmenopausal women who had a mean of 98.3 mg/dL (SD 27.7) for fasting glucose and a log-transformed mean of 4.17 pmol/L (SD 0.77) for insulin. Assuming the same SDs as in the OPACH study, we have 80% power to detect the average changes of 11.1 mg/dL for glucose (SD 27.7) and 0.31 pmol/L (SD 0.77) for (log)insulin in the intervention arms versus no change in controls. Recruitment projections before the commencement of the study indicated 405 participants to be feasible. Recruitment will stop when the study reaches either the required sample size or the maximum number of participants who can be recruited in the study's allotted recruitment timeframe, while complying with the unforeseeable restrictions and conditions related to the COVID-19 pandemic.

To check if randomization achieved balance on key covariates, study groups will be compared based on baseline characteristics using the analysis of variance (for continuous variables) and chi-square (for categorical) variables. Variables that are not balanced across study groups will be adjusted for in subsequent analyses. For intervention effect comparisons, we will apply a mixed effects analysis approach in which all available assessments on an individual can be included in the model. Gaussian link functions will be used for continuous outcomes (eg, biomarkers), and a binomial or loglinear link will be used for binary or categorical outcomes. Biomarker outcomes will be transformed as needed to better approximate the Gaussian distributions for model residuals. The primary superiority analysis comparing the Reducing Sitting and Increasing Transitions interventions with controls will use the intent-to-treat principle. We will include adherence measures to explore intervention differences by compliance level.

Analysis Plans

RCT Analysis Plan for Primary and Secondary Outcomes

We will use mixed effects regression with repeated measures of the biomarker values (at baseline and 3 months) as the outcome variable. The main predictors included in this model will be randomization group, visit (baseline or 3 months) and the group*visit interaction. A subject-specific (random) intercept will be included to model heterogeneity in marker levels. A significant group×time interaction for an intervention will indicate that biomarker changes differ between the intervention and control groups. Additional covariates, that is, stratification variables (obesity status and employment status) and any factors found to be imbalanced between treatment groups at baseline will be included to examine the impact of covariates on estimated treatment effects. By using appropriate contrasts, intervention effect estimates (and 95% CIs) for the group comparisons of primary interest, that is, mean differences between each of the sitting interruption interventions with the control, will be calculated. To model multiple outcomes, we will use the sum of biomarker z-scores as a single outcome in the models, as described earlier, and explore O'Brien test [67] for multiple outcomes and multivariate mixed models. A similar analysis will be conducted for the secondary outcomes, namely, physical, emotional, cognitive functioning, and depressive symptoms, at 0 and 3 months.

For sensitivity analyses, we will include an indicator variable for COVID-19 (yes or no) and interactions, to test if participants who received altered protocols (eg, remote assessments) because of COVID-19 had similar changes compared with those who received the originally planned protocol.

For secondary analysis, we will include the targeted sedentary behavior (eg, minutes spent sitting, number of sit-to-stand transitions) as a time-varying covariate in the mixed models to test dose-response effects, that is, if a greater change in sedentary behavior is associated with greater change in biomarker or blood pressure outcomes.

Exploratory Moderator and Mediation Analysis

Moderators (eg, age) will be tested by including 3-way interaction terms between the putative moderator, time, and treatment condition in the mixed models described in the RCT analysis plan. In addition, accelerometer and activPAL days are nested within participants; therefore, when examining changes in sedentary behavior (outcome), we will further account for this hierarchical structure in the model. The device wear time will be entered as a fixed effect.

To assess whether psychosocial factors (eg, self-reported sleep) statistically mediate the effects of the interventions on sedentary behavior, we will apply the 4-step causal mediation framework to obtain direct and indirect effects [68]. Bootstrap resampling

will be used to compute SEs and to test the significance of indirect or mediated effects [69].

Comparison of 2 Intervention Arms

By using appropriate contrasts in the RCT analysis mixed models, intervention effect estimates (and 95% CIs) for the 2 intervention conditions, that is, the mean differences in outcomes between the sit-to-stand and increased standing arms, will be calculated. The 95% CIs for these contrasts will be useful for quantifying the degree to which these interventions have equivalent effects on the biomarkers. For this analysis, we will conduct an intent-to-treat analysis and per-protocol analysis, as protocol violations and informative dropouts could bias the results toward equivalence.

Results

Recruitment began in May 2018 and is currently ongoing. Data collection is expected to continue through 2022. Biomarker assays will be run thereafter, and data analysis and results are expected at the end of 2022.

Discussion

Principal Findings

Rise for Health will examine whether interrupting sitting time through 2 different behavioral changes in overweight postmenopausal women can impact glycemic control biomarkers of healthy aging and improve physical, emotional, and cognitive functioning. This is the first large-scale RCT to investigate the unique effects of brief sit-to-sand transitions in a real-world setting in postmenopausal women [25,70]. This study will provide important, new evidence to help inform public health and guide clinical and occupational health recommendations regarding the specific health effects of different ways of interrupting sitting.

Despite gaps in the evidence, public health agencies worldwide recommend reductions in sedentary behavior [71,72]. Many agencies suggest engaging in PA as a way to reduce sedentary time, although the goal of increasing exercise may not be possible for many older adults [73]. The World Health Organization recommends that adults aged 65 years or older limit the amount of time being sedentary and replace sedentary time with PA of any intensity and that older adults do more MVPA than recommended as a way to offset the negative impact of sedentary behavior [71]. However, there are many ways to reduce sedentary time, and it is unknown what types of alternate behaviors are beneficial to health and well-being. Disrupting sedentary time by sitting less or more sit-to-stand transitions may be more feasible behavior targets as they do not involve high-intensity or high-impact activity and may be more realistic for populations with some physical limitations. To date, most studies investigating sedentary time in older adults have been small, cross-sectional studies, with only a handful of intervention studies [25]. Little is known about the impact of interrupting sitting behaviors on emotional, cognitive, and functional outcomes, which are important for quality of life and healthy aging [74,75]. Although some previous studies have shown promising improvements on health outcomes, there has been a

call for more rigorous study designs in large samples to study the effects of physical function, quality of life, disease risk, and healthy aging in older adults in a real-world, nonoccupational setting [25,70,76].

There is growing evidence of the importance of sit-to-stand transitions for health, distinct from sedentary time. Laboratory studies have shown that the frequency of disrupting sitting is important and that brief interruptions can increase postural blood flow and muscle contraction and induce changes in blood pressure, heart rate, and vascular tone [77,78]. Our pilot work findings support the paradigm that reducing sitting and increasing sit-to-stand transitions are 2 independent behaviors that require distinct and specific interventions [21]. Previous intervention studies have shown that a decrease in time spent sitting has no effect on sit-to-stand transitions [22,79]. These interventions have generally been aimed at decreasing sedentary time without focusing on sit-to-stand behavior and delivering mixed messages, encouraging participants to sit less, stand more, take breaks, and move more. This general approach makes it difficult to determine which types of alternative behaviors are linked to improved health. Therefore, it is important to study the specific behavioral targets of reducing sitting time and increasing brief transitions independently to examine how these different behaviors impact a variety of health outcomes.

The study limitations will be addressed whenever possible. Difficulty in recruiting a diverse sample or meeting our enrollment goal due to COVID-19 may limit the generalizability of the findings. This study is specifically enrolling older women; therefore, the results may not apply to men or younger women. Other limitations related to the COVID-19 pandemic are currently unknown but may occur if study protocols shift to support remote intervention delivery to maintain safety for participants and study staff. As the limited number of trials published to date are short in duration with small sample sizes, it is not known whether a 3-month intervention is long enough to support changes in our primary and secondary outcomes. A further limitation is that we are not assessing long-term effects or maintenance of effects in this study. A multilevel intervention using policy changes and environmental cues may improve long-term adherence and exceed the individual approach in this study.

Conclusions

Rise for Health is a free-living intervention, RCT, within the STAR program grant, an National Institute of Aging funded program grant designed to provide more rigorous and comprehensive evidence on how to interrupt the sitting time and maximize positive impacts on healthy aging. Overall, this program grant aims to encourage a shift away from energy expenditure as the primary mechanism for health outcomes of reduced sitting to investigate sitting behaviors such as brief sit-to-stand transitions that expend little energy but engage muscles and improve postural blood flow and may impact physical functioning in older adults. Results from Rise for Health will be combined with results from our other STAR projects to collectively inform public health guidelines, occupational health practices, and related policies. By studying 2 distinct behaviors and a wide range of aging-related outcomes,

we will be able to better understand intervention-specific differences in outcomes and, therefore, provide specific guidelines for which alternative behaviors impact what aspects of health and well-being.

Acknowledgments

Conflicts of Interest

None declared.

Multimedia Appendix 1
Measurement and sample intervention schedule.
[PNG File , 332 KB - resprot_v10i5e28684_app1.png]

Multimedia Appendix 2
Peer-review report.
[PDF File (Adobe PDF File), 188 KB - resprot_v10i5e28684_app2.pdf]

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Abbreviations

HOMA-IR: homeostatic model assessment of insulin resistance
MVPA: moderate-to-vigorous physical activity
NIH: National Institutes of Health
OPACH: Objective Physical Activity and Cardiovascular Disease Health in Older Women
PA: physical activity
PROMIS: Patient-Reported Outcomes Measurement Information System

RCT: randomized controlled trial
SPPB: Short Physical Performance Battery
STAR: Sedentary Time and Aging Mortality and Physical Function
UC San Diego: University California, San Diego

Protocol

Engaging Caregivers and Providers of Children With Sickle Cell Anemia in Shared Decision Making for Hydroxyurea: Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: Sickle cell anemia (SCA) is a genetic blood disorder that puts children at a risk of serious medical complications, early morbidity and mortality, and high health care utilization. Until recently, hydroxyurea was the only disease-modifying treatment for this life-threatening disease and has remained the only option for children younger than 5 years. Evidence-based guidelines recommend using a shared decision-making (SDM) approach for offering hydroxyurea to children with SCA (HbSS or HbS/β0 thalassemia) aged as early as 9 months. However, the uptake remains suboptimal, likely because caregivers lack information about hydroxyurea and have concerns about its safety and potential long-term side effects. Moreover, clinicians do not routinely receive training or tools, especially those that provide medical evidence and consider caregivers' preferences and values, to facilitate a shared discussion with caregivers.

Objective: The aim of this study is to understand how best to help parents of young children with sickle cell disease and their clinicians have a shared discussion about hydroxyurea (one that considers medical evidence and parent values and preferences).

Methods: We designed our study to compare the effectiveness of two methods for disseminating hydroxyurea guidelines to facilitate SDM: a clinician pocket guide (ie, usual care) and a clinician hydroxyurea SDM toolkit (H-SDM toolkit). Our primary outcomes are caregiver reports of decisional uncertainty and knowledge of hydroxyurea. The study also assesses the number of children (aged 0-5 years) who were offered and prescribed hydroxyurea and the resultant health outcomes.

Results: The Ethics Committee of the Cincinnati Children's Hospital Medical Center approved this study in November 2017. As of February 2021, we have enrolled 120 caregiver participants.

Conclusions: The long-term objective of this study is to improve the quality of care for children with SCA. Using multicomponent dissemination methods developed in partnership with key stakeholders and designed to address barriers to high-quality care, caregivers of patients with SCA can make informed and shared decisions about their health.

Trial Registration: ClinicalTrials.gov NCT03442114; https://clinicaltrials.gov/ct2/show/NCT03442114

International Registered Report Identifier (IRRID): DERR1-10.2196/27650

Introduction

Background

Sickle cell anemia (SCA) is a genetic blood disorder that affects approximately 100,000 individuals in the United States [1]. It is the most common disorder identified by newborn screening, with approximately 1 in 2000 babies born with SCA in the United States each year [2]. SCA is a chronic disease that is associated with significant morbidity and early mortality [3]. Until 2017, hydroxyurea was the only approved disease-modifying treatment for individuals with SCA, and it has remained the only treatment option for children younger than 5 years [4]. Hydroxyurea has many beneficial effects, including reduced pain and acute chest syndrome episodes, reduced hospital admissions, and less need for blood transfusions, among patients with SCA [5,6]. In 2014, the National Heart, Lung, and Blood Institute (NHLBI) published guidelines that recommended clinicians offer hydroxyurea to children with SCA (HbSS and HbS/β0 thalassemia), beginning

as early as 9 months of age [7]. Previously, medical providers only offered hydroxyurea to children with SCA with persistent pain or other severe SCA-related complications. Despite these guidelines, hydroxyurea uptake remains low in young children with SCA [8]. Barriers to taking hydroxyurea include a lack of caregiver knowledge about hydroxyurea, providers' hesitancy to prescribe hydroxyurea, and concerns about poor adherence to the treatment [9].

NHLBI guidelines encourage using shared decision making (SDM) when providers offer hydroxyurea, which involves a collaborative process wherein clinicians, patients, and families work together to reach a mutual agreement about the course of treatment [7,10]. However, the only widely distributed tool to assist providers in implementing the NHLBI guidelines for hydroxyurea is a clinician pocket guide developed by the American Society of Hematology (ASH) [8]. The pocket guide was a critical first step, but it *only* targeted clinician motivation. Pocket guides do not provide training to build clinician self-efficacy in prescribing medications, feedback to reinforce

behavior change, or decision support tools to help clinicians engage and support caregivers in SDM.

Objectives

We developed the hydroxyurea SDM toolkit (H-SDM toolkit), which is a caregiver-centered, technology-enhanced decision support tool. We designed the H-SDM toolkit to strengthen SDM, reduce caregiver uncertainty, allay potential fears, increase the offering of hydroxyurea, and ultimately improve hydroxyurea uptake [10,11]. In this paper, we present a protocol for a multisite randomized controlled trial (RCT; ENGAGE HU). The objective of the ENGAGE HU trial is to determine whether the use of the H-SDM toolkit is more effective than the ASH clinician pocket guide (ie, usual care) as a dissemination method. This study aims to improve the quality of the available evidence so that caregivers and providers have the appropriate tools to make an informed decision about hydroxyurea.

Methods

Framework

The Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) model provides a framework for evaluating dissemination methods that can improve the sustainable adoption and implementation of effective, generalizable, and evidence-based interventions by attending to 5 factors: (1) *Reach*: does the intervention reach the intended population?; (2) *Efficacy or effectiveness*: does the intervention impact the essential outcomes?; (3) *Adoption*: is the intervention supported by staff, settings, or institutions?; (4) *Implementation*: is the intervention delivered consistently?; and (5) *Maintenance*: what is in place to ensure that the intervention continues over time? [12]. We developed our study plan using RE-AIM because this framework improves the quality, speed, and impact of dissemination methods [13].

Specific Aims

The H-SDM toolkit engages both caregivers and clinicians and targets (1) clinician motivation and self-efficacy and (2) caregiver readiness. Therefore, we propose that it will lead to change in caregiver's and clinician's behavior, which will increase SDM about hydroxyurea between caregivers and clinicians as well as improve decisional outcomes (ie, decisional uncertainty, hydroxyurea knowledge, and satisfaction with the decision-making process; Figure 1) [10]. If caregivers of children with SCA feel more confident and knowledgeable about hydroxyurea and more involved in the decision-making process, then they may be more likely to initiate hydroxyurea and subsequently ensure that their child adheres to the medication. Thus, the primary aims of the ENGAGE HU study are as follows:

- *Aim 1:* To determine whether the H-SDM toolkit is a more effective dissemination method than the ASH clinician pocket guide (ie, usual care) by assessing the following:
  - Caregiver report of decisional uncertainty for hydroxyurea
  - Caregiver report of experiencing SDM while talking with their child's clinician about hydroxyurea.

- *Hypothesis 1:* The H-SDM toolkit dissemination method will result in greater perceptions of SDM and less uncertainty among caregivers of children with SCA than the ASH clinician pocket guide (ie, usual care).
- *Aim 2:* To determine whether the H-SDM toolkit is a more effective dissemination method than the ASH clinician pocket guide (ie, usual care) by assessing the following:
  - Caregiver knowledge of hydroxyurea
  - Whether the children are offered hydroxyurea
  - Number of children with an active hydroxyurea prescription
  - Child health outcomes: pain, cognitive function, SCA-related quality of life, and health care utilization.

- *Hypothesis 2:* The H-SDM toolkit dissemination method will result in greater improvements in caregiver knowledge about hydroxyurea, more children being offered and receiving hydroxyurea, and better health outcomes than the ASH clinician pocket guide (usual care).

Figure 1. Engaging parents of children with sickle cell disease and their providers in shared decision making for hydroxyurea (ENGAGE HU) conceptual model. H-SDM: hydroxyurea shared decision making; SDM: shared decision making.
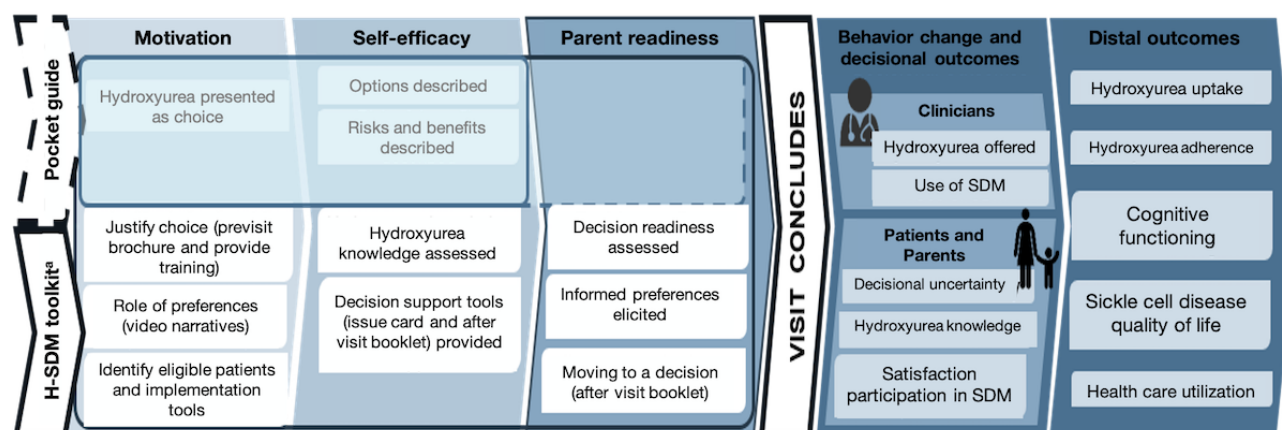
Overview of Study Design

ENGAGE HU is an adapted stepped-wedge, stratified, multicenter RCT [14] with the H-SDM toolkit as the intervention and the ASH clinician pocket guide as the active comparator. We selected sites in the United States with sickle cell clinics that work with patient populations from urban, suburban, and rural communities. Each clinic begins to enroll patients using the ASH clinician pocket guide as the dissemination method. Each site then *crosses over* to using the H-SDM toolkit (Figure

2). Clinician training for the H-SDM toolkit begins during the last month of each usual care period. A stepped-wedge design with sequential assignment was chosen to ensure that all sites received the intervention and could *step in* at different timepoints. All sites will complete the usual care condition first, as clinicians would not be able to unlearn skills gained from the H-SDM toolkit. Each site enrolls approximately 4-5 participants per period. Enrollment ends 44 months after the study initiation (Figure 2).

Figure 2. Study timeline. H-SDM: hydroxyurea shared decision making; IRB: institutional review board.

Sites	0-6 Months	7-22 Months	23-30 Months	31-37 Months	38-44 Months	44-47 Months
Nationwide Children's Hospital / Lurie Children's Hospital / Children's Hospital of Philadelphia	IRB Training Study prep	Usual care	H-SDM toolkit *Training*	H-SDM toolkit	H-SDM toolkit	Dissemination Study closeout
Washington University School of Medicine / Rainbow Babies & Children's Hospital / UCSF Benioff Children's Hospital Oakland	IRB Training Study prep	Usual care	Usual care	H-SDM toolkit *Training*	H-SDM toolkit	Dissemination Study closeout
Baylor College of Medicine / Boston Children's Hospital / Nemours/Alfred I. duPont Hospital for Children / Indiana Thrombosis and Hemophilia Treatment Center	IRB Training Study prep	Usual care	Usual care	Usual care	H-SDM toolkit *Training*	Dissemination Study closeout

Randomization

We chose an adapted stepped-wedge randomized trial (clinic is the unit of randomization) with sites not previously exposed to the H-SDM toolkit. This design maximizes our confidence that differences in outcomes between the groups occur due to the dissemination method and not baseline discrepancies among participant groups, confounding, or chance. We randomize at the site level to reduce the risk of contamination and because the NHLBI guidelines require clinics to make system-level changes to deliver high-quality care. The order in which the sites crossover is random (Figure 2). The randomization minimizes differences among large (>501 patients), medium (270-500 patients), and small (<270 patients) sites.

Patient Involvement

Patients with SCA and their caregivers provided input at several stages of the trial, including development, design, feasibility, and trial conduct. They also assisted with the toolkit components, choice of outcome measures, and recruitment methods. They helped us carefully assess the trial burden on caregivers of patients with SCA. Stakeholders will be coauthors of peer-reviewed publications, and the study results in a format suitable for a nonspecialist audience will be sent to the patients and caregivers.

Eligibility and Consent

Eligibility criteria for the caregiver participants in the ENGAGE HU study include the following: their child has a diagnosis of SCA and receives care at the recruitment site; their child is aged 0-5 years; their child is eligible for hydroxyurea according to NHLBI guidelines (HbSS and HbS/β0 thalassemia); they can participate in both study visits; and they can read, understand, and speak English fluently. Exclusion criteria include their child has an active hydroxyurea prescription filled in the past 3 months; they have previously made a decision about whether to initiate hydroxyurea (after November 2019, we changed this criterion to include whether the research team had approached the caregiver reinitiation of hydroxyurea within the past 3 months); any diagnoses or conditions that, in the opinion of the site investigator or hematologist, would prevent the patient from being a suitable candidate for the study; and their child is a sibling of a participant actively or previously enrolled in the study.

The Cincinnati Children's Hospital Medical Center (CCHMC) is the co-ordinating center (CC) for this multisite trial (Multimedia Appendix 1 [14-39]). The CCHMC oversees the study conduct, regulatory and institutional review board (IRB) administration, and compliance. The protocol for ENGAGE HU includes an IRB-approved waiver of the documentation of consent for clinicians participating in the trial. The trial also has an IRB-approved waiver of consent that permits clinical

sites to generate a list of eligible patients. Caregivers participate in the informed consent process and are required to provide written or electronic consent.

Recruitment and Retention

The ENGAGE HU trial consecutively enrolls caregivers of patients with SCA across the United States. Caregivers are identified as potentially eligible for hydroxyurea by provider referral or electronic health record review. A member of the site research team approaches the child's hematology provider to obtain approval before contacting the potential caregiver participant. Caregivers of patients deemed eligible will receive an invitation via regular mail or phone or may be approached during a clinic visit, with research coordinators at each site screening participants and completing the informed consent process.

Evidence-based strategies for optimizing participation and retention include scheduling visits at times convenient for the family, reminder phone calls, allowing participants to complete questionnaires on the internet, scheduling phone or video problem-solving sessions at a convenient time, and *check-in* calls during the COVID-19 pandemic. In addition, the importance of the follow-up visit is reviewed with each family at baseline to engage them as partners in the research process. We also seek to aid sites in developing solutions to reach nonresponders during weekly study meetings. To improve retention, we collect multiple forms of contact information from multiple contacts (eg, family members and friends) to stay in close contact with families. In addition, we use a graduated

incentive system for visits to reduce attrition. A Stakeholder Advisory Council, whose members include the caregivers of patients with SCA, reviews and provides ongoing feedback on the recruitment and retention plan.

Hydroxyurea Dissemination Methods

H-SDM Toolkit

Guided by the social cognitive theory, and considering preidentified barriers [40], the team designed the H-SDM toolkit to increase the likelihood that caregivers and health care providers would engage with one another to make a joint decision about hydroxyurea. The social cognitive theory posits that behavior change occurs when an individual is motivated, feels confident in his or her ability to perform the new behavior (self-efficacy), and observes that the behavior is successfully performed and reinforced by others (observational learning and reinforcement). The development of the H-SDM toolkit is described in detail elsewhere [11]. Briefly, our research team collaborated with clinicians, educators, community-based organizations, and patients with SCA and their caregivers to identify barriers related to decision making regarding hydroxyurea. We designed the H-SDM toolkit with core and optional components tailored to individuals' needs while also being broadly applicable (Table 1).

Clinicians participate in guided practice using the visit decision aids in an immersive virtual reality environment [41] (Figure 3). The virtual reality simulation was adapted from a general pediatric practice protocol to train clinicians to discuss the influenza vaccine with racial and ethnic minority families [42].

Table 1. Hydroxyurea shared decision-making toolkit components.

Materials	Component	Process	Core	Optional
Virtual reality simulation	Guided practice	Clinicians receive virtual reality training to increase their self-efficacy in describing hydroxyurea risks, benefits, and other treatments; eliciting caregiver preferences; assessing decision readiness; and moving caregivers toward a decision	✓[a]	N/A[b]
Previsit brochure	Decision aid	To increase caregiver motivation to make a decision by providing information about hydroxyurea as a treatment option	N/A	✓
In-visit issue card	Decision aid	To increase caregiver self-efficacy by providing them with the information needed to evaluate the benefits and risks of hydroxyurea and other treatment options	✓	N/A
After-visit booklet	Decision aid	Includes links to reputable resources; caregivers can take notes and take this resource home to share with other caregivers involved in decision making	✓	N/A
Parent video narratives	Decision aid	Four videos (3 mothers and 1 father)—caregivers telling their story about how they made a decision about hydroxyurea	N/A	✓
Previsit planning template	Identifying eligible patients	Secure SharePoint site with electronic health record templates (eg, EPIC builds)	N/A	✓
Care gap report template	Identifying eligible patients	Secure SharePoint site with tools to identify eligible patients who were missed or not approached	N/A	✓
Checklist template	Identifying eligible patients	Secure SharePoint site with a SCA[c] data collection form for tracking whether hydroxyurea was offered and prescribed	N/A	✓
Process map template	Implementation	Sites are provided with quality improvement tools that help integrate guidelines into their care delivery system. Process maps visually describe the flow of work or ideas	✓	N/A
Failure mode effect analysis template	Implementation	Failure mode effect analysis templates assist teams in determining how their clinic process needs to change to incorporate the NHLBI[d] guidelines into routine care	N/A	✓
Plan-do-study-act template	Implementation	Plan-do-study-act templates assist teams in determining how their clinic process needs to change to incorporate the NHLBI guidelines into routine care	N/A	✓
Key driver diagram template	Implementation	Site teams complete key driver diagrams, which are a visual display of a team's theory of what "drives" or contributes to the study aims	N/A	✓
Implementation planning tool	Implementation	Teams are invited to weekly calls and booster sessions to review best practices in the implementation, particularly for the clinical decision support	✓	N/A
Run chart template 1	Monitoring	For use in shared decision making	✓	N/A
Run chart template 2	Monitoring	To track eligible patients who have been offered hydroxyurea	✓	N/A
Run chart template 3	Monitoring	To track hydroxyurea prescriptions	N/A	✓
Hydroxyurea navigator monitoring tool (dose, labs, and adherence)	Monitoring	Table of dates and laboratory values with a way for clinicians to indicate if a value is in range or moving in the right direction	N/A	✓

[a]Check marks indicate whether a component of the toolkit is core or optional.

[b]N/A: not applicable.

[c]SCA: sickle cell anemia.

[d]NHLBI: The National Heart, Lung, and Blood Institute.

Figure 3. The clinical environment viewed through the virtual reality headset.


Usual Care

The ASH clinician pocket guide contains information that may motivate clinicians to use an SDM approach (eg, the NHLBI guidelines). The guide also includes information that may increase clinician confidence in describing hydroxyurea risks, benefits, and other treatments to caregivers. All sites receive printed copies of the guide, a link to download copies, and a link to the app to distribute to their clinicians. Site clinicians also view a live or recorded didactic presentation that reviews the NHLBI guidelines for hydroxyurea. Sites then develop or update their site-specific care guidelines for hydroxyurea and create a plan for implementation.

Procedures

Once the research team obtains consent from interested caregivers, they can complete baseline assessments at that time or a more convenient date. If caregivers prefer or cannot complete measures in person, then they can complete them on internet using Research Electronic Data Capture (REDCap) [43]. If a caregiver does not complete baseline assessments within 30 days of consent, then the caregiver may be rescreened, reconsented, and asked to complete baseline assessments one more time. At baseline, caregiver participants discuss initiating hydroxyurea with providers, and measures may be completed over 1-2 visits with 3 baseline visit types: (1) Full baseline: caregiver completes all baseline measures during one visit, (2) Baseline part 1: caregiver participants complete baseline measures not dependent upon the hydroxyurea discussion, and (3) Baseline part 2: caregiver participants complete baseline measures relevant to hydroxyurea discussion (Table 1).

The follow-up visit occurs between 3 and 7 months after baseline, and caregiver participants can complete measures during a clinic visit or on the internet. After both the baseline and follow-up visits, clinicians or research staff document whether they offered or prescribed hydroxyurea, whether they used Usual Care or H-SDM toolkit, patient's health care utilization, and hematology lab values (Figure 4). Study sites complete a follow-up survey to assess whether and how their site is continuing to implement guidelines and whether they are offering hydroxyurea 3 months after recruitment ends. Caregiver participants are compensated US $40 for completion of baseline measures, US $20 for partial completion, US $20 for hydroxyurea discussion, and US $40 for completing all follow-up measures. We also compensate caregiver participants US $5 each time they refilled hydroxyurea between baseline and follow-up time points, verified by electronic medical record review.

Figure 4. Study flowchart. H-SDM: hydroxyurea shared decision making; SCD: Sickle Cell Disease.
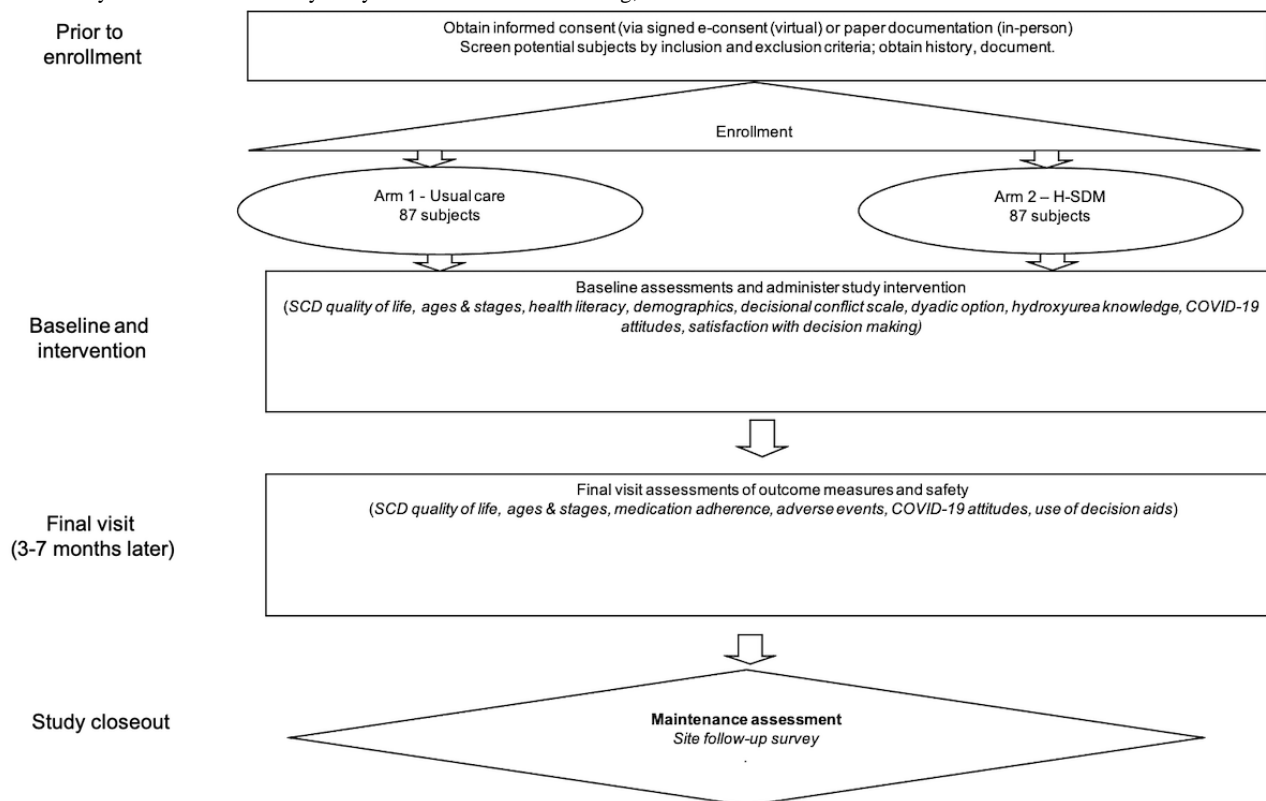
Primary Outcomes

The decisional conflict scale (DCS) is a 16-item measure that assesses decisional uncertainty [15]. Items are rated on a 4-point Likert scale of 0=*strongly agree* to 4=*strongly disagree*. To calculate the total score, the 16 items are summed, divided by 16, and multiplied by 25. The scores range from 0 to 100. The dyadic OPTION (observing patient involvement) scale is a measure of the caregiver perception of clinician behaviors involved in SDM [16]. Parents respond to the following item: "My doctor and I made the decision together." The scores range from 0 to 100 (Table 2).

Table 2. Primary and secondary outcome measures and covariates and fidelity assessments completed at baseline and follow-up visits in the engaging caregivers and providers of children with sickle cell anemia in shared decision making for hydroxyurea trial.

Construct	Measure	Brief description	Baseline	Follow-up
Primary outcomes				
Caregiver-reported decisional uncertainty	Decisional conflict scale [15]–effectiveness	Measures uncertainty experienced when feeling uninformed about options, unclear about personal values, or unsupported in making a choice	✓[a]	N/A[b]
Caregiver-reported perception of shared decision making	Dyadic OPTION [16]–effectiveness	Describes clinician behaviors to involve a patient or caregiver in decision making	✓	N/A
Secondary outcomes				
Caregiver-reported satisfaction with decision making	6-item survey [17,44]–effectiveness	Three items adapted from the empirical research related to procedural justice and 3 items assessing the influence of faith on decision making	✓	✓
Caregiver-reported hydroxyurea knowledge	8-item survey–effectiveness	Hydroxyurea knowledge survey (8 items): developed based on the existing literature, the Ottawa Knowledge User Manual, and it was used by caregiver and clinician stakeholders in our pilot work	✓	✓
Caregiver report of SCD[c]-specific quality of life and pain	PedsQL[d] SCD module [18]–effectiveness	Measures several domains of health-related quality of life including pain impact, fatigue, pain management, emotions, communication, and treatment adherence	✓	✓
Caregiver report of neurocognitive functioning	Ages and stages questionnaire [45]–effectiveness	Reliable, accurate developmental and social emotional screener for children aged between 2 and 60 months	✓	✓
Caregiver report of hydroxyurea adherence	Medical adherence measure subscale [46]–effectiveness	A 9-item survey that measures adherence problems and the extent of nonadherence in pediatric populations	N/A	✓
Caregiver report of continued use of decision aids	H-SDM[e] follow-up survey	For the H-SDM condition, caregiver report of continued use of decision aids: previsit brochure, postvisit booklet, and narrative videos, including sharing information with others	N/A	✓
Hydroxyurea uptake	Active hydroxyurea prescription–effectiveness	One item reported by the research coordinator. They report whether patients enrolled in the study have an active prescription for hydroxyurea using the EMR[f] (prescription in the last 6 months)	✓	✓
Hydroxyurea adherence	Lab values and pharmacy refill records–effectiveness	Labs reported by the research coordinator based on the EMR (past 12 months): HbF[g] level, which increases when taking hydroxyurea as prescribed, ANC[h], which decreases when taking hydroxyurea as prescribed, and MCV[i], which increases when taking hydroxyurea as prescribed	✓	✓
Hydroxyurea offered	1 item reported by research coordinator–reach	1 of 3 responses completed by the research coordinator based on a review of EMR data: hydroxyurea was not offered, offered, or previously prescribed. If not offered, coordinators choose a reason why (ie, not eligible because the patient is on transfusions)	✓	✓
Health care utilization	Hospitalizations, emergency room visits, and ill visits–effectiveness	EMR data on the number of hospitalizations, ill visits, and emergency room visits in the 6 months before enrollment (if possible, some participants may be 9 months of age) and the 6 months after enrollment	✓	✓
Covariates				
Demographics	Demographics survey	10-item survey assessing family demographics including patient and caregiver age, gender, race and ethnicity, socioeconomic status, insurance (public vs private), and caregiver highest level of education completed	✓	N/A
Health literacy	Newest vital sign [19]	Newest vital sign (3 min): tests literacy skills for both numbers and words	✓	N/A

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Construct	Measure	Brief description	Baseline	Follow-up
Caregiver report of the effects of COVID-19	CEFIS[j] [47]	The CEFIS was designed to be used in ongoing and new studies where COVID-19 may impact study outcomes. It conceptualizes the exposure to potentially traumatic aspects of COVID-19 and assesses the pandemic's impact on the family	✓	✓
Caregiver report of telemedicine use	COVID-19 and telemedicine use survey [48]	Items from the telemedicine usability questionnaire assess the impact of telemedicine on care	✓	✓
Fidelity				
Caregiver-reported fidelity	H-SDM toolkit parent checklist	Checklist to assess the toolkit components that were used during the hydroxyurea discussion with the clinician	✓	N/A
Research coordinator observation of decision making	Observer OPTION scale [20]–implementation	Observer quantifies clinician behaviors to involve a caregiver in decision making. A total score is calculated, ranging from 0 (no involvement) to 100 (exemplary involvement)	✓	N/A
Intervention fidelity	Intervention fidelity checklist–implementation	Checklist to assess if the clinician used the intervention materials	✓	N/A
Study site report of continued use of intervention	Follow-up survey–maintenance	Survey to assess the continued implementation of the sites' guidelines and clinical characteristics to understand barriers and facilitators to maintain implementation	N/A	1-3 months after enrollment ends

[a]The check mark indicates that participants completed the measure either at baseline, follow-up, or both.

[b]N/A: not applicable.

[c]SCD: sickle cell disease.

[d]PedsQL: Pediatric Quality of Life.

[e]H-SDM: hydroxyurea shared decision making.

[f]EMR: emergency medical record.

[g]HbF: fetal hemoglobin.

[h]ANC: absolute neutrophil count.

[i]MCV: mean corpuscular volume.

[j]CEFIS: COVID-19 Exposure and Family Impact Survey.

Secondary Outcomes

A 6-item survey assesses satisfaction with decision making [17,44], and an 8-item survey assesses hydroxyurea knowledge. If the Cronbach alpha for items on these scales is acceptable (≥.70), then we will sum the ratings to obtain a total score; otherwise, we will analyze items separately. The medical adherence measure assesses problems associated with hydroxyurea adherence [46]. Nonadherence and late adherence are calculated as a continuous variable (0%-100%). The Pediatric Quality of Life Inventory Sickle Cell Module [18] is a 43-item scale with 9 dimensions that assesses health-related quality of life in patients with SCA. Caregivers rated how much of a problem an issue had been for a child on a 5-point scale of *Never* to *Almost Always*. Responses are reverse scored and linearly transformed to a 0-100 scale. Total scores are the sum of the items divided by the number of items answered. The Ages and Stages Questionnaire [45] is a set of questionnaires in which caregivers' complete questions appropriate for their child's developmental stage. Each developmental area is scored on a 3-point scale of 0=*not yet*, 5=*sometimes*, and 10=*yes* and then totaled and compared with area cut-off scores. The H-SDM toolkit follow-up survey measures caregivers' continued use of decision aids (Table 2).

Covariates

Covariate analyses will include data from the caregiver participant completed Demographics Survey and the Newest Vital Sign Survey [19]. The Newest Vital Sign Survey contains 10 items that assess health literacy skills using a mix of free response, yes or no, and Likert scale questions such as "how confident are you filling out medical forms by yourself?" The research team reviews the electronic health records to collect data on hydroxyurea (ie, if offered, if there is active prescription, adherence) based on lab values in the past 12 months, pharmacy refill records, and health care utilization.

To understand how the COVID-19 pandemic may impact trial study outcomes (eg, differential levels of distress), we added 2 additional measures in May 2020. The caregiver participants complete the COVID-19 Exposure and Family Impact Survey (CEFIS) [47]. The CEFIS contains following subscales: part 1 (exposure) comprises 25 items (yes or no responses) and part 2 (impact) comprises 12 items with 10 items using a 4-point scale rating impact on caregiver participant's and family's life and 2 items that use a 10-point distress scale. Part 3 is an open-ended question, so that participants could expand upon their experiences. Higher scores denote a more negative impact or exposure. The caregiver participants also complete the COVID-19 and telemedicine use survey [48], which contains 24 items rated on a 7-point Likert scale of 1=*completely disagree*

to 7=*completely agree*, with statements such as "telehealth improves my access to health care services."

Fidelity Assessments

The site study coordinator completes the intervention fidelity checklist and assesses whether the clinician used the treatment materials outlined in the protocol. The number of fidelity assessments that sites complete is determined based on site-specific expectations for enrollment. We developed the parent checklist specifically for this study to assess the H-SDM toolkit components used during the hydroxyurea discussion with the clinician. To ensure reliability, 2 research coordinators from the CC site independently code the recorded visits using the Observer OPTION scale [20]. Clinicians must obtain a score of 80 or higher. If a score of less than 80 is received, then it indicates that the clinician or site needs additional training (1-hour video conference call). Encounters will continue to be reviewed for fidelity to ensure that the clinician or site is implementing 80% of the required toolkit components. Finally, a follow-up survey 1-3 months after enrollment ends assesses whether sites have continued implementing the H-SDM toolkit guidelines.

Data Analyses

Data quality will be maintained through double data entry from site research team members and data quality checks from the coordinating site coordinator that assesses the conformance, completeness, and plausibility of electronic REDCap data. The coordinating site manager will also monitor data quality through random inspections. Any reliability issues were addressed with additional training. Discrepancies will be resolved by checking source data and, if necessary, by returning to patient charts to correct any inaccuracies.

All analyses will be conducted using Stata version 16 [49]. Before conducting analyses, the primary and secondary outcome measures' psychometric properties will be assessed (eg, the measures' dimensionality). The characteristics of the sites (eg, number of clinicians) and participants (eg, health literacy) will be summarized using descriptive statistics. Additional health care utilization variables will be analyzed as count variables and examined in the exploratory analyses.

Primary Outcomes Analyses

To examine differences between usual care and H-SDM toolkit groups on the DCS scale assessed at a single time point during the intervention session, a linear mixed-effects regression model with a robust variance estimator and maximum likelihood estimation will be used, with observations clustered within site and alpha set to .05. To examine differences between the usual care and H-SDM toolkit groups on the OPTION scale, we will conduct a logistic mixed-effects regression model with a robust variance estimator, maximum likelihood estimation, and observations clustered within site with alpha set to .05.

Secondary Outcomes Analyses

Parental knowledge and child health outcomes will be analyzed using linear mixed-effect regression models, with observations clustered within the site. To account for possible type I error inflation due to a large number of secondary outcomes, we will

use the Benjamini-Hochberg procedure [50] to decrease the false discovery rate, with the overall alpha set to .05. For health care utilization outcomes, generalized mixed-effect regression models will be employed, with binary outcomes estimated using logistic models and count outcomes analyzed with negative binomial models. The interaction between these demographic variables and treatment conditions will be included in the regression models. We will examine the impact of the COVID-19 pandemic on our trial outcomes by assessing the interaction between our treatment groups and scores on the CEFIS in regression models. Observations will be coded as occurring prepandemic or *during pandemic*, regardless of treatment condition assignment.

Subgroup Analyses

We will compare the characteristics of the following subgroups on outcome variables: (1) caregiver participants who enroll versus those who decline, (2) dropouts versus completers, (3) clinicians who adopt the H-SDM toolkit versus those who do not, (4) sites who adopt the full H-SDM toolkit versus those that adopt only the core components, (5) sites that continue to implement guidelines versus those who do not, and (6) observations collected prepandemic versus during the pandemic.

Process Improvement Analyses

During the H-SDM toolkit period, data are tracked on monthly run charts, which will be converted into p-charts or control charts to determine if the process of offering hydroxyurea is under control (ie, minimal variation in the data) and if there are any notable changes (ie, factors that change the process). The upper and lower control limits will be calculated as 3 sigma from the mean (ie, standard Shewhart chart method) [21]. We will consider any data point outside the control limit variation from a special cause.

Fidelity Analyses

We will examine the differences between sites that continue to implement the intervention components and those who discontinue the toolkit use.

Statistical Power

We based sample size calculations on the smallest effect sizes (Cohen *d*) reported in previous studies using the DCS (effect sizes range from *d*=0.4 to 1.2) [22], our primary outcome, and a stepped-wedge design (eg, Hussey and Hughes approach) [14,23]. We calculated power analyses using the optimal design [51] power analysis software. With our planned sample size of n=87 per group (total sample size N=174) and up to 10%-15% missing data on our primary outcome, we will have at least 80% power to detect a standardized effect size difference of *d*=0.40 between our treatment groups on our primary outcome.

Data and Safety Monitoring

The study oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) comprising members having expertise in SDM, hematology, psychology, biostatistics as well as a parent of a young child with SCA and an adult patient living with SCA. The DSMB will assess safety and efficacy data (if applicable), along with study's progress and data integrity. These experts will review and evaluate the accumulated data

for participant safety, adverse events, and study's conduct and progress every 6 months. The DSMB will make recommendations to the appropriate regulatory agencies (IRB and Patient-Centered Outcomes Research Institute [PCORI]) concerning the continuation, modification, or termination of the study. Given the study is low risk, there are 2 conference calls scheduled each year.

Although no adverse events are anticipated, we will ensure that each site has procedures to refer any parents who become upset to appropriate resources for follow-up. The principal investigator (PI), a clinical psychologist with experience in managing parental distress, will provide study staff and clinician training. The PI and site PI will be notified if any individual needs psychological follow-up due to study participation. The IRB at CCHMC will be notified as soon as the immediate needs of the participant are addressed. For any severe adverse events (ie, life-threatening), the study staff will inform the PI within 1 working day. All serious adverse events will be reported to the IRB within 48 hours of the event.

Results

The ENGAGE HU trial was funded in August 2017, and the Ethics Committee of CCHMC approved the study (Approval No. 2017-6612) in November 2017. Patient recruitment started in July 2018 and will end in November 2021. The study will be completed in February 2022. As of February 2021, we have enrolled 120 caregiver participants. We expect to disseminate the findings of the trial through peer-reviewed journals in the summer of 2022.

Discussion

Principal Findings

The ENGAGE HU trial compares the existing ASH clinician pocket guide with the H-SDM toolkit, which is a caregiver-centered, technology-enhanced decision support toolkit to help clinicians implement SDM for hydroxyurea [11]. We designed the H-SDM toolkit components to increase the likelihood that caregivers and health care providers would make a change in their behaviors (ie, engage with one another to make a decision about hydroxyurea). The H-SDM toolkit targets the worries, fears, and uncertainty of caregivers regarding hydroxyurea initiation. Improving hydroxyurea uptake is an important issue, as it is efficacious for patients with SCA. Given the broad stakeholder input and our preliminary studies, we believe that the H-SDM toolkit dissemination method has the potential to promote SDM and enhance the quality of care provided to children with SCA [52].

Strengths and Limitations

Several aspects of this trial will enable the rapid adoption of findings into practice. First, we developed the H-SDM toolkit with substantial clinician and caregiver input; thus, it contains components these stakeholders felt were feasible, acceptable, and essential for improving clinical care. Second, we designed the H-SDM toolkit with core and optional components so that it can be tailored to the needs of individual families and be broadly applicable across many clinical settings. Third, virtual reality simulation provides guided practice in facilitating an SDM process. It is also a low-cost clinician training intervention that will be made accessible on national SCA-focused websites shared across SCA networks. Virtual reality training can occur in person or using web-based video conferencing tools (eg, Zoom or Microsoft Teams) [41], which is especially useful in the context of the ongoing COVID-19 pandemic. Finally, sites included in this trial were selected because their patient populations mirror the larger US SCA population with respect to economics, geography, and racial and ethnic diversity. This diversity increases the applicability of our findings to nonstudy settings and increases the available study pool.

There are some limitations to this study that should be acknowledged. A critical consideration for the ENGAGE HU trial is that SCA primarily affects individuals of African and Hispanic or Latino descent. Although the ENGAGE HU trial design includes best-practice strategies for recruiting people of color in research, we may experience recruitment difficulties because potential participants are mistrustful or have child care and transportation issues [53]. Furthermore, a successful and timely completion of clinical trials in the SCA population is compounded, as it is a rare disease with a smaller pool of available participants [54]. A potential barrier to intervention fidelity is the intrinsic difficulty in changing behavior. Given our goals to alter caregiver-clinician interactions, we address this barrier through guided practice in the virtual reality environment and audio recordings of a percentage of caregiver-clinician hydroxyurea interactions. These interventions should foster fidelity. Our pilot work indicates that clinicians currently using the toolkit decision aids find them beneficial and recommend them to others [11]. Ultimately, we hope that our study findings will have a substantial impact on improving health outcomes and decreasing health care costs in pediatric SCA and other chronic conditions.

Authors' Contributions

LC, LS, WB, FR, MK, MB, KS, MT, CQ, and RW designed this study; JP, CM, and LC designed the statistical analysis plan; LC and CN obtained permission from the ethics committees; AH, HS, CN, YL, SB, AT, JR, AY, KW, AK, CC, SC, CP, AH, SR, LN, EM, AS, and SR carried out this trial; AH and LC drafted this manuscript; and all authors read, carefully reviewed, and approved the final manuscript.

Conflicts of Interest

Author REW receives hydroxyurea donations for investigator-initiated research studies from Bristol Myers-Squibb Foundation and Addmedica, Inc. LN received research funding (2018-2020) from Patient-Centered Outcomes Research Institute, National Heart, Lung, and Blood Institute, Seattle Children's Research Grants, Doris Duke Foundation, Health Resources and Services Administration, Terumo Corporation, Bluebird Bio, Sancillo and Company, Celgene Corporation, Imara Corporation, Sangamo Therapeutics, Silarus Therapeutics, Pfizer, Global Blood Therapeutics, La Jolla Pharmaceuticals, Mast Therapeutics, and Selexys Pharmaceuticals. She was also a consultant for Apopharma, Bayer-Global, Novartis, Pfizer, Emmaus Medical, and CTD Holdings. None of the research funding or consultancy were related to the research conducted. The other authors have no conflicts to declare.

Multimedia Appendix 1
Peer-review report.
[PDF File (Adobe PDF File), 581 KB - resprot_v10i5e27650_app1.pdf]

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Abbreviations

ASH: American Society of Hematology
CC: co-ordinating center
CCHMC: Cincinnati Children's Hospital Medical Center
CEFIS: COVID-19 Exposure and Family Impact Survey
DCS: Decisional Conflict Scale
DSMB: Data and Safety Monitoring Board
H-SDM: hydroxyurea shared decision making
IRB: institutional review board
NHLBI: The National Heart, Lung, and Blood Institute
PCORI: Patient-Centered Outcomes Research Institute
PI: principal investigator
RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
SCA: sickle cell anemia
SDM: shared decision making

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<u>Protocol</u>

Determining the Effectiveness of a New Device for Hand Therapy (The FEPSim Device): Feasibility Protocol for a Randomized Controlled Trial Study

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Abstract

Background: Impairments of the forearm, wrist, and hand affect a sizable proportion of individuals and impose a significant economic burden on health care systems. FEPSim is a medical device for hand and wrist rehabilitation. The FEPSim device could be part of the standard of care for upper extremity rehabilitation during therapeutic activities to increase range of motion, dexterity, and strength. FEPSim has not yet been tested in a health care setting; therefore, a trial of the effectiveness of FEPSim in upper extremity rehabilitation is warranted.

Objective: This study aims to assess the feasibility of conducting a definitive trial in terms of recruitment, eligibility criteria, the type and number of diagnoses included, the length and dosage of the intervention, and data collection methods. This study also aims to gather clinical and statistical information as well as information related to the cost and usability, which allows for an economic evaluation of the device.

Methods: The trial will use a randomized controlled design comprising 47 intervention participants and 47 control group participants. Participants will be adults (age≥18 years) attending outpatient rehabilitation with limitations in their forearm, wrist, or hand function due to distal radial or ulnar fractures, stroke, or osteoarthritis. This study's primary outcome variables are related to patients' range of motion and strength, specifically active and passive wrist flexion and extension range of motion; active and passive forearm pronation and supination range of motion; grip strength; and pinch strength. The secondary outcome variables are related to patients' perceived wrist pain and disability in activities of daily living. The patients' perceived wrist pain and disability in activities of daily living will be measured using the patient-rated wrist evaluation questionnaire. The control group will receive the standard of care at each of the 2 hospital facilities (Glenrose Rehabilitation and Royal Alexandra Hospitals). The intervention group will receive the same standard of care as the control group at each facility and will use the FEPSim device for therapeutic activities to increase strength, range of motion, resistance, and dexterity. All the participants will be assessed at baseline (week 0); weeks 2, 4, and 8; and postintervention (week 10).

Results: The FEPSim study was launched in April 2020. This study is currently on hold because of the global COVID-19 pandemic. The recruitment process is expected to resume by September 2020, and the primary impact analysis is expected to be conducted by December 2020.

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Conclusions: This study will provide valuable information on the measurement of comparative intervention effects, technology acceptance by hand therapists, and how associated treatment and product costs will contribute to the evidence planning process, which will be crucial for the future adoption of FEPSim.

Introduction

Background and Rationale

People affected by musculoskeletal disorders (MSDs) of the forearm and wrist, such as fractures (including those exacerbated by osteoporosis) and osteoarthritis, as well as people who have had a stroke will experience impairments of the upper limbs [1]. Impairments of the upper limbs affect functioning in everyday life and are correlated with a low quality of life [2]. Impairments of the forearm, wrist, and hand represent a health-related problem that affects a sizable proportion of individuals and impose a significant economic burden for health care systems. For example, in Alberta, Canada, by 2017, forearm fractures accounted for 17,031 cases with an incidence rate of 441 (new cases), the prevalence of osteoporosis accounted for 174,481 cases with an incidence rate of 18,603 (new cases); 21.00% (36,641/174,481) of people who have osteoporosis will have a fracture (eg, wrist fractures) [3]; the prevalence of different types of strokes accounted for 5277 cases with an incidence rate of 115 (new cases); 49.54% (2614/5277) of people who had a stroke also experienced an upper limb impairment; and the prevalence of osteoarthritis accounted for 449,561 cases with an incidence rate of 34,479 (new cases). The economic burden on Alberta's health system as a result of caring for impairments of the forearm, wrist, and hand is significant and is expected to increase along with the projected increase in the age and size of the population. By 2017, the average cost of hospital inpatient care in Alberta totaled CAD $18,642,407 (US $15,287,926.24), an increase of 7.7% compared with the average cost in 2016 [4].

FEPSim, developed by Karma Machining & Manufacturing Ltd, is a medical device for hand and wrist rehabilitation. The FEPSim device could be part of the standard of care for upper extremity rehabilitation during therapeutic activities designed to increase range of motion, dexterity, and strength. These activities include controlled movements, strengthening, and exercises for retraining different grasp patterns that are used for activities of daily living and work tasks. Grading these activities is important to achieve therapeutic objectives and measure improvement. However, the equipment that is usually available in clinical settings does not allow therapists to ascertain their patients' range of motion or the strength of their arms and hands (eg, wrist pronation or supination and flexion or extension) during functional hand movements and grasp patterns. FEPSim is a medical device that was developed for upper extremity rehabilitation and is used to strengthen the hand and wrist with movements such as wrist flexion and extension; hand and forearm pronation and supination; and different grasp patterns such as power grasp, spherical grasp, lateral grip, and disk grasp. FEPSim can be adjusted according to the patient's capabilities during the rehabilitation process, thus allowing the therapist to grade the activities in terms of resistance and repetitions of any given exercise. FEPSim also allows the therapist to ascertain the patient's strength and the degrees of range of motion that are achieved during active movements of the hand or forearm.

The FEPSim device appears to have potential advantages over current technologies. Hand therapy devices fall into 1 of the following 2 categories:

1. Low-cost and portable devices (average price: CAD $127.07 [US $104.16]) designed to offer specific hand therapies (eg, pronation or supination), such as *Rolyan Pronation/Supination* (CAD $188.57 [US $154.58]), or strengthen the forearm, such as *The Pronator* (CAD $108.64 [US $ 89.05]; a price list is available at Performance Health Trademarks [5]). The main disadvantage of these devices is that important measurements during hand therapy activities cannot be taken directly from them, and they are not adjustable.

2. High-cost (portable and nonportable devices) commercial electromechanical devices designed to simulate the basic motions are required by the upper extremities in most occupations and to conduct hand therapy. This is the case for the Baltimore Therapeutic Equipment (BTE) work simulator and SaeboReJoyce [6]. For example, the estimated price of the BTE is between CAD $60,012.80 (US $49,193.99) and CAD $113,357.52 (US $92,921.99; email communication with the BTE Senior National Sales Representative) [7], whereas the SaeboReJoyce costs CAD $17,350.68 (US $14,222.79) [8]. The high cost of the BTE and SaeboReJoyce means that these devices are simply not affordable in many health care settings; thus, the FEPSim device could be a more affordable alternative for hand therapy purposes. The current prototype selling price of an FEPSim device is approximately CAD $6000 (US $4920; unit cost; eg, cost of goods sold). After evaluation and market analysis, to determine the scale of production, the FEPSim device should retail for less than CAD $1300 (US $ 1065.64) if the company adopts injection molding and brings in more purchased parts, with future models bringing costs down further. In addition, FEPSim has other potential advantages, such as compactness, portability, and ease of use.

Robots could be an alternative to assist in the rehabilitation process of the hand. However, these robotic systems are not yet available in hand therapy settings. A recent survey that aimed to examine patents and developments for hand rehabilitation robots found 28 systems, among which only 1, the Hand Exoskeleton Rehabilitation Robot, was designed to provide continuous passive motion (ie, the robot executes the motion of the patient's upper limbs) as well as active independent movements (ie, the patient performs a motion according to his or her own ability) to the fingers and the thumb [9]. In another review, only 2 robotic devices were found for active independent movement of the hand [10]. All these robotic devices for hand rehabilitation were still in the prototype design phase, which corresponds to a technology readiness scale lower than 5 [11]; therefore, they have not yet been tested in real rehabilitation contexts.

Hand Therapy: Existing Knowledge

The standard of care for rehabilitation for impairments of the forearm, wrist, and hand includes a combination of modalities and techniques such as immobilization, management of scar tissue, sensory modification, edema management, and therapeutic activities to increase the range of motion; dexterity and strength; and, ultimately, hand function [2]. The current evidence for the therapeutic standard of care activities depends on the medical condition and the strategies or modalities used to achieve therapeutic outcomes. In general, Roll and Hardison [2] found that for all MSDs, the strongest evidence for occupational therapy interventions supports postsurgical early active motion protocols and splinting for various conditions. However, few studies have shown significant differences in long-term outcomes among the compared interventions. For osteoarthritis, in particular, there is limited evidence that education and exercise can help patients regain function and reduce pain, whereas the evidence for the use of splinting for the same purposes is mixed. A systematic literature review summarized the outcomes of 26 studies for rehabilitation after distal radial fractures, finding that all the studies had low-quality designs and no clinically essential outcome differences among the modalities implemented in the interventions. The outcomes were categorized as functional (eg, range of motion, pain, grip strength, and activities of daily living), clinical (eg, residual soft tissue swelling), and resources (eg, number of outpatient attendances). The authors also found that, despite a lack of evidence for greater effects regarding long-term (3 months) goals, early occupational therapy led to more short-term improvements in gripping, pinching, and range of motion [12].

Strokes also affect hand function. The interventions that have been effective in managing spasticity are constraint-induced movement therapy, mirror therapy, and functional skill retraining. Furthermore, the recommended activities are passive range of motion (PROM) and active range of motion (AROM) activities, along with movements and functional activities with high levels of repetition [13]. Another review stated that a patient with a neurological condition that affects his or her hand movement (eg, stroke) needs to repeat a motion 300 to 400 times to learn a movement, but in current therapy sessions, the standard is closer to 30 repetitions. In a clinical setting, the recommended dosage would be a 60-minute session, 3 times a week for 6 weeks, where the use of technology can help achieve more repetitions in a shorter period of time [14]. Burns may also affect hand function. In general, the standard of care includes edema management, splinting, patient caregiver education, range of motion and strengthening, scar management, and retraining in activities of daily living [15]. We did not find any research that examined the evidence for these modalities. Finally, a literature review about the cost-effectiveness of physiotherapy interventions found only 2 studies about hand rehabilitation in neurological conditions. None of these studies reported any significant cost-effectiveness between the interventions under study. However, one study in which a high-tech device (ie, a robotic system) was used to support hand therapy showed that a group that used robot intervention used less health care, which reduced the overall cost [16].

Evaluation Objectives and Research Questions

FEPSim has not yet been tested in a health care setting; therefore, a trial of the effectiveness of FEPSim in upper extremity rehabilitation is warranted. The primary objective of this study is to assess the feasibility of conducting a definitive trial in terms of recruitment, eligibility criteria, the type and number of diagnoses included, the length and dosage of the intervention, and the data collection methods. This study also aims to gather clinical and statistical information as well as information related to the costs and usability (adoption) of the new technology used in this study. Thus, this study has 6 secondary objectives:

1. To explore the clinical effectiveness of adding the FEPSim device to the standard of care for patients with injuries and clinical conditions of the forearm, wrist, and hand.
2. To assess the outcome measures for measuring changes in the dependent variables.
3. To gather and synthesize the data, from which the sample size of a definitive randomized controlled trial (RCT) can be estimated.
4. To measure the key outcome domains (for completion rates, missing data, estimates, variances, and 95% CI for the differences between the intervention and control groups) for patients with injuries and clinical conditions of the forearm, wrist, and hand.
5. To examine the total and component costs associated with the FEPSim device and with standard of care interventions for patients with injuries and clinical conditions of the forearm, wrist, and hand from an institutional perspective (ie, hospitals).
6. To investigate the usability of the FEPSim device by therapists.

Methods

Study Design

This study will use a multimethod research design. The *Methods* section will be presented with regard to the objectives of the study.

Primary Objective and Secondary Objectives 1 to 4: Research Design

The feasibility parallel-group RCT will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines for randomized feasibility studies [17]. The experimental group will receive an intervention consisting of sessions with the FEPSim device plus the standard of care, whereas the control group will only receive the standard of care for hand therapy.

Secondary Objective 5: Study Design

For the economic evaluation component of this study, we will follow the Consolidated Health Economic Evaluation Reporting Standards [18] and Guidelines for the Economic Evaluation of Health Technologies: Canada [19].

Secondary Objective 6: Study Design

For the usability component of this study, we will follow a qualitative description design [20].

Study Setting

The study will be conducted in 2 health care facilities: the Royal Alexandra Hospital Outpatient Clinic and the Glenrose Rehabilitation Hospital Specialized Rehabilitation Outpatient Program Hand Class. Both institutions are located in Edmonton, Alberta, Canada.

Eligibility Criteria

Inclusion Criteria: Participants (Patients)

This study will include outpatient adults (≥18 years) with limitations in their forearm, wrist, or hand function due to distal radial or ulnar fractures, stroke, or osteoarthritis (eg, patients who have undergone a wrist salvage procedure).

Inclusion Criteria: Participants (Therapists)

This study will include hand therapists from hand therapy services who have used the FEPSim device.

Exclusion Criteria: Participants (Patients)

Outpatients will not be included in our study if they (1) have chronic regional pain syndrome as these participants' baseline measurements would differ too much and they would experience abnormal pain responses; (2) report subjective or patient limitations that prevent them from participating (eg, excessive pain and edema); (3) are unable to participate in the program (outpatient hand clinic) twice a week (eg, transportation and limited buy-in); (4) have limitations in their reading and listening comprehension of the English language that prevent them from understanding the patient-rated wrist evaluation (PRWE) questionnaire; or (5) have limitations in following instructions due to a severe cognitive impairment.

Interventions

The eligible participants will be randomly assigned in a 1:1 ratio to either the experimental group or the control group.

Control Group

This group will receive the standard of care at each hospital, which consists of immobilization for 7 to 8 weeks (for fractures) after the time of the injury or surgery, followed by hand therapy

sessions for 10 weeks to manage scar tissue, sensory modifications, and edema as well as therapeutic activities to increase strength, range of motion, and dexterity. These therapeutic activities will be carried out using the equipment and materials available at each hospital, including weights and elastic or gripping equipment and materials. The sessions' length and frequency will depend on the patients' needs and diagnoses. The length of each session will be between 30 minutes and 45 minutes, and they will be carried out once or twice per week.

Experimental (Intervention) Group

This group will receive the same standard of care as the control group at each hospital, which consists of immobilization for 7 to 8 weeks after the time of the injury or surgery, followed by hand therapy sessions for 10 weeks to manage scar tissue, sensory alterations, and edema. The experimental group will use the FEPSim device for therapeutic activities to increase strength, range of motion, and dexterity. For this group, the sessions' length and frequency will depend on the patients' needs and diagnoses. The length of each session will be between 30 minutes and 45 minutes, and they will be carried out once or twice per week.

Outcome Variables

Primary Objective and Secondary Objectives 1 to 4: Primary Outcome Variables

The retention rates and intervention compliance will be calculated for the primary objective. The retention rates will be calculated according to the participants' discontinuation of the interventions and their absence at the posttest at week 10. Intervention compliance means all of the hand rehabilitation sessions are completed by each group [21]. This study's primary outcome variables for secondary objectives 1 to 4 are related to range of motion and strength: (1) AROM and PROM of wrist flexion and extension and forearm pronation and supination, (2) grip strength, and (3) pinch strength.

Primary Objective and Secondary Objectives 1 to 4: Secondary Outcome Variables

The secondary outcome variables are the patients' perceived wrist pain and disability in activities of daily living.

Primary Objective and Secondary Objectives 1 to 4: Confounding Variables

The confounding effects of the participants' age, gender, and medical condition (distal radial or ulnar fractures, stroke, or osteoarthritis); whether the participants are taking any pain medication; what activities the participants perform at home or work; and the therapist providing the intervention will be determined.

Secondary Objective 5: Estimating the Costs and Resource Use

This study aims to ascertain which factors result in differences in costs or outcomes when comparing the standard of care with the FEPSim device. The estimated costs of the interventions will be from an institutional perspective, that is, the Glenrose Rehabilitation and Royal Alexandra Hospitals. To estimate the resource use and costs, we will use a single study–based

economic evaluation approach (patient-level data). The costs will include resources related to the following categories [19]: cost of the time spent by the human resources (hand therapists and support personnel, if applicable) involved in each of the interventions; this time will be converted to cost based on the average salary for each level of staff. It will also include the time human resources spend on the training sessions, learning to use the FEPSim device (ie, training sessions), and seeking technical support (in the intervention group).

Secondary Objective 6

We will determine the usability and technology acceptance of the FEPSim device based on the Unified Theory of Acceptance and Use of Technology constructs, that is, performance expectancy (FEPSim was useful); effort expectancy (learning to use FEPSim was easy); facilitating condition (using FEPSim was well suited to my needs); social influence (people who are important to me think that I should use FEPSim); behavioral intention to use FEPSim (I plan to use FEPSim in the near future); and actual use of FEPSim, if applicable [22].

Participant Timeline

This feasibility trial consists of a 10-week intervention treatment phase; this study does not have a follow-up phase. The total trial data collection period will be 9 months. As shown in Figures 1 and 2 and in Table 1, measurements will be taken at 4 points in time for each group: at baseline (week 0); during weeks 2, 4, and 8; and after the intervention (week 10).

Figure 1. Flow of participants. AROM: active range of motion; PROM: passive range of motion; PRWE: patient-rated wrist evaluation questionnaire; T0: data collection point 1.
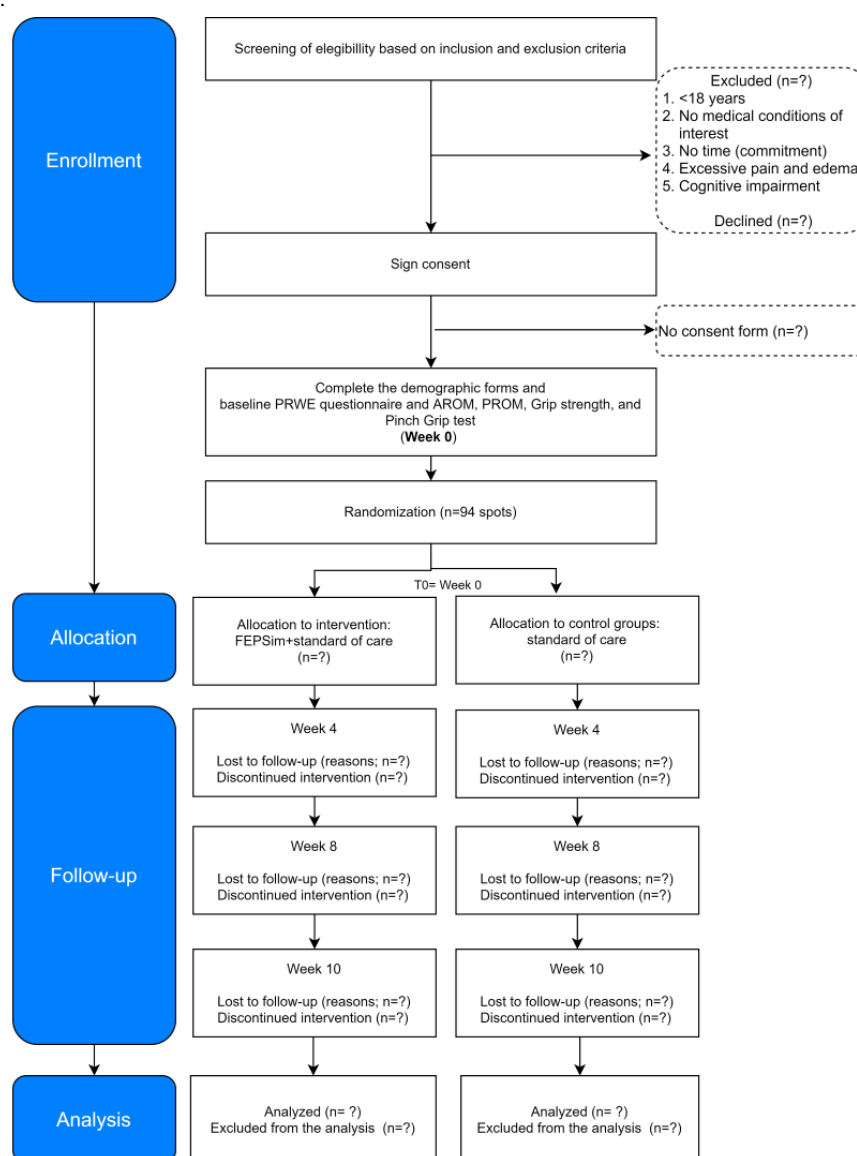
Figure 2. Study design schema (primary objective and secondary objectives 1-4). AROM: active range of motion; PROM: passive range of motion; PRWE: patient-rated wrist evaluation questionnaire.
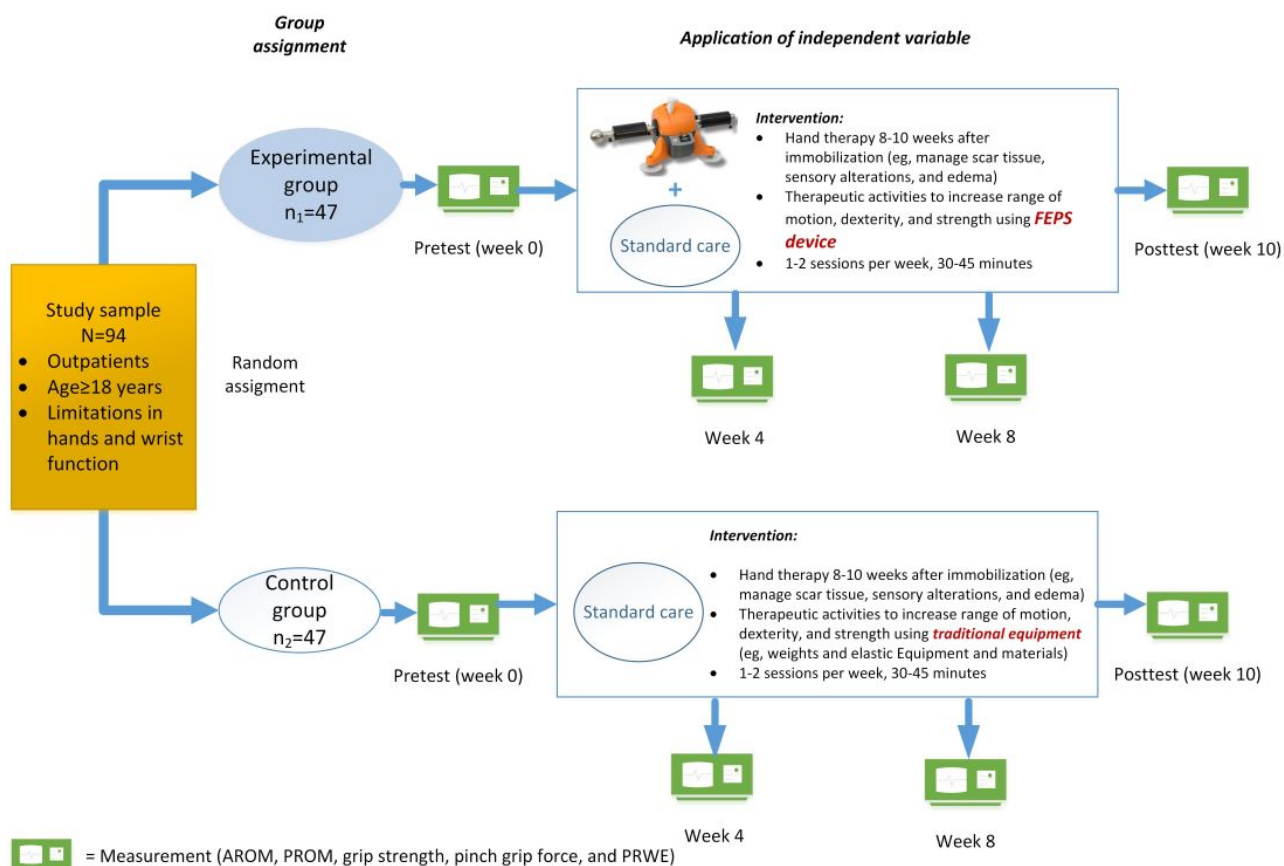
Table 1. Key variables and measurements.

Variables	Participants	Measurement	T_0[a]	T_1[b]	T_2[c]	T_3[d]
Primary outcome						
AROM[e]	Patients	Goniometer	✓	✓	✓	✓
PROM[f]	Patients	Goniometer	✓	✓	✓	✓
Grip strength	Patients	Dynamometer	✓	✓	✓	✓
Pinch grip	Patients	Pinch meter	✓	✓	✓	✓
Secondary outcomes						
Perceived wrist pain and disability during daily life activities	Patients	PRWE[g] questionnaire	✓	✓	✓	✓
Measures of usability and technology acceptance						
Performance expectancy	Therapists	Semistructured interview				✓
Effort expectancy	Therapists	Semistructured interview				✓
Facilitating condition	Therapists	Semistructured interview				✓
Social influence	Therapists	Semistructured interview				✓
Behavioral intention to use the FEPSim	Therapists	Semistructured interview				✓
Actual use of the FEPSim	Therapists	Semistructured interview				✓
Measurements of economic evaluation						
Costs	N/A[h]	Questionnaire for costs associated with use of the FEPSim and provision of the intervention	✓			✓
Covariates						
Demographic variables	Patients	Self-report assessment questionnaire	✓			
Medical condition (distal radial or ulnar fractures, stroke, or osteoarthritis)	Patients	Therapist records	✓			
Whether the participant is taking any pain medication	Patients	Self-report assessment questionnaire	✓	✓	✓	✓
Activities the participant preforms at home or work	Patients	Self-report assessment questionnaire	✓	✓	✓	✓

[a]T_0: data collection point 1.

[b]T_1: data collection point 2.

[c]T_2: data collection point 3.

[d]T_3: data collection point 4.

[e]AROM: active range of motion.

[f]PROM: passive range of motion.

[g]PRWE: patient-rated wrist evaluation.

[h]N/A: not applicable.

Sample Size

Primary Objective and Secondary Objectives 1 to 4

As this is a feasibility study, a sample size calculation is not required [17]. However, we can estimate the number of participants we will be able to recruit during the data collection period. According to the clinical partners at the 2 hospitals involved in this study, approximately 167 patients who potentially meet the inclusion criteria will be admitted (accessible population). We aim to recruit 47 participants for each group, for a total sample size of 94 participants, to compensate for a 30% dropout rate. Thus, the recruitment of 94 participants represents 56.3 % (94/167) of the participation rate. This number is based on our ability to detect a small effect size (Cohen d=0.25) with 80% power and an α of .05 (two-sided). The sample size calculations were estimated using G*Power software version 3.1.9.4 (Universitat Kiel) [23].

Secondary Objective 6

Ten hand therapists from the hand therapy services who have used the FEPSim device will be recruited. Individual interviews will be conducted until either redundancy or theoretical saturation of the data has been achieved [24].

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Recruitment

Participants: Patients

An invitation to participate will be posted in several locations at the Glenrose Rehabilitation and Royal Alexandra Hospitals. Hand therapists at both the hospitals will support the recruitment strategies, including the provision of information sessions and one-on-one conversations with potential participants. The first contact with a potential participant will be made through one of the hand therapists not involved in the research team. Therapists who are already involved in the clinical care of the patients will then determine the individuals' willingness to be approached by the hand therapist researcher regarding participation and obtain their consent for the study.

Participants: Therapists

The study coordinator will send out an invitation to participate via email to potential participating therapists, and posters will be put up in the therapists' staff rooms at the Glenrose Rehabilitation and Royal Alexandra Hospitals.

Allocation: Sequence Generation

Probability sampling stratified by medical condition (wrist fractures, acquired brain injuries, burns, or osteoarthritis) will be used. Random sequence generation will be prepared in advance by a research team member (AMC Sr) on an Excel file spreadsheet (RAND function) using permuted block randomization with a block size of 4 and a ratio of 1:1.

Allocation: Concealment Mechanism

Allocation concealment will be ensured, as we will not release the randomization code until the patients have been recruited in the trial and all the baseline measurements have been completed.

Allocation: Implementation

If a potential participant meets the inclusion criteria, the hand therapist researchers (CH, DY, GD, and JS) will ask the study coordinator (AML) to check whether a place is available in the study for that participant in a given strata (ie, medical condition). If a place is available, then one of the therapist researchers (CH or DY) or another therapist involved in the recruitment process (JS or GD) will invite the participant to participate in the study, explain the study to him or her, and ask him or her to sign the consent form. If a potential participant is assigned to a particular therapist researcher (CH, DY, JS, or GD), this therapist will not invite this participant to participate in the study. Instead, a secondary therapist researcher will do so. As a result, the freedom to decline will not be compromised. Once the participants or their substitute decision makers have signed the consent form and given their assent, the therapist researchers (CH or DY) will inform the study coordinator (AML). The study coordinator (AML) will allocate each participant to one arm of the trial according to the allocation protocol and assign a code. This code will be provided to the therapist researchers (CH or DY) and research assistants (RAs).

Blinding (Masking)

The assessments of range of motion and strength measurements and the PRWE questionnaire will be conducted by RAs blinded to the treatment allocation. Due to the nature of the intervention, neither the participants nor the therapist can be blinded to the treatment allocation, but they are strongly encouraged not to disclose the participants' allocation status during the assessments. An RA will enter the data onto a computer on separate datasheets, and a senior RA will conduct the data analysis under the supervision of the principal investigators (AMC Sr and AMRR).

Data Collection Methods

Primary Objective and Secondary Objectives 1 to 4: Primary Outcome Variables

The AROM and PROM of the wrist extension or flexion, radial and ulnar deviation, and pronation and supination will be measured using a goniometer (Baseline 360-degree, 12-inch clear plastic goniometer); the grip strength will be measured using a dynamometer (Baseline Lite hydraulic, 200 lb); and the pinch strength will be measured using a pinch gauge or pinch meter (Jamar pinch gauges).

Primary Objective and Secondary Objectives 1 to 4: Secondary Outcome Variables

The patients' perceived wrist pain and disability in activities of daily living will be measured using the PRWE [25]. The PRWE is a 15-item questionnaire that assesses 3 components: pain, function during specific activities of daily living, and function during usual activities (personal care, household work, work, and recreational activities). Studies have found this questionnaire to be a valid and reliable assessment tool for evaluating patient-based pain and disability levels in routine clinical practice [26].

All hand therapy sessions for both groups will be conducted in the hand therapy area at the Glenrose Rehabilitation and Royal Alexandra Hospitals by the staff hand therapists. The length and frequency of the sessions for the participants in both groups will be recorded by the therapists. The RAs will measure the AROM, PROM, grip strength, and pinch strength. They will also administer the PRWE to all the participants before (week 0) and after the intervention (week 10) and during weeks 2, 4, and 8. The total time taken to administer the measures will be approximately 60 minutes. The RAs will be trained in the administration of the outcome measurements and adequate use of the assessment tools (eg, dynamometer, goniometer, and pinch meter) by experienced hand therapists.

Secondary Objective 5: Estimating the Costs and Resource Use

To estimate the resource use and costs, we will use a single study–based economic evaluation approach (patient-level data). The costs will include resources related to the following categories: (1) the time human resources spend on the sessions will be monitored during the study, whereas the information on the average salaries of the human resources will be taken from the records at each hospital; (2) the capital cost of the equipment used in each intervention and depreciation of the equipment will be calculated using the straight-line depreciation approach; (3) therapeutic supplies (eg, weights and elastic or squeezing supplies); (4) consumables (eg, bandages and sanitization

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wipes); (5) cost of sterilization, if needed; (6) allowance costs (if any); and (7) maintenance costs (eg, calibration, preventive, and corrective maintenance of equipment). The information on the costs will be taken from the financial records at each hospital. In addition, we will conduct face-to-face interviews with the financial departments at both hospitals to identify the cost components and costing method.

Secondary Objective 6: Usability and Technology Acceptance

Once the data collection for the primary objective is completed, semistructured interviews (topic guided) will be conducted with the hand therapists who have agreed to participate and signed a consent form. The interviews with the therapists who used the FEPSim device during their interventions will be audiotaped for later analysis by the team members. The interviews will be conducted by one RA. To ensure anonymity, the therapists' responses will not be connected to their identities.

Data Analyses

Primary Objective and Secondary Objectives 1 to 4

Data analyses will be conducted using the intention-to-treat principle. Complete case analysis will be the primary method for dealing with missing data equal to or more than 10%. This is the most common method for dealing with missing data and reducing the risk of bias [27]. For missing data of less than 10%, we will use a simple imputation method by replacing the missing data with the average participants in the same strata (ie, medical condition). The analyses will focus on descriptive statistics and CI estimation rather than formal hypothesis testing [28]. Descriptive statistics will be used to characterize the groups at the pretest and posttest as well as during weeks 2, 4, and 8. The outcome variables as well as other data such as the length and dosage of each intervention will be summarized as n (%), mean (SD), or median (IQR), as appropriate. The retention rates, intervention compliance, and missing data will be summarized for outcomes related to the secondary objectives, which, together with the estimates, will assist in calculating the sample size for a definitive trial. As this study aims to assess the feasibility of conducting a definitive trial, clinical effectiveness is a secondary objective (ie, the study's proof-of-concept element). In this regard, comparisons of the outcome variables at the pretest (week 0) and posttest (week 10) within the groups will be performed using a paired two-tailed t test (or a Wilcoxon signed-rank test if the data are not normally distributed) for AROM, PROM, grip strength, and pinch grip force and a Wilcoxon signed-rank test for the PRWE. Comparisons between the groups at the pretest and posttest will be performed using a t test (or a Mann-Whitney U test if the data are not normally distributed) for AROM, PROM, and grip strength and a Mann-Whitney U test for the PRWE. With our sample size, there would be a power of 0.8 to detect a medium effect size of Cohen d=0.25. However, we are aware that our study might be underpowered due to the sample size. If no statistically significant differences are found, our results will be classified as inconclusive rather than negative. We will report 95% CIs and interpret the level of uncertainty based on them [28]. In addition, we will explore the effects of the covariates using general linear models or multilevel mixed models when

appropriate. All the α levels of significance will be set at $P \leq .05$ (two-tailed).

Secondary Objective 5: Estimating the Costs and Resource Use

For each intervention, descriptive statistics will be used to characterize the categories of the estimated costs (ie, mean [SD] or median [IQR] as appropriate). In this study, missing data costs will be replaced by means or medians, as appropriate. We will quantify uncertainties by reporting the differences between the means and 95% CIs for the categories of the comparator groups' estimated costs and then interpret the levels of uncertainty based on these [28] and by conducting statistical tests (ie, a t test or Mann-Whitney U, test as appropriate), while looking for differences in each category of estimated costs between the comparator groups. All α levels of significance will be set at $P \leq .05$ (two-tailed).

Secondary Objective 6: Usability and Technology Acceptance

The audiotapes will be transcribed, and content analysis will be performed. The content analysis will be data driven. The data codes will be generated inductively by the collected data. Along with coding, a small number of themes or categories will be generated. The analyses will be performed by an RA, and agreement in the interpretations will be achieved through a discussion between the research team members. The validity of the interpretations will be discussed with and agreed upon by every member of the research team.

Quantitative analyses will be conducted using the SPSS version 27.0, and qualitative analyses will be conducted using NVivo10 (QSR International) software.

Ethics and Dissemination

Research Ethics Approval

All procedures are approved by the ethics committee of Alberta University and the Northern Alberta Clinical Trials Research Centre, Canada.

Incentives

All participants will receive a coffee shop gift card after completing the study. The value of the coffee shop gift card will be CAD $25 (US $20.49).

Withdrawal From the Study

The participants and substitute decision makers can request to withdraw from the study at any time, either verbally or in writing. The participants will be able to withdraw from the study at any time before the group analysis is calculated. If a participant withdraws, their information will not be taken into account for analysis. In the event that a participant requests to have their data destroyed, the research team will honor this request by shredding and recycling the paper records and erasing any records stored on a computer hard drive using commercial software apps designed to remove all data from storage devices. However, once all the participants' data have been analyzed, a participant cannot withdraw. The participants will be informed of this in the consent letter. The deadline for withdrawal will

be once all the participants' data have been collected and the data analysis is underway. This will be around the 16th month of the study.

Consent or Assent

Signed consent will be obtained from all participants in the study. For those who are unable to give their informed consent, one of the therapist researchers (CH or DY) or another therapist involved in the recruitment process (JS or GD) will approach each potential participant and his or her substitute decision maker to provide information about the study. If these potential participants and their substitute decision makers give their consent, the substitute decision makers will sign the consent form, and we will seek the potential participants' assent.

Confidentiality

We will assign numerical codes to the participants instead of using their names or other identifiers. Only the study coordinator will have access to the master list where these codes are linked to the participants' first names. With the exception of direct conversations with each participant, their names will not be used, only their numbers will be used. Hard copies of the consent forms, questionnaires, and study notes will be kept in a locked filing cabinet in a laboratory (Corbett Hall 1-45, Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, Canada). All the deidentified electronic study documents will be encrypted and stored on a password-protected computer located in a laboratory (Corbett Hall 1-45, Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, Canada).

Access to Data

All the principal investigators will be given access to the cleaned data sets. The master list will be stored on a password-protected computer located in the principal investigator's laboratory (Corbett Hall 1-45, Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, Canada). Only the study coordinator will have access to this master list. The data will be retained for 5 years. There are no plans for future use of the data other than publishing them in peer-reviewed journals and at conferences. The data will not become part of a data repository and will not be involved in the creation of a research database or registry for future research use. After 5 years, the data will be destroyed. This will be done by shredding the paper records. Records stored on a computer hard drive will be erased using commercial software apps designed to remove all data from storage devices.

Quality Assurance and Safety

We have established an advisory committee to monitor the progress of the study and, if necessary, to provide recommendations to the team members for discontinuation, modification, or continuation of the study. This committee will include our current partners, as follows: (1) Glenrose Rehabilitation Hospital, (2) Royal Alexandra Hospital, (3) experts in the areas of economics and commercialization and experts in health technology assessment, (4) patient representatives who have undergone hand therapy, and (5) certified hand therapists.

We will follow the CONSORT guidelines for clinical trial feasibility [17]. In addition, we will assess the quality of our study using the PEDro (Physiotherapy Evidence Database) scale [24].

Results

The FEPSim study was launched in April 2020. Currently, this study is on hold because of the global COVID-19 pandemic. The recruitment process is expected to resume by September 2020, and the primary impact analysis is expected to be conducted by December 2020.

The results of this project will inform the development of best practices for clients with clinical conditions of the forearm, wrist, and hand, which impact the health of more than 35,072 Albertans annually. Improved rehabilitation can decrease the time needed to achieve functional outcomes, thereby decreasing health care costs. Returning patients more quickly to their valued occupations, including work, can decrease the costs associated with home care and other social services and reduce injury-related work time loss. FEPSim takes up little space, is much less expensive than comparable devices, and can easily be implemented throughout the public and private sectors in Alberta's health system. This project is an excellent example of how industries and the health care system can support each other to grow and diversify Alberta's economy and promote the entry of this valuable technology into the global rehabilitation market.

Discussion

The primary objective of this study is to assess the feasibility of conducting a definitive trial on the effectiveness and cost-effectiveness of the FEPSim device for individuals with medical conditions that affect hand function. The level of evidence for the rehabilitation of hand function due to MSDs and neurological injuries and diseases is conflicting and differs according to the medical condition as well as the strategies or modalities implemented and the equipment and materials used during the sessions. The equipment that is currently available for hand therapy is either low cost or does not allow therapists to grade their therapeutic activities and exercises accurately, or it consists of high-tech devices that many clinicians or health care systems cannot afford. FEPSim has the potential to become a sound alternative in the midpoint between these 2 extremes. FEPSim has a technological readiness level of 7 [11]; thus, it has a sufficient level of readiness that can be tested in a real-world clinical setting. This feasibility study is the first RCT to evaluate the potential benefits of the FEPSim, not only in terms of functional outcome variables but also in terms of the costs associated with the delivery of hand rehabilitation in 2 large hospitals. Conducting this RCT will provide valuable information. First, the estimates can be used for sample size calculations in future RCTs. Second, as we will measure the patients' outcome variables on 4 different occasions during the intervention, the results of this study will guide therapists by providing the expected percentage of a patient's improvement and data on how the progress is made over a period of 10 weeks. The literature suggests that early hand therapy has an effect on

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range of motion and strength [12]; thus, this study will provide information about FEPSim's potential to speed up the patient recovery process and reduce the length of treatment, which in turn may reduce treatment costs. In addition, the findings of this project can be used by therapists to develop exercise or activity standard protocols for hand rehabilitation interventions using the FEPSim device. Third, the estimations of the resource use and associated costs of the interventions during each arm of the trial will inform individuals who are responsible for

purchasing or procurement decisions and who work with hospital budgets. The results of this project will provide them with information about the feasibility of adopting FEPSim.

In conclusion, this study will provide valuable information, such as the measurement of comparative intervention effects, technology acceptance by hand therapists, the associated costs of treatment, and product costs. This will contribute to the evidence planning process, which will be crucial for the future adoption of FEPSim.

Acknowledgments

Authors' Contributions

AMC Sr, AMRR, and CG led the overall design of the evaluation; GG also contributed to the design. AMC Sr drafted the manuscript, and AMRR, CG, GG, AML, CH, DY, JS, and GD edited and reviewed the manuscript. AMC Sr is the principal investigator of this study.

Conflicts of Interest

None declared.

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Abbreviations

AICE: Accelerating Innovation Into Care
AROM: active range of motion
BTE: Baltimore Therapeutic Equipment
CONSORT: Consolidated Standards of Reporting Trials
MSD: musculoskeletal disorder
PEDro: Physiotherapy Evidence Database
PROM: passive range of motion
PRWE: patient-rated wrist evaluation
RA: research assistant
RCT: randomized controlled trial

Protocol

Chest Computed Tomography for the Diagnosis of COVID-19 in Emergency Trauma Surgery Patients Who Require Urgent Care During the Pandemic: Protocol for an Umbrella Review

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Abstract

Background: Many health care facilities in low- and middle-income countries are inadequately resourced. COVID-19 has the potential to decimate surgical health care services unless health systems take stringent measures to protect health care workers from viral exposure and ensure the continuity of specialized care for patients. Among these measures, the timely diagnosis of COVID-19 is paramount to ensure the use of protective measures and isolation of patients to prevent transmission to health care personnel caring for patients with an unknown COVID-19 status or contact during the pandemic. Besides molecular and antibody tests, chest computed tomography (CT) has been assessed as a potential tool to aid in the screening or diagnosis of COVID-19 and could be valuable in the emergency care setting.

Objective: This paper presents the protocol for an umbrella review that aims to identify and summarize the available literature on the diagnostic accuracy of chest CT for COVID-19 in trauma surgery patients requiring urgent care. The objective is to inform future recommendations on emergency care for this category of patients.

Methods: We will conduct several searches in the L·OVE (Living Overview of Evidence) platform for COVID-19, a system that performs automated regular searches in PubMed, Embase, Cochrane Central Register of Controlled Trials, and over 30 other sources. The search results will be presented according to PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis). This review will preferentially consider systematic reviews of diagnostic test accuracy studies, as well as individual studies of such design, if not included in the systematic reviews, that assessed the sensitivity and specificity of chest CT in emergency trauma surgery patients. Critical appraisal of the included studies for risk of bias will be conducted. Data will be extracted using a standardized data extraction tool. Findings will be summarized narratively, and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach will be used to grade the certainty of evidence.

Results: Ethics approval is not required for this systematic review, as there will be no patient involvement. The search for this systematic review commenced in October 2020, and we expect to publish the findings in early 2021. The plan for dissemination

is to publish the findings in a peer-reviewed journal and present our results at conferences that engage the most pertinent stakeholders.

Conclusions: During the COVID-19 pandemic, protecting health care workers from infection is essential. Up-to-date information on the efficacy of diagnostic tests for detecting COVID-19 is essential. This review will serve an important role as a thorough summary to inform evidence-based recommendations on establishing effective policy and clinical guideline recommendations.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42020198267; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=198267

International Registered Report Identifier (IRRID): PRR1-10.2196/25207

Introduction

Many health care facilities in low- and middle-income countries are inadequately resourced. COVID-19 has the potential to decimate their surgical health care services unless health systems take stringent measures to protect health care workers (HCWs) from viral exposure. A recent study showed that 15.6% of patients with confirmed COVID-19 are symptomatic and that nearly half of patients with no symptoms at the time of testing will develop symptoms later [1]. Furthermore, the preoperative evaluation of emergency trauma patients is limited. These factors impede and confound diagnostic triage. Improper infection prevention may create a "superspreader" event in a high-volume health care facility or reduce personnel availability. Consequently, the infection control strategy of trauma surgery staff and in-hospital patients is a top priority for not only low-resource environments but for all emergency trauma facilities with patients presenting with both potential and suspected COVID-19 infection.

In addition to adequate personal protective equipment, appropriate diagnostic testing for patients presenting with an indication for emergency trauma surgery may lead to lower rates of COVID-19 infection among trauma surgery staff and among patients when not isolated. The Prehospital Index (PHI) is a triage-oriented trauma severity scoring system comprising four components: systolic blood pressure, pulse, respiratory status, and level of consciousness, each scored 0 to 5 [2]. A PHI of 4 to 20 indicates major trauma, defined as a patient likely to die within 72 hours after an injury or who requires general or neurosurgical operative intervention within 24 hours. Blunt force trauma, penetrating thoracic and abdominal injuries, severe traumatic brain injury, tension or open pneumothorax, cardiac tamponade, and massive hemothorax are etiologies that will continue to present to emergency departments as indicators for emergency trauma surgery during the COVID-19 period. Time is of the essence for these patients. Thus, guideline recommendations for the diagnostic evaluation for COVID-19 infection must consider time as a resource and allow an evidence-based practice to assuage the cost and benefits of COVID diagnostics for both the patient and for the protection of the trauma surgery staff providing care.

The primary objective of this review is to summarize the diagnostic accuracy of chest computed tomography (CT) imaging for the timely detection of COVID-19, and thus lead to the timely isolation of patients and adequate protection measures to reduce the risk of transmission between patients and the health personnel caring for patients undergoing emergency trauma surgery. The purpose of the review is to inform recommendations for the rational use of chest CT on patients presenting to the emergency department with major trauma, particularly in low-resource environments, where the high costs of the indiscriminate use of diagnostic tools must be avoided without compromising the safety of HCWs or the care of trauma patients. A preliminary search of the International Prospective Registry of Systematic Reviews (PROSPERO), MEDLINE, the Cochrane Database of Systematic Reviews, and the JBI Database of Systematic Reviews and Implementation Reports was conducted, and no current or underway reviews on this topic were identified.

Methods

Protocol Registration

The review was registered on PROSPERO (CRD42020198267) and will follow the reporting guidelines of PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis). Any changes to the protocol will be amended in PROSPERO and reported in the final review. The authors will include a detailed description of any changes along with a justification during the publication of the review. This review was conducted following the JBI (Joanna Briggs Institute) methodology for systematic reviews [3]. The protocol adheres to the PRISMA guidelines for protocols (PRISMA-P 2015) [4].

Patient and Public Involvement

Patients and the public were not involved in the design of this umbrella review protocol.

Study Design

A broad evidence synthesis of peer-reviewed and gray literature following the PRISMA approach by Moher et al [5] is planned for this review. Figure 1 summarizes the planned stages of the review as described in this protocol.

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Figure 1. Summary of the review process. CENTRAL: Cochrane Central Register of Controlled Trials; JBI SUMARI: Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information; AMSTAR II: A Measurement Tool to Assess Systematic Reviews II; QUADAS 2: Quality Assessment of Diagnostic Accuracy Studies 2.
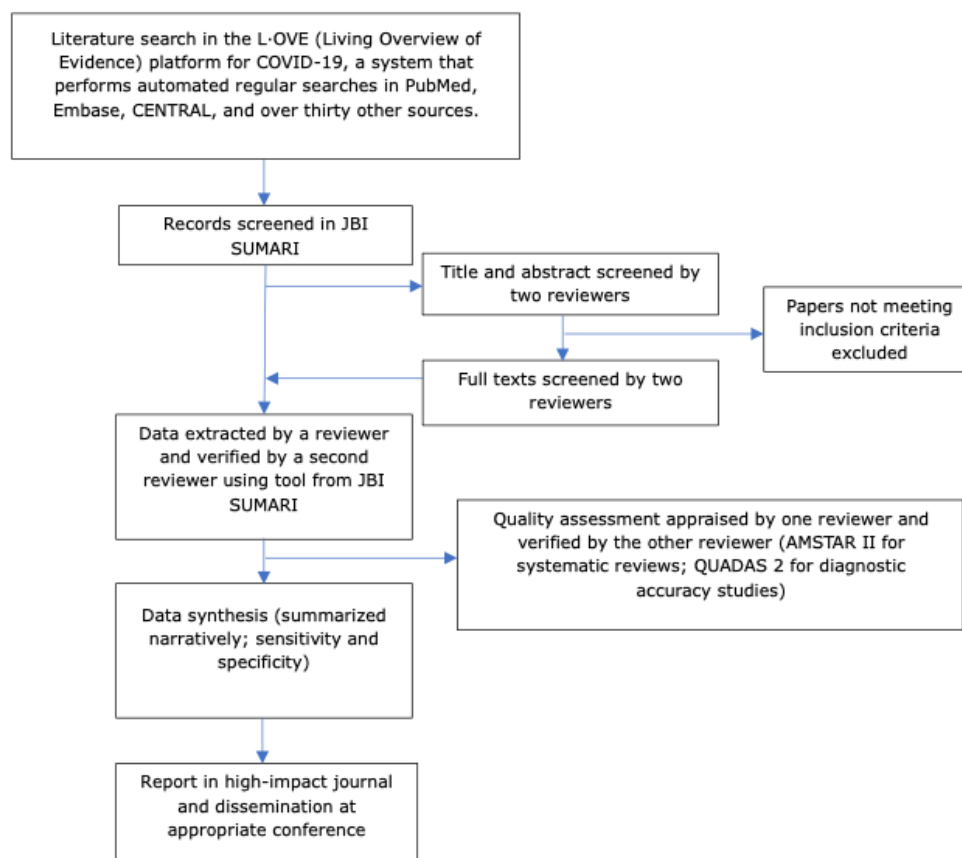
Data Source and Search Strategy

We will conduct several searches in the L·OVE (Living Overview of Evidence) platform for COVID-19, a system that performs automated regular searches in PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and over 30 other sources. When compared to manual searches, this platform consistently identifies all the available studies associated with the terms of interest [6-10]. It allows for a fast (automated) search that is easy to update—a crucial element given the urgent need to answer the research question rapidly and thoroughly. We will search for systematic reviews and diagnostic test accuracy (DTA) studies evaluating chest CTs for the diagnosis of COVID-19 in patients presenting with an indication for emergency trauma surgery. Other in-hospital clinical settings will be considered for inclusion and synthesis if evidence for the trauma surgery setting is not available. Different clinical settings will be treated as subgroups from which extrapolation will be possible when considered adequate.

Selection of Studies

Following the search, all identified citations will be collated and uploaded into EndNote X9 (Clarivate Analytics). The citations will then be imported into JBI SUMARI (Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information) for the review process. Two independent

reviewers will examine titles and abstracts for eligibility. The full text of selected studies will be retrieved and assessed. Full-text studies that do not meet the inclusion criteria will be excluded, and a list of such excluded studies will be provided. Disagreements between the reviewers during title and abstract screening or full-text screening will be resolved by consensus or with a third reviewer. The results of the search will be reported in full in the final report and presented via a PRISMA flow diagram [5].

Eligibility Criteria

Inclusion Criteria

Participants

The review will preferentially include studies involving emergency trauma surgery patients during the COVID-19 pandemic. Given the likelihood that reports on this specific population are scarce or even nonexistent, if unavailable or insufficient, we will consider studies of patients in any in-hospital setting such as the emergency room, critical care, or general wards, since we consider generalization of such results to be adequate for our question. Studies summarizing the available evidence for other viral respiratory illnesses will not be considered since we do not consider that diagnostic accuracy can be extrapolated to COVID-19.

Diagnostic Tests

The diagnostic test under consideration is chest CT for which sensitivity or specificity is assessed.

Reference Standard

No individual test is currently considered a true reference ("gold") standard for COVID-19 diagnosis. We will include studies that used a reference standard of multiple/sequential reverse transcriptase–polymerase chain reaction (RT-PCR), or a composite of viral culture/RT-PCR, and clinical features of COVID-19.

Types of Studies

This review will consider systematic reviews of DTA studies and individual DTA studies, if not included in systematic reviews, that fulfill population and diagnostic test criteria. We will also include reports on implementation strategies and costs that could inform recommendations for various resource settings. Only studies published in English or Spanish will be included. We will include preprint studies identified in our search, but no ongoing studies will be considered. Ongoing studies will be counted as excluded studies in the corresponding tables and PRISMA diagram.

Exclusion Criteria

We did not identify pertinent exclusion criteria for this review.

Quality Assessment of Included Studies

Eligible studies will be critically appraised by 2 independent reviewers. We will use the AMSTAR (A Measurement Tool to Assess Systematic Reviews) tool to assess the risk of bias in the systematic reviews, and the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool for individual diagnostic test accuracy studies [11-13]. The results of the risk of bias assessment will be reported narratively and inform the overall certainty of the review findings. Disagreements will be solved by consensus or by a third reviewer.

Data Extraction

Data will be extracted from the included studies by a reviewer and verified by a second reviewer using a data extraction tool from JBI SUMARI [3]. The data extracted will include specific details about the populations, study methods, diagnostic tests, diagnostic accuracy, setting, risk of bias of individual studies, and quality of the evidence. Disagreements will be solved by consensus.

Data Synthesis

Studies will be summarized narratively. Sensitivity and specificity from systematic reviews and from individual studies not included in the systematic reviews will be reported. We do not plan on performing meta-analyses unless we identify primary studies not contained in the included systematic reviews, and such studies are sufficiently homogeneous regarding design, setting, diagnostic tests, and reference standard to consider a meta-analysis adequate. The results for clinically homogeneous studies would be meta-analyzed using RStudio software (RStudio, PBC).

Assessing Certainty in the Findings

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach for grading the certainty of evidence will be reported [14,15]. The certainty of findings derived from the individual quality of the systematic reviews and overall consistency of the results will be detailed.

Data Statement

This review will be based on previously published data. Any relevant data will be published with the review as either an appendix or as an online supplement.

Results

No ethical approval will be required, as this review is based on already published data and does not involve interaction with human subjects. The search for this systematic review commenced in October 2020, and we expect to publish the findings in early 2021. The plan for dissemination is to publish the review in a peer-reviewed journal and present the findings at high-level international conferences that engage the most pertinent stakeholders.

Discussion

This protocol has been rigorously developed and designed specifically to identify and summarize the available literature regarding the efficacy of chest CT for patients presenting with an indication for emergency trauma surgery to reduce the risk of COVID-19 infection transmission to the health personnel caring for these patients in low-resource environments. Given the limited recent evidence associated with the primary objective, findings from the review will be critical for researchers, policy makers, and government and nongovernmental organizations for developing recommendations on diagnostic testing for COVID-19 in emergency trauma surgery settings, especially in low- and middle-income countries.

To the best of our knowledge, this protocol provides a detailed description of the first umbrella review on the accuracy of chest CT imaging for the diagnosis of COVID-19 infection. One strength of this research is that it is being conducted by a multidisciplinary team with experience in conducting high-quality evidence synthesis. One limitation is the possibility that new studies will have been published at the time of review publication that were not available at the time of writing the review.

During the COVID-19 pandemic, protecting HCWs from infection is essential and up-to-date information on the accuracy of diagnostic tests for COVID-19 is of great importance.

Acknowledgments

Authors' Contributions

AR, PJH, and AK conceived the review. DG and AG designed the review. DG and AG refined the review design and were involved in the initial drafting of the manuscript. All authors were involved in subsequent manuscript draft reviews and updates and approved the final version of this protocol.

Conflicts of Interest

None declared.

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Abbreviations

AMSTAR: A Measurement Tool to Assess Systematic Reviews
CENTRAL: Cochrane Central Register of Controlled Trials
CT: computed tomography
DTA: diagnostic test accuracy
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
HCW: health care worker
JBI: Joanna Briggs Institute
JBI SUMARI: Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information
L·OVE: Living Overview of Evidence
PHI: Prehospital Index
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: International Prospective Registry of Systematic Reviews
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies 2
RT-PCR: reverse transcriptase–polymerase chain reaction

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Protocol

Efficacy and Safety of Drug Combinations for Chronic Pelvic Pain: Protocol for a Systematic Review

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Abstract

Background: Chronic pelvic pain with various etiologies and mechanisms affects men and women and is a major challenge. Monotherapy is often unsuccessful for chronic pelvic pain, and combinations of different classes of medications are frequently prescribed, with the expectation of improved outcomes. Although a number of combination trials for chronic pelvic pain have been reported, we are not aware of any systematic reviews of the available evidence on combination drug therapy for chronic pelvic pain.

Objective: We have developed a protocol for a systematic review to evaluate available evidence of the efficacy and safety of drug combinations for chronic pelvic pain.

Methods: This systematic review will involve a detailed search of randomized controlled trials investigating drug combinations to treat chronic pelvic pain in adults. The databases searched will include the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE from their inception until the date the searches are run to identify relevant studies. The primary outcome will be pain relief measured using validated scoring tools. Secondary outcomes, where reported, will include the following: adverse events, serious adverse events, sexual function, quality of life, and depression and anxiety. Methodological quality of each included study will be assessed using the Cochrane Risk of Bias Tool.

Results: The systematic review defined by this protocol is expected to synthesize available good quality evidence on combination drug therapy in chronic pelvic pain, which may help guide future research and treatment choices for patients and their health care providers.

Conclusions: This review will provide a clearer understanding of the efficacy and safety of combination pharmacological therapy for chronic pelvic pain.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42020192231; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=192231

International Registered Report Identifier (IRRID):   PRR1-10.2196/21909

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KEYWORDS

chronic pelvic pain; combination therapy; clinical studies; systematic review; chronic prostatitis; chronic pelvic pain syndrome; CPPS; interstitial cystitis; bladder pain syndrome; efficacy; safety; drug; pain; pelvis; chronic pain; protocol; therapy; treatment; combination

Introduction

Description of the Condition

Chronic pelvic pain is a highly prevalent condition affecting both men and women. Similar to other chronic pain disorders, it is poorly understood and is associated with various etiologies, broad definitions, treatments that are mostly empirical, and unsatisfactory patient outcomes [1]. There are three frequently studied pelvic pain disorders: interstitial cystitis/bladder pain syndrome (IC/BPS) in men and women, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) in men, and chronic pelvic pain (CPP) in women [1].

CPP in women is the most common reason for referral to women's health specialists, accounting for up to 20% of all outpatient appointments in secondary care [2]. In primary care, it has an incidence of 38 per 1000 women, comparable to back pain (41 per 1000). CPP has global prevalence rates ranging from 2.1% to 24% [2], with estimates as high as 14.7% and 25% in the United States and United Kingdom, respectively [3-5]. It accounts for 1 in 10 outpatient gynecological visits [6], and it is the indication for 40% of laparoscopies and 15% of hysterectomies in the United States [7,8]. It is also associated with significant costs to the health care system, with US $881.5 million per year being devoted in the United States [4], and £158 million in the United Kingdom [9]. The focus of CPP of various etiologies can be experienced in anatomic locations such as the pelvis, anterior abdominal wall, lower back or buttocks, or genitalia (vulva and/or vagina) and can frequently lead to limitations in daily home life and activities [10], including sexual dysfunction. Furthermore, it often requires medical treatment, and can be responsible for a significant amount of missed work [4]. There are numerous proposed causes of CPP [10] involving the gynecologic, urologic, gastrointestinal, musculoskeletal, and neurologic systems, although their pathophysiologic mechanisms are not well understood. Furthermore, for a large proportion of patients, there is no identifiable cause of pain, even after laparoscopic investigation [8,11]. Consequently, CPP presents a great challenge to patients and clinicians, leading to unsatisfactory treatment with minimal pain relief [12,13].

CP/CPPS is the most common urological disorder for men under 50 years and is the third most common diagnosis for men over 50 [14]. One study following 1310 patients across 16 years found an average age of 45 years [15]. It is estimated that up to 10% of males will experience symptoms of CP/CPPS at some point in their lifetime. The global prevalence of prostatitis is estimated to be around 7.1%. It constitutes 1% of primary care visits and 8% of urology consultations in the United States [16], affecting men of all ages and ethnicities, with a mean age of onset of 42 years [14]. The National Institutes of Health (NIH) classification categorized four categories of prostatitis, with the noninfectious type—Category III (chronic nonbacterial prostatitis/chronic pelvic pain syndrome)—being the most common form of symptomatic prostatitis, making up around 90%-95% of prostatitis diagnoses [17]. The two main clinical features of CP/CPPS are pelvic pain and lower urinary tract symptoms (LUTS) [17]. Patients typically report pain in the perineum, penis, testicles, scrotum, or suprapubic region, which can be exacerbated on ejaculation [18]. Common urinary symptoms include storage and voiding LUTS. Consequently, the syndrome is associated with significant decrease in quality of life and in many cases sexual dysfunction [15,17]. Similar to CPP in women, there are various pathophysiological mechanisms proposed, such as infection [19], inflammation [20], neurologic, psychosocial, neuropathic, muscle dysfunction, and psychiatric factors [21-23].

IC/BPS has an estimated prevalence of 3%-7% in women and 2%-4% in men, translating to over 10 million affected individuals in the United States [24,25]. Approximately 90% of patients are female, and 95% of patients have a median age of 40 years [24]. Interestingly, of men who have IC/BPS, about 17% have been found to also have CP/CPPS [25]. Furthermore, a significant proportion of patients have also been found to have conditions such as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome, which can add complexities to management of this condition [26]. Patients with IC/BPS frequently experience pain or discomfort perceived to be related to the urinary bladder, and lower urinary tract symptoms such urinary urgency, frequency, and dysuria [27]. They also experience significant feelings of helplessness, depression, lack of control, and catastrophizing, further reducing the quality of life for these patients [28]. Despite its wide prevalence, the majority of pharmacological interventions used are off-label [27], and have scarce or contradictory evidence supporting them [27,29-34]. One study of the literature found a disconnect between guidelines for treatment and the actual effectiveness in clinical practice, indicating the need for integrating evidence from a variety of potential treatments [35].

Description of the Intervention

As there are numerous contributing factors to chronic pain in the pelvic region, several interventions have been proposed for its treatment, with diverse mechanisms of action. These include α-blockers, 5-α-reductase inhibitors, quinolones/tetracyclines, phytotherapy, nonsteroidal anti-inflammatory drugs, neuromodulators, opioids, muscle relaxants, and cannabinoids [36-38]. Despite numerous pharmacological interventions available, monotherapy has not been found to be significant in successfully treating chronic pelvic pain, pointing to a multimodal approach for treatment [39-41]. This approach combines both pharmacological agents and nonpharmacological therapy (eg, bladder training, mindfulness) [42,43]. One method of multimodal therapy is employing combination pharmacological therapy. With any one pharmacological agent, there are often significant adverse events that must be balanced in order to ensure patient compliance and safety [44].

Combination therapy has been proposed as an alternative to monotherapy to minimize the adverse events of any one pharmacological agent, while combining the efficacy of multiple agents.

Why It Is Important to Perform This Review

Although conditions producing chronic pelvic pain may occur separately in patients, chronic pain disorders are often found to co-occur in patients, leading to the NIH creating the term chronic overlapping pain conditions [45]. Clinical studies of chronic overlapping pain conditions have shown that comorbid pain conditions may exacerbate each other, and treatment of one pain syndrome may result in improvement of another as well [46,47]. As a result, it is worthwhile to investigate these disorders collectively when assessing the efficacy of potential treatments. It is important to investigate combination pharmacological therapy, as currently there are a great number of treatment options available for clinicians, each with a different efficacy and safety profile. Such a wide array of treatments can pose a challenge for clinicians trying to find the most evidence-based treatments for their patients in an individualized manner. Although it is recognized that there are major differences between genders in etiology, presenting phenotype, and outcomes in various types of CPP, we wanted to examine conditions affecting all genders (such as interstitial cystitis) and different gender-specific disease processes (eg, scrotal contents pain in males versus endometriosis in females) and determine similarities and differences in therapeutic efficacy of the multimedical therapies in those of different genders. By including both males and females in our review, we can ensure that evidence in this area is not missed. This systematic review seeks to synthesize the available data for all combination pharmacological therapies and facilitate clinicians in this decision-making process. Thus, we aim to conduct a systematic review to evaluate the efficacy and safety of combination pharmacological therapy for treating chronic pelvic pain.

Objective

The objective of this review is to evaluate available clinical studies describing the efficacy and safety of combination drug therapies for the treatment of chronic pelvic pain.

Methods

Study Registration

This protocol is developed in accordance with PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines [48] (Multimedia Appendix 1) and PRISMA Harms guidelines [49] and is registered in the PROSPERO (International Prospective Register of Systematic Reviews) register (registration number CRD42020192231).

Types of Studies

This review will include double-blind, randomized, controlled clinical trials (RCTs) of combination drug therapies in the treatment of chronic pelvic pain of any etiology—with an outcome measure of pain intensity or pain relief, assessed by a validated measurement tool. Included trials will compare combinations of two or more different drugs to at least one of the combination's single agent components for the treatment of chronic pelvic pain. RCTs with less than 10 participants will be excluded to minimize study bias. Only English-language studies will be included.

Types of Participants

We will include studies involving women, men, or both, aged 18 years and over, who report CPP of any etiology lasting for at least three months. The diagnosis of these conditions may have been made by a medical specialist, or a medical diagnosis made as part of the study procedures. We will exclude trials of primary or secondary dysmenorrhea.

Types of Interventions

We will include any combination of two or more drugs administered systemically by any route of administration. We will include studies comparing combination drug therapy with at least one of the combination's single agent components and also possibly placebo, or other pharmacological interventions.

Types of Outcome Measures

The primary outcome for this review will be pain intensity or pain relief, assessed by a validated measurement tool. Secondary outcomes will include adverse events, serious adverse events, sexual dysfunction, health-related quality of life, depression and anxiety, and urinary symptoms.

Search Methods for Identification of Studies

We will conduct a detailed search for clinical studies using CENTRAL, MEDLINE, and EMBASE from the dates of their establishment to the time the searches are conducted. We will search the clinical trial registry platform ClinicalTrials.gov to identify unpublished RCTs. We will also review the bibliographies of any clinical studies identified for relevance to identify additional published or unpublished data. The search strategy was developed in consultation with a librarian specializing in literature searches (Multimedia Appendix 2).

Data Collection and Analysis

Two reviewers (MM and RP) will independently evaluate studies for eligibility using the Covidence systematic review platform. Screening will be performed on titles and abstracts, thereafter full-text screening will be performed on citations that are determined to meet inclusion criteria. Reasons for study exclusion will be recorded. Any disagreements between the two reviewers will be resolved by discussion and consensus; if necessary, a third reviewer (IG) will be consulted. The planned selection process is shown in a PRISMA-P flowchart (Figure 1). Data extraction from included studies will be performed independently by two reviewers using predesigned data extraction forms. Forms will be piloted and revised if necessary. They will include the following variables:

- Publication details: first author's name, publication year, country, language
- Study design: participant inclusion and exclusion criteria, randomization method, blinding method and assessment, number of participants by study and intervention arm, type of control, follow-up time, attrition rate, use of other treatments

- Participant characteristics: demographic, sample size, average age, sex distribution, presence of pain condition leading to chronic pelvic pain (such as chronic prostatitis), duration of chronic pelvic pain, comorbid pain conditions, presence of psychiatric conditions, baseline pain scores, baseline secondary outcome scores (sleep, quality of life, etc)
- Intervention and comparator details: details of pharmacological agents used (dose, route, frequency, duration), comparator used and details (placebo, active pharmacological agent)

- Outcome details: method of pain assessment (validated pain scale, etc), mean and standard deviation of pain scores and all continuous secondary outcomes, assessment timepoints, frequencies of adverse events and serious adverse events, method of adverse event assessment
- Other details: dropout rate with reasons, funding sources, conflicts of interest

Study authors will be contacted as required to request missing or incomplete data, and to clarify methods or findings.

Figure 1. PRISMA flow diagram of study selection. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
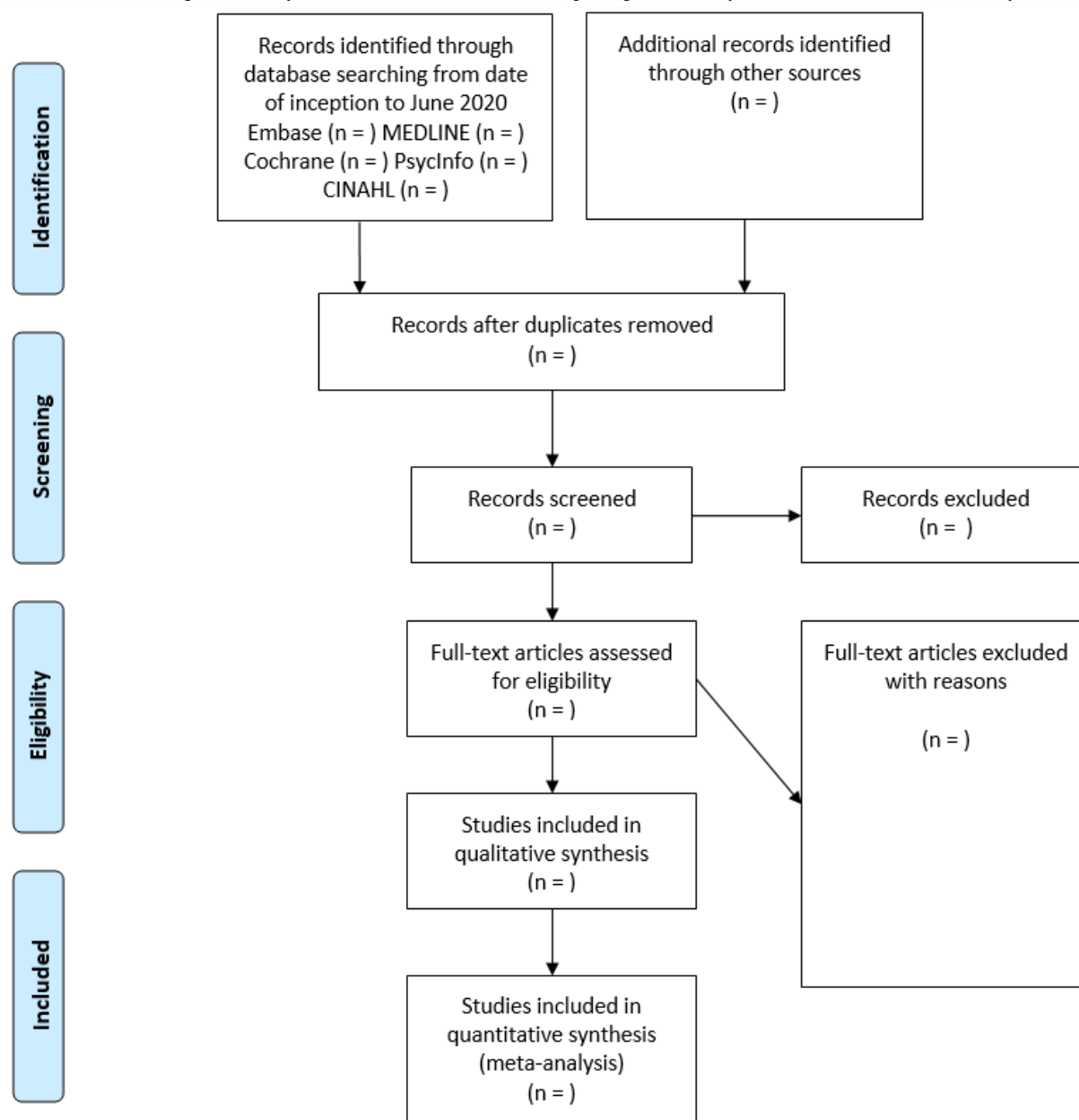
Assessment of Risk of Bias

Risk of bias for each study included in the review will be independently assessed by two reviewers using the criteria outlined in the Cochrane Handbook for Systematic Review of Interventions [50]. Disagreements between reviewers will be resolved through discussion and consensus and—if necessary—a

third reviewer (IG) will be consulted. The following data on risk of bias will be assessed for each study: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and study personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias),

(6) selective reporting (reporting bias), and (7) other potential sources of bias. Each domain will be judged as "low risk," "high risk," or "unclear risk" of bias, and individual bias items will be evaluated as described in the Cochrane Handbook for Systematic Reviews of Interventions [50].

Measures of Treatment Effect

We expect that there will be a limited scope for meta-analysis because of the range of different outcomes measured across the small number of existing trials. However, where studies have used the same combination and comparator, with the same outcome measure, we will pool the results using a random-effect meta-analysis with an inverse variance method. We plan to calculate mean differences for continuous outcomes and, if needed, the standardized mean differences. If we employ standardized mean differences, we plan to transform these scores to a 0-10 scale to obtain the mean difference. If a meta-analysis if not feasible, we will provide a narrative synthesis of the findings from the included studies, structured around the type of intervention, target population characteristics, and outcome. A descriptive approach will be used to evaluate how combination drug therapies differ from monotherapy or other comparators, in managing other features of chronic pelvic pain such as anxiety, depression, quality of life, and functional disability. Any comparisons of multiple drug combinations and other placebo or active comparators will also be analyzed. In studies where more than one active treatment group is present, the control treatment group will be divided among the active treatment arms. The software RevMan (version 5.3; The Cochrane Collaboration, The Nordic Cochrane Centre) will be used for analysis. Heterogeneity between the studies within a meta-analysis will be assessed using the I^2 statistic if the number of included studies is >10, in keeping with Cochrane best practices [50]. There are no pre-specified subgroup analyses planned at this time.

Ethics and Dissemination

This review does not require ethical approval because no personal data collection is involved. The results of this systematic review will be published in a peer-reviewed journal.

Results

To date, the protocol has been registered in PROSPERO and the search strategy has been finalized for starting data screening. Results are expected in September 2021.

Discussion

Chronic pelvic pain syndromes have a significant prevalence among males and females, and the wide variety of etiologies for them creates a challenge for clinicians in their management. It has significant negative impact on patients' quality of life, functioning, productivity in employment, relationships, and sexual function, which all contribute to the significant economic burden on the health care system [2,3,51]. As seen with the recent opioid crisis, management of chronic pain without evidence-based guidelines can have profound effects on patients' morbidity and mortality rates, with deaths in the United States alone quadrupling over the last 15 years [52]. In a similar fashion, the overprescribing of certain classes of pharmacological therapies for chronic pelvic pain may lead to significant adverse events, a reduction in patient compliance, and a trajectory of persistent pain.

This review seeks to synthesize the evidence of efficacy and safety behind the combination of pharmacological agents in managing chronic pelvic pain. This synthesis will provide health care professionals with information on which pharmacological agents, and in what combination, are the most efficacious for certain etiologies of chronic pelvic pain (eg, IC/BPS vs CP/CPPS and CPP). Additionally, this review seeks to provide information on the safety and potential adverse events associated with pharmacological agents. This information can aid clinicians in tailoring a treatment approach for a specific patient and counselling them appropriately on both therapeutic benefit and side effects to better manage expectations and promote adherence to treatment.

Authors' Contributions

All authors contributed to conceptualization. MM and RP will be responsible for data curation and will be directly overseen by IG. The investigation will be conducted by MM and IG with specific input from all other coauthors. The methodology will be conducted by MM and IG with specific input from all other coauthors. MM and IG will write the initial draft with specific input from all other coauthors. All authors will contribute to reviewing and editing the manuscript.

Conflicts of Interest

UW reports research grants from NIH and serves on the External Consultant Board for the NIH Preclinical Screening Platform for Pain, a novel preclinical pain therapy screening platform that has been launched at the National Institute for Neurological Disorders and Stroke as part of the NIH Helping to End Addiction Long-term Initiative. In her capacity as a special government employee of the Food and Drug Administration (FDA), UW has served as a voting member of the FDA Anesthetic and Analgesic Drug Products Advisory Committee. She has served as a consultant for Grünenthal GmbH and Ironwood Pharmaceuticals Inc,

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist.
[PDF File (Adobe PDF File), 167 KB - resprot_v10i5e21909_app1.pdf]

Multimedia Appendix 2
Search strategy developed for EMBASE.
[DOCX File , 16 KB - resprot_v10i5e21909_app2.docx]

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Abbreviations

AE: adverse event
CIHR: Canadian Institutes of Health Research
CP/CPPS: chronic prostatitis/chronic pelvic pain syndrome
CPP: chronic pelvic pain
IC/BPS: interstitial cystitis/bladder pain syndrome
LUTS: lower urinary tract symptoms
NIH: National Institutes of Health
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PROSPERO: International Prospective Register of Systematic Reviews
RCT: randomized controlled trial

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Protocol

Suicide Prevention Among College Students Before and During the COVID-19 Pandemic: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: Suicide is the second leading cause of death for college-aged individuals worldwide and in the United States. Recent studies have identified preliminary evidence of widening disparities in suicidal behaviors across sex, sexual orientation, race/ethnicity, age, and socioeconomic status among college students. Few systematic reviews and meta-analyses offer a comprehensive understanding of on-campus and off-campus suicide interventions, nor is collated information available for different types of screening, assessment, treatment, and postvention plans. Further challenges have been identified since the COVID-19 pandemic, calling for cost-effective and innovative interventions to address increased rates of suicidal behaviors among college students facing unprecedented stressors.

Objective: This research protocol describes the first systematic review and meta-analysis to identify the most effective and cost-effective intervention components for universal and targeted (indicated and selected) suicide prevention among college students in a global context. Special attention will be placed on disparities in suicide prevention across sociodemographic subgroups, inclusive interventions beyond campus, global context, and intervention responses to the COVID-19 pandemic.

Methods: A sensitive search strategy will be executed across MEDLINE (Ovid), EMBASE, PsycINFO (EBSCO), ERIC (EBSCO), Cochrane Library, Dissertations and Theses Global (ProQuest), Scopus, Global Index Medicus, SciELO, African Journals Online, Global Health (CABI), and Google Scholar. Data extraction and evaluation will be conducted by three independent researchers. Risk of bias will be assessed. A multilevel meta-regression model and subgroup analysis will be used to analyze the data and estimate effect sizes.

Results: The initial search was completed in December 2020 and updated with additional other-language studies in March 2020. We expect the results to be submitted for publication in mid-2021.

Conclusions: Despite increasing rates of suicidal behaviors among college students, few preventative efforts have targeted this population, and fewer focus on factors that might place specific demographic groups at heightened risk. The impact of COVID-19 on suicidal behaviors among college students highlights and exacerbates the urgent need for rapid and effective interventions that might differ from traditional approaches. This equity-focused study will address these gaps and provide a valuable analysis of the effectiveness of suicide prevention programs and interventions. Findings will inform clinicians, researchers, policy makers,

families, and organizations about evidence-based interventions for reducing the gaps in the suicide crisis among college students from different sociodemographic groups.

Introduction

Background

Suicide is the second leading cause of death for college-aged individuals worldwide and in the United States [1-7]. Globally, results from the World Health Organization World Mental Health International College Student Surveys indicated that 32.7% of college students seriously thought about suicide, and 4.3% attempted suicide, between 2014 and 2017 [3]. In the United States, one-fifth of college student participants in a recent national survey reported suicidal ideation, with 9% reporting suicide attempts [4]. Between 2007 and 2017, past-year suicidal ideation among college students nearly doubled (from 5.8% to 10.8%) [7]. Based on the Household Pulse Survey by the Centers for Disease Control and Prevention (CDC) conducted from February 17 to March 1, 2021, 42.2% of participants aged 18-29 years reported indicators of depression in the past week [8]. Notably, colleges and universities (hereafter "colleges") have been identified as potential sites for suicide clusters where a substantial number of suicides could occur rapidly within a short time frame [9]. The trauma associated with exposure to a young person's suicide significantly increases widespread anxiety and panic, and causes prolonged grief across victims, families, and communities [10]. There is an urgent need for research to develop effective, innovative, and accessible suicide prevention programs and interventions for college students.

In addition, recent studies have identified preliminary evidence of widening disparities in suicide across sex, sexual orientation, race/ethnicity, age, and socioeconomic status subgroups among college students [4,11,12]. Since 2000, female college students have reported a higher prevalence of suicidal ideation, planning, and attempts than their male counterparts in the United States [13,14]. Bisexual and transgender students were 2-3 times more likely to report suicidality than heterosexual and gay/lesbian students in 2015 [4]. In 2017, Black college students reported the highest rate of suicide attempts among college students (2.6% versus 1.4% among White students) [11]. There are sociodemographic differences in barriers to using mental health services on college campuses [12,15]. However, evidence-based suicide programs tailored to meet the unique needs of specific demographic groups are few. There is a need to develop culturally adaptive suicide interventions, given emerging evidence that experiences of structural discrimination, minority stress, adverse childhood experiences, social discord, and cultural sanctions might disproportionately affect the risk of suicidal behavior [16,17].

Further challenges for student mental health have been identified during the COVID-19 pandemic. In a recent CDC survey, young adults aged 18-24 years reported significantly greater rates of suicidal ideation than the general population during the pandemic (25.5% versus 10.7%) [18]. However, existing studies have focused on primary and secondary school students [19,20], and actions to tackle the impact of the COVID-19 pandemic on mental health among college students has not been comprehensively understood. The new challenge calls for proactive and effective responses from policy makers, researchers, and the global community to prevent youth suicide [21,22]. Telepsychiatry interventions and digital tools (eg, mobile apps, internet chatbots, videoconferencing) have proliferated rapidly in response to the COVID-19 emergency [23]. It is therefore important to review suicide prevention studies conducted after the onset of the COVID-19 pandemic to address pandemic-specific suicide risk [21]. If such studies have been published, preliminary results should also be synthesized, and service gaps identified [22].

Rationale

Suicidal behaviors among college students can have wide-ranging adverse effects on well-being and development, including low academic achievement [24,25], chronic physical health conditions [26], and reduced labor market performance [27]. Early identification, effective treatment, and appropriate interventions for students have the potential to save students' lives and improve societal well-being and social capital [3]. Despite recent attention to the alarming rates of suicidal behaviors among college students [3,4,7,28], there has been less research comparatively addressing suicide prevention and early intervention for college students than for primary and secondary school students [29]. This is troubling because the college years represent a critical and unique developmental stage [30] characterized by dynamic social role transitions, new living situations, and changing relationships [31]. It is important to understand and design college-specific intervention programs targeting the developmental stress-diathesis factors [32] during the transition from adolescence to emerging adulthood.

Existing systematic reviews on suicide prevention among college students are generally strong but are limited by their narrow foci in terms of populations, interventions, comparisons, and outcomes, as well as a lack of guidance from a theoretical framework. First, most previous reviews focus on symptomatic students [33], but evidence suggests a need for additional focus on those at risk but undiagnosed or untreated. To address this gap, this study will not be restricted to studies of students with

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a current diagnosis. Second, many campus counseling centers are underresourced, and college students have to use off-campus mental health services [12,34]. However, previous reviews predominantly focus on on-campus settings [35]. Conceptually, this may be related to a gap recently identified by the US Preventive Services Task Force: the lack of effective interventions linking clinical and community resources [36,37]. This study will extend the previous review by deliberately attempting to build a comprehensive understanding of available on-campus and off-campus services (eg, those in the community) and interventions. Third, consideration of the disparities faced by specific sociodemographic student groups is needed to improve screening and referral systems targeting high-risk groups [38]. Previous reviews exclude studies on interventions targeting high-risk populations (eg, sexual minorities), and no reviews have delineated differential intervention effects. This study will add to existing knowledge by exploring suicide interventions tailored to specific sociodemographic groups and assess their intervention outcomes.

Fourth, the interventions included in previous systematic reviews have been concentrated on gatekeeper programs with outcomes that do not directly measure suicidal behaviors (eg, many such programs assess secondary outcomes, including knowledge, skills, attitudes, or awareness) [33,35,39]. Our proposed study will include both primary suicide assessment (eg, suicidal ideation, plan, planning, and attempts) and secondary outcomes (eg, attitudes). Additionally, we plan to evaluate the cost-effectiveness (ie, costs of death prevented using the incremental cost-effectiveness ratio [ICER]) of the interventions where data are available, which has not been attempted in previous reviews.

Fifth, as one might expect, no reviews have examined the adaptability of suicide prevention programs in the context of the COVID-19 pandemic. This information will be important to inform the emerging transformation and proliferation of telepsychiatry in terms of the ways in which it might increase the accessibility of mental health services for college students [21-23,40]. Digital interventions provide the opportunity to reach at-risk college students who experience barriers to accessing traditional mental health services [41]. This study will add a specific focus on suicide interventions implemented during the COVID-19 pandemic when available.

Sixth, most existing reviews only consider studies conducted on college campuses in the United States [33,35,39], limiting the chance to learn from other developed and developing countries. This study will not limit the search criteria by geographic location, potentially adding informative global experiences to the existing body of knowledge. Finally, few reviews have adapted an evidence-based theoretical framework to guide the synthesis, with selected exceptions. Reviews that applied the two-paradigm framework (Clinical Intervention Zone, Prevention Zone) [35,39] and social-ecological model [42,43] suggest the need for more theoretically sound reviews with public health perspectives to offer a rigorous evaluation of existing efforts as a whole and within each level or paradigm. None of the existing systematic reviews have adopted a health equity framework [44,45] to guide the review process. This study will use a logic framework (Figure 1) based on PRISMA-E (Preferred Reporting Items for Systematic Review and Meta-Analysis – Equity; Multimedia Appendix 1), relevant guides, and previous empirical studies.

Figure 1. Logic model depicting potential sources of disparity in response to suicide prevention among college students.
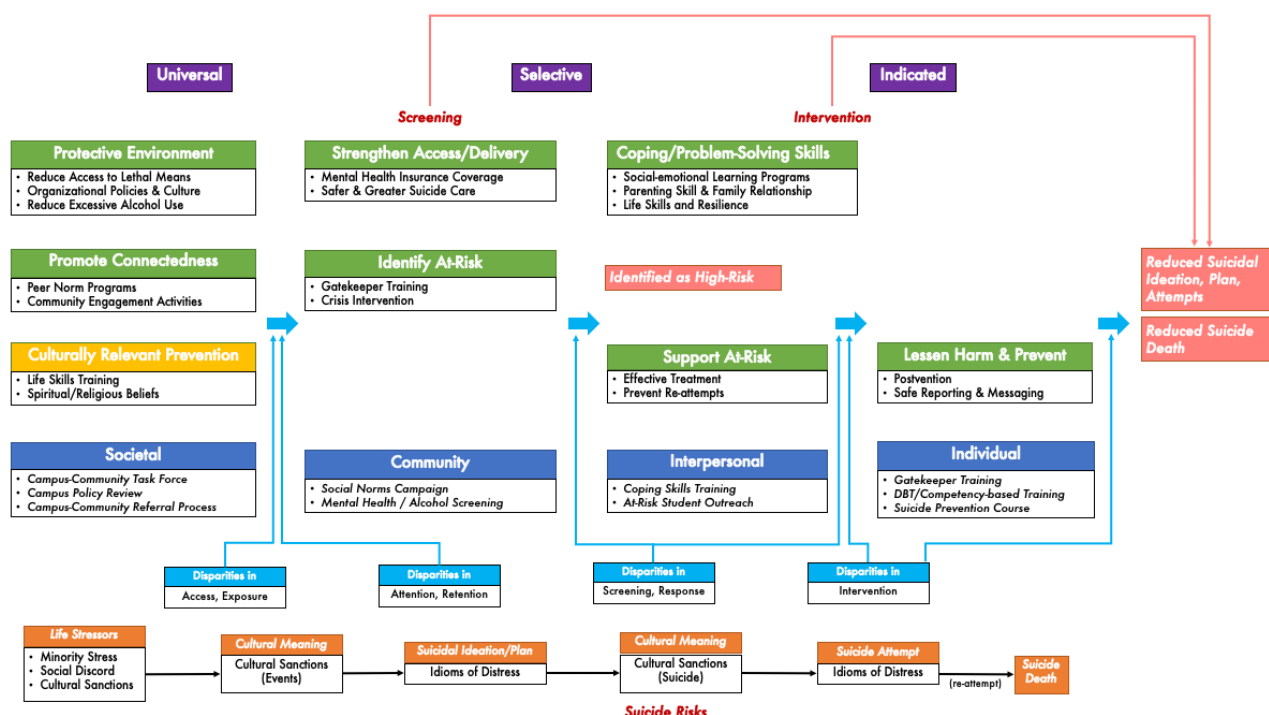
Objectives

This protocol articulates our plan to conduct a comprehensive systematic review and meta-analysis to identify the most effective and cost-effective intervention components for universal and targeted (indicated and selected) suicide prevention among college students. This project will accomplish the following objectives: (1) analyze all student participants with a focus on disparities in suicide, (2) include on-campus and off-campus programs (in-person and virtual), (3) examine broader outcomes specific to suicidal behaviors, and other secondary outcomes that might reduce suicide (eg, knowledge, attitudes), (4) incorporate US and non-US studies, and (5) adhere to a theoretically developed logic framework (Figure 1). To offer a breadth of program evolution across various eras, our review will not limit the study time frame, though it will focus on the development of novel interventions prior to and during the COVID-19 pandemic. If a paucity of studies during the COVID-19 pandemic is identified, we will summarize the existing findings and reinforce the importance of understanding the potential effects of the COVID-19 pandemic on this body of literature [59].

We will attempt to clearly answer the following research questions:

1. What are the existing college-based and community-based suicide interventions for college students?
2. What are the common elements/types of suicide prevention interventions for college students?
3. What are the health and social outcomes of interest of the selected interventions?
4. Is there sufficient variability in interventions concerning the population, interventions, controls, and outcomes, based on the reported results and discussions?
5. Which components or combinations of components of suicide interventions are effective, and for which outcomes (primary versus secondary), demographic subgroups, settings (on-campus versus off-campus), and delivery method (in-person versus digital)?
6. Are there existing suicide intervention programs tailored to students from specific sociodemographic subpopulations? If so, what elements of the intervention are tailored?
7. Which suicide intervention has been the most efficacious and effective during the COVID-19 pandemic?
8. Which suicide intervention is the most cost-effective based on standard economic evaluation?

Cost-effectiveness will be measured by the values of ICERs that are available in the identified studies, or calculated given the availability of costs (eg, health care sector costs, nonmedical costs, and costs of productivity losses) reported in the studies [60].

Knowledge generated from our study will identify gaps in the evidence base and inform college leaders, policy actors, health care practitioners, clinicians, parents, and society about feasible approaches to screen and support at-risk college students across sociodemographic characteristics.

Methods

Overview

This protocol was developed using the 2015 PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) recommended checklist for systematic review protocols [61]. The systematic review and meta-analysis will be conducted and reported in accordance with the PRISMA statement [62] and the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions [63]. Given our specific focus on at-risk subpopulations (eg, racial/ethnic minorities, sexual minority students) and interventions aimed at reducing barriers to seeking help among college students across sex, race/ethnicity, sexual orientation, and socioeconomic status, we further adapted the PRISMA statement on equity-focused systematic reviews (PRISMA-E 2012) [46,64-67] to improve transparency and completeness in reporting health equity–focused systematic reviews, in addition to the previous PRISMA-E checklist developed by Moher and colleagues [68,69]. The review team is composed of researchers across disciplines with diverse backgrounds.

Eligibility Criteria

Types of Participants

This review will consider studies involving college students (aged ≥18 years). We will also examine subpopulations across age, race/ethnicity, sex, sexual orientation, and socioeconomic status [70-73].

Types of Interventions

All programs that have at least one component intended to address suicide are eligible for inclusion. This includes programs that address general suicidal thoughts and behaviors, specific suicidal thoughts and behaviors, awareness of suicidal behaviors, help-seeking behaviors, or a combination of conditions. Included interventions will be broadly defined and include universal, indicated, or selected interventions at the individual, family, and school levels. Possible intervention mechanisms will include psychological (eg, cognitive behavioral therapy, psychodynamic psychotherapy), pharmacological (eg, antidepressants) [74], psychosocial (eg, restricting access to lethal means, screening for high-risk persons), educational (eg, education and awareness programs for the general public and professionals; media reporting of suicide), and physical (eg, exercise, occupational therapy) interventions to prevent/reduce suicidal ideation and behaviors. Interventions targeting secondary outcomes such as awareness of suicide and help-seeking behaviors will also be included. Interventions designed to primarily target behaviors that are risk factors for suicidal behaviors (eg, substance abuse) but that do not specifically address any of the components above will be excluded. Interventions focusing on gatekeepers (eg, families, teachers, health care providers) will be included. We will include randomized controlled trials (RCTs), pseudo-RCTs, observational pretest/posttest designs, and ecological or population-based studies that evaluate the effectiveness of suicide interventions.

Types of Prevention Settings

We will include all relevant settings, including campuses, community centers, digital tools, and hybrid (in-person and virtual) models. We will conceptualize digital tools, broadly, as internet-based interventions, chatbots, mobile device interventions, and social media interventions. We will not restrict inclusion criteria based on geographic location.

Types of Outcomes

The primary outcomes will include suicide-specific outcomes, suicidal ideation, suicidal thoughts, and suicidal behaviors (completed suicide or suicide attempts). If multiple measures of suicide are used, we will prioritize data extraction as follows: (1) validated questionnaires (eg, the Columbia-Suicide Severity Rating Scale [75] or Beck Scale for Suicide Ideation [76]), (2) clinician ratings, and (3) single-item analysis of other self-reported rating scales (eg, question 9 from the Patient Health Questionnaire-9 [77]). The secondary outcomes will include changes in suicide-related knowledge, attitudes, and behaviors. To examine equity-focused interventions, outcomes associated with inequality (eg, barriers to accessing care) will be included.

Information Sources

We conducted a systematic search of the following databases from their inception until December 8, 2020: MEDLINE (Ovid), EMBASE, PsycINFO (EBSCO), ERIC (EBSCO), Cochrane Library, Dissertations and Theses Global (ProQuest), Scopus, and Google Scholar. For Google Scholar, all references on the first 10 pages, excluding books, will be retrieved. Including 10-20 pages (100-200 items) of references is suggested to achieve an optimal collection of the most relevant references [78]. On March 25, 2021, we expanded our search to include Global Index Medicus, SciELO, African Journals Online, and Global Health (CABI) in order to capture literature from low- and middle-income countries. Including such information sources may improve our ability to identify studies specifically relevant to suicide risks among sociodemographic subpopulations. Editorials, news items, conference proceedings and abstracts, patents, legal findings, and commentaries will be excluded. We will not restrict the search by language or publication date. We plan to use Google Translate (Google) for the purpose of data extraction of non–English language articles and to consult translators and colleagues proficient in the language, consistent with previous systematic reviews which included worldwide study context [79,80]. Researchers from our study team are native speakers of Chinese (YX) and proficient in Spanish (AM). We will screen relevant review articles and the reference lists of all included studies (backward search) for additional eligible studies. We will further screen studies that cited the included studies and relevant reviews (forward search). We will perform hand searches. We will include grey literature in ProQuest Dissertations and Theses dissemination from inception until December 8, 2020, in the systematic review, but not in the meta-analysis. We will also contact three experts in suicide prevention that we have identified to potentially obtain additional sources.

Search Strategy

The database search strategies were developed by a health sciences librarian (RH) with expertise in literature searches. Known relevant articles collected by the authors were analyzed to select keywords and subject headings. An initial search strategy in MEDLINE Ovid was then iteratively developed by adding or removing additional keywords and subject headings until all known relevant articles were retrieved by the search, and no new relevant articles were found. The final search terms incorporated numerous headings, keywords, and publication types associated with three main concepts: college students, suicide, and intervention/prevention. In keeping with the health equity focus of the review, terms related to potentially underresourced college populations, such as nontraditional, commuter, foreign, international, or first-generation, were specifically included. Terms for prevention were purposely kept broad to encompass a wide range of possible interventions. The full search strategies for all information sources are provided in Multimedia Appendix 2.

Study Records

Data Management

Identified articles are imported into EndNote 20 software (Clarivate Analytics), where duplicate references are removed. The remaining references are imported and managed in Covidence software (Veritas Health Innovation) for screening.

Selection Process

A total of two reviewers (NJ and AM) will independently screen the studies for eligibility (making a yes or no selection). Potential discrepancies during any step of the screening for inclusion/exclusion will be resolved by a third reviewer (YX). First, the reviewers will screen titles and abstracts identified in the databases. The team will then obtain and screen full-text articles. Studies that do not meet the eligibility criteria will be moved to an exclusion folder. All reviewers will strictly adhere to the inclusion and exclusion criteria. Final selected articles will be approved by the consensus of all reviewers and sent to an expert consultant for potential suggestions. The selection process will be displayed in a PRISMA flowchart [81].

Logic Framework

Figure 1 illustrates the logic framework that we will employ during the review process. The logic framework recognizes that the causal chain of events linking preventative efforts to reduced suicidal behaviors can lead to differences in effects between socioeconomically disadvantaged and advantaged students in at least four ways: disparities in access/exposure, attention/retention, screening/response, and interventions.

Data Collection Process

Data abstraction will occur independently and in duplicate using a piloted standard data collection form. Data extraction will include three categories: (1) study population and design, (2) intervention, and (3) outcome. Specific items in the extraction form will include study design, participant characteristics, geographic location, sample size, intervention methods, comparison intervention methods, primary and secondary outcomes, theoretical basis, mode of delivery, suicide prevention

strategies, control condition, intensity and frequency of intervention, and treatment engagement (retention and attrition). Following PRISMA-E [44,45,67], we will include participant characteristics mapped to PROGRESS (place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, and social capital).

Risk of Bias Assessment

For RCTs and pseudo-RCTs, reviewers will use the Cochrane Collaboration's Risk of Bias tool [82]. Randomization procedures, bias, allocation, outcome assessor, reporting of findings, and losses to follow-up will be assessed. Studies will be classified as having a low, high, or unclear risk of bias. For non-RCTs (eg, controlled before/after designed studies), reviewers will use the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for evaluating the risk of bias in estimates [83]. The ROBINS-I assesses confounding participant selection, classification of the intervention, departures from the intended intervention, missing data, measurement of outcomes, selection of the reported results, and overall bias. Studies will be classified as being of low, moderate, serious, or critical risk of bias.

Data Synthesis

Qualitative Synthesis

If the selected studies contain large amounts of heterogeneity or lack sufficient numbers to conduct the meta-analysis, we will follow the Narrative Synthesis in Systematic Reviews tool [84] and the PRISMA guidelines [81] to undertake a full narrative review. Following the PRISMA-E checklist [64], we will report both relative and absolute differences in intervention outcomes between sociodemographic groups. We will discuss the extent and limits of applicability to students across sex, race/ethnicity, age, and socioeconomic status. We will further provide implications for research, practice, or policy related to health equity in suicide prevention among college students where relevant (eg, types of interventions needed to address increasing suicide attempts among young Black males).

Meta-analysis

Should we identify a sufficient number of articles with low heterogeneity, we will conduct a meta-analysis among the final selected studies.

RevMan 5.3 will be used for all analyses. For continuous data, we will report the mean differences between groups and the 95% CI. We will calculate the standardized mean difference and 95% CI if different measurement tools were used for the same outcome, and the standard deviation if not reported [63]. We will use a random effects meta-analysis model given the possibility that there will be different types of interventions, heterogeneous characteristics of participants and comparators, and different intervention effects.

We will use χ^2, I^2, and T^2 to assess heterogeneity [85]. Specifically, χ^2 assesses the compatibility of observed differences in results (χ^2 with $P<.01$ will be considered substantial heterogeneity). The I^2 statistic represents the proportion of the total variation across studies due to

heterogeneity ($I^2<40\%$ indicates insignificant heterogeneity) [63], while T^2 estimates the between-study variance in a random effects meta-analysis ($T^2>1$ indicates substantial heterogeneity).

Sensitivity analysis will be conducted by examining whether excluding studies identified as having a greater risk of bias affects the effect sizes and comparisons between intervention and control groups.

Publication bias will be assessed by funnel plots and Egger test [86].

Sensitivity Analysis

With our comprehensive inclusion criteria, it is expected that the selected studies will include multiple study designs (eg, RCTs, non-RCTs, and observational studies). Recent studies report improved diagnostic accuracy after including different study designs in meta-analyses [86,87]. We plan to first conduct an analysis among combined RCTs and pseudo-RCTs, followed by separate subgroup analyses by study design to investigate the impact on the magnitude of the effect size observed for the included interventions.

Subgroup Analysis

Given the focus of this study on investigating health disparities, we plan to conduct subgroup analyses by sociodemographic characteristics and by pre-pandemic and pandemic periods when there are sufficient studies to do so. To increase the statistical rigor of our meta-analysis, we will include an independent meta-analysis statistician to review all our work as a blinded reviewer.

Evaluation of Cost-Effectiveness

We plan to evaluate the cost-effectiveness of the studies based on the reported ICER and the strength of evidence. We will classify interventions into cost-saving (better health outcomes and costs less than controlled group) or cost-neutral (ICER=0); very cost-effective ($0 < ICER ≤ $25,000 per quality-adjusted life-years [QALY] or life-years gained [LYG]); cost-effective ($25,000 < ICER ≤ $50,000 per QALY or LYG); marginally cost-effective ($50,000 < ICER ≤ $100,000 per QALY or LYG); or not cost-effective (>$100,000 per QALY or LYG) [60]. The strength of evidence (strong, supportive, or uncertain) will be assessed using criteria from a previous systematic review [88]. If there are no reported direct health care costs or evaluation of cost-effectiveness in the identified studies, we will summarize the data as reported in a previous review on depression intervention [89].

Ethics and Dissemination

No ethical approval is required for this protocol and proposed systematic review as we will only use data from previously published papers that have themselves received ethics clearance and used proper informed consent procedures. The results of our systematic review and meta-analysis will be published in a peer-reviewed journal.

Results

The systematic review and meta-analysis are currently in progress and expected to be finished by summer 2021. We welcome comments from reviewers and will be flexible in adjusting based on concerns related screening and data analysis to improve scientific rigor. Our final manuscript is expected to be submitted to peer-reviewed journals by August 2021.

Discussion

Principal Findings

Suicide is a significant public health crisis among college students worldwide [1-7]. However, there is a lack of research pertaining to effective suicide prevention programs among college students, particularly programs that could be tailored to target the unique needs of student subgroups (eg, sex, sexual orientation, race/ethnicity, age, and socioeconomic status). Although the impact of the COVID-19 pandemic on suicidal behaviors among college students has been recognized [18], little is known about possible suicide prevention programs for college students during the pandemic and their differences in crisis management that differ from pre–COVID-19 intervention programs.

Our systematic review and meta-analysis will address a significant lack of outcomes research examining the efficacy and effectiveness of available suicide prevention programs among college students. The strengths of our study are the inclusion of intervention and prevention programs with various study designs, settings, and modes of delivery across countries, and a specific focus on health equity. Our findings will inform clinicians, researchers, policy makers, families, and higher education organizations in reducing the gaps in the suicide crisis among college students from different sociodemographic subgroups.

Limitations

Given the broad inclusion criteria, there may be high heterogeneity among the included studies. There may also be a small number of studies focused on newly developed interventions (eg, mobile technologies), which may have limited representativeness. We plan to follow established guidelines for handling heterogeneity [63,81,90,91]. We are minimizing the potential risk of studies being excluded during selection by following a rigorous protocol, conducting a prescreening training, including multiple coders, and employing cross-validation through a third reviewer. We will conduct sensitivity analysis by considering duplicate data extraction to minimize extraction errors [92,93]. We will include an external meta-analysis statistician to detect any scientific and statistical errors during the meta-analysis [94]. We are also aware that some community-based interventions may not have identified participants as college students, and thus, it may be difficult to identify data to examine any potential differences between on-campus and off-campus services. In such a case, we will summarize findings from the existing studies that report college students as the study sample. By submitting our protocol for review, we will also adjust for any critical threats not identified by the team prior to conducting the study.

Implication

To the best of our knowledge, this will be the first systematic review and meta-analysis to examine the effectiveness of suicide prevention interventions among college students in such a wide-ranging and comprehensive manner. In addition, if possible, comparing pre-pandemic interventions and interventions during the pandemic could offer guidance for future initiatives and emerging needs.

Authors' Contributions

YX conceptualized, designed, and initiated the study, drafted the initial manuscript, and reviewed and revised the manuscript. RH contributed to the analytic plan. The other authors reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Checklist of items for reporting equity-focused systematic reviews (PRISMA-E 2012).
[DOCX File , 35 KB - resprot_v10i5e26948_app1.docx]

Multimedia Appendix 2
Search strategies and updated number of results on March 24, 2021.
[DOCX File , 30 KB - resprot_v10i5e26948_app2.docx]

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Abbreviations

CDC: Centers for Disease Control and Prevention
ICER: incremental cost-effectiveness ratio
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
RCT: randomized controlled trial
ROBINS-I: Risk of Bias in Non-randomized Studies of Interventions

<u>Protocol</u>

Advantages and Challenges in Using Telehealth for Home-Based Palliative Care: Protocol for a Systematic Mixed Studies Review

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Abstract

Background: Given the increasing number of people in need of palliative care services and the current health care professional workforce strain, providing equitable, quality palliative care has become a challenge. Telehealth could be an innovative approach to palliative care delivery, enabling patients to spend more time or even remain at home, if they wish, throughout the illness trajectory. However, no previous systematic mixed studies reviews have synthesized evidence on patients' experiences of the advantages and challenges of telehealth for home-based palliative care.

Objective: The aim of this systematic mixed studies review is to critically appraise and synthesize findings from studies that investigated patients' use of telehealth in home-based palliative care with a focus on the advantages and challenges experienced by the patients.

Methods: This article describes the protocol for a systematic mixed studies review with a convergent design. The reporting will be guided by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. A systematic search was performed in eight databases for studies published from January 2010 to June 2020. The search will be updated in 2021. Pairs of authors will independently assess eligibility, extract data, and assess methodological quality. The data will then be analyzed using thematic synthesis.

Results: We describe the rationale and design of a systematic mixed studies review. The database searches were performed on June 25, 2020. Assessment of eligibility and further steps have not yet been performed. Results are anticipated by August 2021.

Conclusions: Following the ethos of patient-centered palliative care, this systematic mixed studies review could lead to recommendations for practice and policy, enabling the development and implementation of telehealth applications and services that align with patients' preferences and needs at home.

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KEYWORDS

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Introduction

Background

Palliative care is an approach that aims to improve the quality of life of patients and their families facing problems associated with life-threatening illness, regardless of diagnosis [1]. Historically, palliative care has been strongly associated with end-of-life care and cancer. Today, however, providers strive to introduce palliative care earlier in the illness trajectory [2] and to broaden the scope to include, for example, neurological diseases, lung conditions, frailty, cognitive impairment, and the presence of multiple comorbidities [3]. Recently, the need to change from disease-centered to patient-centered care has been highlighted [2,4,5]. This shift compels health care professionals to become more responsive to individual patient preferences, needs, and values, in addition to ensuring that patients' values guide their clinical decision-making. Patients receiving palliative care often want to spend as much time as possible in their homes, and some even want to die at home [6,7].

Early integration of home-based palliative care for patients with life-threatening illness may improve patient and family satisfaction; improve patient quality of life; improve symptoms such as pain, fatigue, and nausea; and reduce aggressive treatment at the end of life; in addition to reducing hospital length of stay and hospitalization [8]. Feeling secure seems to be a core mechanism of palliative care enabling patients to stay at home [9,10]. While being cared for by a present and available team, patients may feel more supported and that someone shares the responsibilities of managing their illness [10].

Current ongoing circumstances present challenges in providing palliative care. Recently, the COVID-19 pandemic has resulted in an emphasis on telehealth. As telehealth applies to palliative care, it could potentially overcome obstacles when physical distancing requirements and lockdowns would otherwise limit access, subsequently increasing isolation and suffering [11,12]. In addition, it appears unclear how health care professionals are to treat the increased number of patients with palliative care needs [13]. Furthermore, there are concerns regarding future workforce strain in palliative care, both due to population growth and aging, and because a large proportion of the health care professionals retire or leave this area of practice, resulting in insufficient numbers to cover the shortfall [14]. The United Nations Agenda 2030 Sustainable Development Goal 3 highlights the right to health and well-being, with an emphasis on access to quality health care services [15]. Taken together, these challenges call for innovation and change in models of home-based palliative care delivery. Telehealth could be an important service addition to deliver high-quality home-based palliative care, enabling patients to spend as much as time as possible at home. Telehealth may empower patients to manage their illness, improve patient quality of life, decrease hospital admissions, and improve access to home care palliative care services [16,17].

Telehealth is defined as "the provision of healthcare remotely by means of a variety of telecommunication tools" [18]. Patients receiving palliative care and their next of kin have expressed that telehealth should be offered as a supplement to exiting services and should be used based on personal choices [19]. Health care professionals may be reluctant to use telehealth in palliative care. Previous research has identified concerns about increased focus on the patients' physical problems, and that telehealth could have a negative effect on contact with patients [20,21].

The technology acceptance model (TAM) [22] is a theoretical model that has been used in studies regarding acceptance of technology in health care [23-25]. The goal of using the TAM theory is to elaborate the use of technology and users' behaviors, in addition to better understanding acceptance of technology. Usability and ease of use are commonly associated with the user's acceptance of the technology.

Systematic reviews have examined the use of telehealth in pediatric palliative care [26,27]. One systematic review of qualitative and quantitative studies examined existing information and communication technology (ICT) systems intended to support pain management in patients with cancer who were receiving palliative care. This review categorized these ICT systems as emergent; however, none of them had been implemented yet in clinical practice. The studies included were not limited to patients' experiences of using these ICT systems in the home setting [28]. Two other systematic reviews have identified mobile apps developed and used in palliative care; however, neither of these reviews investigated patients' experiences using these apps [29,30]. Systematic reviews have also examined the effectiveness of telehealth interventions and information needs in palliative care [31], as well as patient-reported outcomes such as quality of life, symptom management, and satisfaction [32]. Capurro et al [31] found that management of pain and other burdensome symptoms, and care in general, were the most frequent information needs in palliative care.

Another systematic review examined the use of telehealth in the monitoring of patients with chronic diseases at home to consider what could be adapted for patients receiving palliative care. However, the included studies were not limited to patients in a palliative care trajectory, nor did the results address the patients' experiences of using telehealth at home [33]. Furthermore, an integrated review examined the use of video consultations in palliative care based on the views of patients, relatives, and health care professionals. The results suggested that video consultation is feasible in palliative care when used for communication between patients, relatives, or health care professionals, and for clinical assessments and symptom management. An important limitation with this review was that only one person performed the screening and data extraction [34].

Why This Review is Needed

Recently, our group published a scoping review of patients' experiences of using telehealth in palliative home care [35]. The results indicated that telehealth was easy and effortless to use, improved access to health care professionals at home, and enhanced patients' feelings of safety and security. However, due to the scoping review design, the methodological quality of the included studies was not appraised, and the results of the included studies were grouped and not synthesized.

Consequently, robust inferences and recommendations for policy and practice cannot be drawn or stated from the results. Another limitation was that 11 of the included studies were published before 2010, while studies on telehealth in palliative care have increasingly been published in the last 2 years. Furthermore, previous reviews have highlighted negative aspects of telehealth in general [17,36]. However, our review found that future systematic reviews should highlight the thus far neglected negative aspects of telehealth in palliative care [35].

Performing a scoping review is regarded as helpful in determining the value of undertaking a full systematic review [37]. Accordingly, based on this initial review, we conclude that the rationale and feasibility for a full systematic review using a systematic mixed studies review design is evident. To our knowledge, no systematic mixed studies reviews of primary research have synthesized evidence on patients' experiences of the advantages and challenges using telehealth in home-based palliative care. Such a review could enable a comprehensive and rich understanding of the complex interventions and phenomena [38] occasioned by innovations such as telehealth for palliative care. Consequently, this systematic mixed studies review aims to critically appraise and synthesize findings from studies that investigated patients' use of telehealth in home-based palliative care by answering the following research question: What do patients experience as the advantages and challenges of using telehealth in home-based palliative care?

Methods

Design

This systematic mixed studies review will employ a convergent design [38]. Studies will be included irrespective of their study design, and results from the included studies will be integrated using qualitative data transformation techniques. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement will guide the reporting of the review [39].

Eligibility Criteria

Inclusion and exclusion criteria are described in Table 1. Included studies are limited to those published in peer-reviewed journals. Consequently, publications such as PhD theses will be excluded.

Table 1. Inclusion and exclusion criteria.

Category	Inclusion criteria	Exclusion criteria
Type of studies	Any type of quantitative, qualitative, or mixed methods study on the phenomenon of interest published in peer-reviewed journals	Any type of review, PhD thesis, conference abstracts, editorials, comments, or letters
Period	From January 1, 2010 to the updated search	Before January 1, 2010 and after the updated search
Language	Portuguese, Spanish, Danish, Norwegian, Swedish, or English	All other languages
Participants	Home-based patients aged 18 years or older in a palliative care trajectory, regardless of diagnosis	Patients 17 years or younger; not in a palliative care trajectory; or using telehealth in a nursing home, hospice, or hospital setting
Phenomenon of interest	Home-based patients' experience of using telehealth with follow-up from health care professionals	Home-based patients' experience of using telehealth without follow-up from health care professionals; or patients' experience of using telehealth in a hospital, nursing home, or hospice
Outcomes	Patients' subjective and objective outcomes	Proxy-reported outcomes

Search Strategy

A systematic search was performed using the databases CINAHL, EMBASE, Medline, PsycINFO, Web of Science, Literature in the Health Sciences in Latin America and the Caribbean (LILACS), the Cochrane Central Register of Controlled Trials (CENTRAL), and Allied and Complementary Medicine (AMED) on June 25, 2020. The search strategy was built in Medline by FP, an experienced research librarian, and SS using text words and subject headings adopted for each of the databases used (see Multimedia Appendix 1). A second research librarian critically reviewed the search strategy. The search will be updated in 2021, approximately 2 months prior to submission of the manuscript for publication. We will contact authors of relevant conference abstracts to clarify whether the results have been published in a peer-reviewed journal. A manual search will be performed to screen the reference lists of the included papers and JMIR journals, as well as identifying references that cited the included articles after publication

Study Selection

The identified publications were imported to EndNote for removal of duplicates. Rayyan QCRI will be used to facilitate storage, organization, and blinding of the identified publications [40]. Pairs of reviewers will independently assess whether titles, abstracts, and full-text publications meet the eligibility criteria. If there is any doubt about whether a publication meets these criteria, an additional reviewer will perform an independent assessment and discussions to reach negotiated consensus will take place [41].

Appraisal of Methodological Quality

The methodological quality of the included studies will be independently appraised by pairs of reviewers using the relevant Johanne Briggs Institute critical appraisal tools based on the

study design. If there is any conflict among the reviewers, a third reviewer will perform an independent appraisal and discussions to reach negotiated consensus will take place [41].

Data Extraction

Data will be extracted from the included papers using a standardized data collection form by pairs of reviewers independently. The following data will be included: authors, year of publication, country of origin, aim of the study, study population and sample size, theoretical framework for the telehealth intervention, telehealth application, design and methods, and findings related to the research questions of the review.

Data Synthesis

Data from the results section of the included papers will be extracted independently by pairs of reviewers. Results from studies that will include qualitative, quantitative, and mixed methods data will be transformed into a qualitative format [38]. Numerical data presented in tables and figures will be described with words. This will be supported by the authors' description of the results from the results section of the included papers.

The data material will be analyzed using inductive thematic synthesis [38,42], which has previously been used in systematic mixed studies reviews with a convergent design [26,43]. NVivo (version 12) will be used to facilitate the storage and synthesis of data.

The extracted data material will be read several times to obtain an understanding of the material as a whole. The data material will be coded line by line according to its content and meaning. Text that has a code applied will be examined to check the consistency of interpretation and whether additional coding will be needed. Based on similarities and differences between the codes, the codes will be sorted into descriptive themes closely matching the results of the included studies. To generate analytical themes, the descriptive themes will be interpreted and abstracted, guided by the research question [42,44]. This will enable the analysis to go beyond the content of the included papers. The first author will be responsible for analyzing the data and developing codes and themes. The second author and the last author will read the data material and participate in discussions regarding the emerging codes and themes. The final themes will be decided by consensus among all authors. This could facilitate competing interpretations and thereby enhance credibility, dependability, and reflexivity.

Results

We introduced the rationale and design of a systematic mixed studies review to critically appraise and synthesize findings to answer our research question: What do patients experience as the advantages and challenges when using telehealth in home-based palliative care? The database searches were performed on June 25, 2020, which identified 15,993 publications. After removal of 6799 duplicates, we will screen titles, abstracts, and full text of 9194 publications, in addition to manual searches and contacting researchers in this field. Results are anticipated by August 2021.

Discussion

The results will be discussed in light of the TAM owing to its importance of understanding what influences patients' acceptance of technology. Our review could contribute recommendations for practice and policy, enabling the implementation of patient-centered telehealth services that align with patient preferences, needs, and values.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy used in Medline.
[DOCX File , 23 KB - resprot_v10i5e22626_app1.docx]

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Abbreviations

ICT: information and communications technology
TAM: technology acceptance model

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Protocol

Respiratory and Cardiovascular Health Effects of e-Cigarette Substitution: Protocol for Two Living Systematic Reviews

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Abstract

Background: Despite the clear risks of tobacco use, millions of people continue to smoke. Electronic nicotine delivery systems (ENDS), commonly called e-cigarettes, have been proposed as a substitute for those who are unwilling or unable to quit. Current systematic and narrative reviews on the health effects of ENDS use, particularly respiratory and cardiovascular effects, have come to differing conclusions.

Objective: We conducted two systematic reviews to critically assess and synthesize available human studies on the respiratory and cardiovascular health effects of ENDS substitution for people who smoke. The primary goal is to provide clinicians with evidence on the health effects of ENDS substitution to inform their treatment recommendations and plans. The twin goal of the reviews is to promote health literacy in ENDS users with facts on the health effects of ENDS.

Methods: These two reviews will be living systematic reviews. The systematic reviews will be initiated through a baseline review. Studies will be evaluated using the JBI quality assessment tools and a checklist of biases drawn from the Centre for Evidence Based Medicine Catalogue of Bias. A narrative synthesis is planned because of the heterogeneity of data. A search for recently published studies will be conducted every 3 months, and an updated review will be published every 6 months for the duration of the project or possibly longer.

Results: The baseline and updated reviews will be published in a peer-reviewed journal. The findings of the reviews will be reported in a white paper for clinicians and a fact sheet for people who use ENDS.

Conclusions: The substitution of ENDS for cigarettes is one way to potentially reduce the risks of smoking. Clinicians and their patients need to understand the potential benefits and possible risks of substituting ENDS for cigarettes. Our living systematic reviews seek to highlight the best and most up-to-date evidence in this highly contentious and fast-moving field of research.

Trial Registration: PROSPERO CRD42021239094; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=239094

International Registered Report Identifier (IRRID): DERR1-10.2196/29084

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Introduction

Background

There are 1.3 billion people worldwide who use tobacco, and more than 7 million of them die annually from its use [1]. Up to 11.5% of the global mortality can be linked to smoking [2]. For respiratory diseases, smoking is the attributable mortality risk factor for 64.21% of lung, tracheal, and bronchial cancer; 63.44% of laryngeal cancer; 48.47% of chronic obstructive pulmonary disease; 15.52% of tuberculosis; 11.93% of asthma; and 11.04% of lower respiratory infections [3]. For cardiovascular diseases, smoking was the attributable risk factor for 34.6% of deaths from aortic aneurysm, 26.8% from peripheral artery disease, 18.41% from ischemic heart disease, and 14.2% from stroke [4]. Smoking is one of the primary acquired risk factors for atherosclerotic disease [4].

Despite the clear risks of tobacco use, millions of people continue to smoke. Smoking has pleasurable effects [5], and some smoke for emotional regulation or to self-medicate their symptoms of schizophrenia or Parkinson disease [6]. For those who want to quit, the success rate for cessation attempts is low—approximately 7% at 6 months [7,8]. Furthermore, presently around 70% of the world's population has no access to appropriate tobacco cessation services [9]. Quitting smoking is difficult, many have no support to quit, and some people do not wish to quit.

Electronic nicotine delivery systems (ENDS), commonly called e-cigarettes, have been proposed as a substitute for those who are unwilling or unable to quit [10,11]. A review by the US National Academies of Sciences, Engineering, and Medicine (NASEM) [12] states the following: "There is substantial evidence that, except for nicotine, under typical conditions of use, exposure to potentially toxic substances from e-cigarettes is significantly lower compared with combustible tobacco cigarettes." The acceptability of ENDS among people who smoke is demonstrated by its rapid uptake; in 2018, there were 41 million people using ENDS compared with 7 million users in 2011 [13]. Clinicians want to know the health effects of ENDS use, asking "are e-cigarettes marginally safer, thus still too risky to substitute for combustible products, or are they substantially safer?" [14].

Prior Reviews: Respiratory Effects

There have been 3 recent systematic reviews published on the respiratory effects of ENDS. The study by Bals et al [15], which was prepared for the European Respiratory Society, is based on studies published through August 2016, rendering it out-of-date. The review by Wang et al [16] exclusively included in vitro and in vivo studies but not human studies. Goniewicz et al [17] analyzed only cross-sectional studies of risk. Although they found a 40% reduction in adverse pulmonary outcomes, cross-sectional studies can only demonstrate an association not causation.

In addition, 4 narrative reviews on the pulmonary effects of ENDS have been published since 2019; they were conducted with a combination of in vitro, in vivo, emission toxicology, and human studies. The reviewers came to diametrically opposed conclusions regarding the respiratory effects. Gotts et al [18] and Miyashita and Foley [19] concluded that there is sufficient evidence of respiratory harm from ENDS use. In contrast, Traboulsi et al [20] presented evidence of both beneficial and adverse effects for people who smoked, whereas Polosa et al ([21] disclosure: RP and RO are coauthors) argued that ENDS substitution resulted in primarily beneficial health effects.

Prior Reviews: Cardiovascular Effects

Recent systematic reviews offer substantially different conclusions on the cardiovascular effects of ENDS, some suggesting harm and others not finding harm, whereas still others stating that there is a lack of evidence. One systematic review of in vitro, animal, and human studies presented the conclusion that "most studies suggest potential for cardiovascular harm" caused by sympathetic nerve activation, oxidative stress, endothelial dysfunction, and platelet activation [22]. Another systematic review found no indications of a significant increase or reduction in cardiovascular disease outcomes (stroke, myocardial infarction, and coronary heart disease) among former smokers who transitioned to ENDS based on cross-sectional population studies of ENDS users [17]. Benowitz and Fraiman [23] concluded that ENDS use is likely to be associated with lower cardiovascular risks than cigarette smoking, based on toxicity studies, known mechanisms, and laboratory models. Two current systematic reviews of human studies on the cardiovascular effects of ENDS displayed more agreement on study evidence, finding lower acute effects and no chronic increases in heart rate and blood pressure for ENDS use compared with smoking [24,25].

Conversely, some reviewers claim that evidence is lacking or insufficient. The NASEM stated that "there is no available evidence whether or not e-cigarette use is associated with clinical cardiovascular outcomes (coronary heart disease, stroke, and peripheral artery disease) and subclinical atherosclerosis (carotid intima-media thickness and coronary artery calcifications)" [12]. D'Amario et al [26] stated that there is a lack of clear or conclusive data on ENDS use and cardiovascular health. MacDonald and Middlekauff [27] concluded their narrative review of human and emission toxicology studies by stating that "the effects of ECs on long-term cardiovascular health are inconclusive, but concerning." Buchanan et al [28] in their narrative review of preclinical and clinical studies even dismiss the available literature: "While the current but still limited literature suggests that e-cigarette use may lead to fewer negative cardiovascular effects than conventional cigarettes, our review supports that there is not sufficient data to conclusively make these resolutions."

An umbrella review [29] (review of reviews) included 7 systematic reviews but did not include the NASEM review. The umbrella review included 3 reviews conducted in 2016 or earlier when substantially fewer studies had been published and 1 review that contributed only 2 case studies from cannabinoid ENDS use. The remaining 3 systematic reviews are discussed in the previous paragraphs. The reviewers suggest that ENDS may provide a strategy for harm reduction with the caveat of the need for more studies.

Research Question

Ascertaining the real-life effects of ENDS substitution on respiratory and cardiovascular health is complex. The complexity is because of the frequent use of ENDS in combination with conventional cigarettes, the differences in ENDS products, variations in the nicotine concentration of liquids, and the varying levels of daily exposure. There is an urgent need for a current systematic review of research, given the disagreements among prior reviews. Many of the available reviews have limitations arising from their reliance on nonhuman study data. Furthermore, several reviews have shown evidence of biased reporting. In addition, findings from recently published studies not covered in these reviews may render their conclusions obsolete. By conducting 2 living systematic reviews, we aim to answer the question: "What are the respiratory and cardiovascular health effects resulting from the substitution of ENDS for conventional cigarettes?"

Population, Intervention, Comparator, and Outcomes Criteria

The following summarize the population, intervention, comparator, and outcomes criteria:

- Population: adults who smoke cigarettes.
- Intervention: substitution of ENDS for cigarettes.
- Comparator: participants who continue to smoke, baseline changes in respiratory or cardiovascular tests of study participants who substitute ENDS for smoking (within-subject), or comparisons with documented smoking outcomes.
- Outcomes (respiratory): changes in chronic cough, phlegm, wheezing, dyspnea, exacerbations of asthma and chronic obstructive pulmonary disease, or changes in testing, including forced expiratory volume, chest x-rays, and computed tomography scans.
- Outcomes (cardiovascular): measures of cardiovascular function, including blood pressure, heart rate, carotid intima-media thickness, and coronary artery calcifications, or changes in cardiovascular disease symptoms (clinical observation or self-reported).

Objectives

We are conducting 2 systematic reviews to critically assess and synthesize available human studies on the respiratory and cardiovascular health effects of ENDS substitution for people who smoke. We will provide an even-handed assessment of the data, considering all health effects, both potentially adverse and beneficial. The primary goal is to provide clinicians with evidence on the health effects of ENDS substitution for people who smoke to inform their treatment recommendations and plans. The twin goals of the reviews include promoting health literacy in ENDS users with facts on the health effects of ENDS with a white paper drawn from the review. These 2 systematic reviews will be conducted with the living methodology to keep the information up to date and complete, as described in the following sections.

Methods

Overview

The protocol conforms to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols) requirements [30]; the completed checklist is provided in Multimedia Appendix 1. This protocol is registered with PROSPERO (CRD42021239094). Any deviations from this protocol will be reported in the reviews. These reviews are being conducted concurrently, so there is an overlap between their methodological procedures. Nevertheless, each review has unique testing data and differing effect modifications from participants' smoking history that necessitate conducting separate reviews for respiratory and cardiovascular health effects.

These 2 reviews will be living systematic reviews. Living systematic reviews are a recent innovation for conducting systematic reviews that incorporate evidence from studies as they are published [31,32]. Living systematic reviews follow the established methods of conducting a systematic review and in addition perform searches and publish updated reviews at prespecified intervals. This enhancement overcomes the major issue of systematic reviews becoming outdated soon after publication [33].

The Cochrane guidelines [32] specify 3 conditions to justify conducting a living systematic review: (1) a lack of high-quality studies or certainty about them, (2) the priority of the evidence for decision making, and (3) emerging data that have a significant impact on the conclusions of previous reviews. Our review questions satisfy all of the above conditions. First, there are a relatively limited number of human studies on the health effects of ENDS, contributing to the uncertainty of their clinical impact [27,34,35]. Second, decisions by clinicians and policy makers are often based on beliefs that are not supported by the available studies [36-38]. Research evidence on the health risks of ENDS is a priority for decision making because ENDS could represent an excellent tobacco harm reduction opportunity [34] if their long-term risk reduction when compared with smoking would be demonstrated. Finally, new evidence is being published that is expected to impact existing knowledge. Indeed, the research output on ENDS has increased rapidly since 2018 [39,40]. Our preliminary search of articles on ENDS in PubMed retrieved 1332 articles published in 2019 and 1565 articles published in 2020 (search in Multimedia Appendix 1). The living systematic review format is clearly in order.

The review team comprised RO, the project leader, with extensive experience in conducting literature reviews and a substantial background in tobacco control, tobacco harm reduction, and ENDS. The research team comprised 4 fellows: MAQ, GRMLR, and DCO, each having literature review experience as the first author of a narrative review, and RWMV, who has substantial experience in literature reviews. MAQ and GRMLR are clinicians, and DCO has worked as a pharmacist. MAQ has a background in tobacco control and tobacco harm reduction.

The processes that will be conducted to create the baseline reviews are described in the following sections.

Study Selection

Study designs selected for the reviews include randomized and nonrandomized controlled trials and clinical trials, prospective and retrospective cohort studies, and case-control studies. A gray literature search was performed. Database searches were performed separately for the cardiovascular and respiratory studies. Supplementary searches were conducted after the database search and after the full paper selection.

Gray Literature Search

A search for articles on ENDS not published in peer-reviewed journals was conducted on January 13, 2021, on the websites of 41 cardiovascular medical organizations and 53 respiratory medical organizations (Multimedia Appendix 1). No gray literature was found.

Database Search and Secondary Searches

The databases searched included Scopus, PubMed, and CENTRAL Cochrane Library.

The keywords used for the search included the following: ENDS keywords were *electronic cigarettes* and *e-cigarettes*. Vapor or vapor were not used as keywords, as these terms retrieve many chemical studies. Cardiovascular keywords were cardiovascular, heart, circulatory, arterial, and stroke. The respiratory keywords were lung, pulmonary, and respiratory.

The text fields searched were title and abstract in PubMed; title, abstract, and keywords in Scopus; and trials in Cochrane Library.

The search dates were from 2010 to January 31, 2021. The start date of 2010 is the date of publication of the first peer-reviewed research studies on ENDS.

The languages searched were English, French, Spanish, and studies in any language with an English abstract.

In compliance with PRISMA-P, an example of the search strategy is reported in the Multimedia Appendix 1.

The retrievals were entered into EndNote for bibliographic management. Paper retrieval duplicates were removed. There were 374 retrievals cardiovascular outcomes and 703 retrievals for respiratory outcomes.

The first exclusion of articles was performed on titles, and where a title was not sufficient for a determination, the abstract was reviewed. There were five categories of exclusion criteria. The first category was article types: editorials, commentaries, letters, news articles, issue introductions, and reviews. The second category was studies that were not peer reviewed, including conference abstracts, unpublished clinical trials, and preprint articles. The third category was articles without an English abstract (except for those in French or Spanish). The fourth category was studies exclusively on EVALI (e-cigarette or vaping product use–associated lung injury) because most EVALI cases were linked to black market tetrahydrocannabinol products not commercial ENDS [41]. The fifth category was the study design, including in vitro, inhalation toxicology, biomarker,

animal, cross-sectional studies, and studies conducted exclusively with youth.

The exclusion process was conducted independently by 2 reviewers, and all discrepancies were resolved by discussion between the reviewers. One study in a nonincluded language was excluded. The number of studies after title and abstract exclusion was 43 cardiovascular outcomes studies and 23 respiratory outcomes studies.

As a supplementary search, the reviews discussed in the introduction [15,18-28] were searched independently by 2 reviewers for studies with the exclusion criteria above.

The second process of inclusion and exclusion was a full-paper review. There were 3 inclusion criteria. First, studies were limited to the research designs of randomized controlled trials, nonrandomized clinical studies, prospective or retrospective cohort studies, and case series. Second, a study was required to have either a comparator of participants who smoked combustible tobacco (cigarettes) or a before and after testing of participants who had substituted ENDS for smoking. Third, the study had to report outcome data on cardiovascular or respiratory function or diseases. All 3 aforementioned criteria had to be met for a study to be included.

The review team members were trained and supervised on the inclusion criteria on 5 studies. The inclusion and exclusion of studies was conducted independently by 2 reviewers, and discrepancies were resolved by a discussion. The reviewers achieved 95% (63/66) agreement on the inclusion and exclusion of studies. The project leader made the final decision on the studies that were questioned.

After this step, the reference lists of all included studies were reviewed for additional studies and were citation chased in Google Scholar. A list of studies excluded during the full-paper review is reported in the Multimedia Appendix 1.

The search processes yielded 27 cardiovascular outcomes studies and 19 respiratory outcomes studies that are listed in the Multimedia Appendix 1. The list of the included studies for each review will be sent to 2 medical experts for examination to ensure that no relevant studies have been missed. Any additional studies will be reported in the review.

Data Extraction Process

The data extraction process is being conducted with a data extraction form. The reviewers were trained using calibration exercises to ensure consistency. Data are being extracted independently by 2 reviewers and will then cross-checked by the reviewers for accuracy and completeness. Any discrepancies in data extraction will be rectified by discussion. The data extraction items were drawn from inventories by JBI and the Cochrane Collaboration [42,43]. The data extraction form is provided in Multimedia Appendix 1. The categories include bibliographic details, population data, description of the intervention, respiratory or cardiovascular functioning or disease outcomes, data analysis, and study conclusions. If the published data are judged as insufficient or missing, the corresponding author will be sent an email with a request for additional details.

Two additional examinations of each study are being performed. The first is a check for internal discrepancies in the reporting of data [44] (Multimedia Appendix 1). The second is a comparison of the study as it was conducted with its protocol or clinical trial registration where one is available (form in Multimedia Appendix 1).

The completed data extraction forms will be submitted to the Systematic Review Data Repository at the Agency for Healthcare Research and Quality [45], an open access database.

Data from these studies will be reported in two ways. First, individual studies will be presented with a brief narrative description. Second, study tables will be constructed with items from the data extraction and quality assessments (see the following section).

Quality Assessment and Risk of Bias

A quality assessment of each study is being conducted using the JBI quality assessment tool for its research design [46]. Reviewers were trained on the JBI quality assessment tools with an examination of their questions and a discussion of examples of quality issues. The quality assessment of the statistical analyses will be double-checked by a reviewer (RO or RWMV) with training in biomedical statistics.

Bias is being assessed with observations of biases listed in the Oxford Centre for Evidence-Based Medicine *Catalogue of Bias* [47] applicable to the study designs in the review. The review team prepared a set of prompting questions for each type of bias and was briefed on common examples. The checklist of biases is provided in Multimedia Appendix 1.

Quality assessment and risk of bias observations are being made concurrently with the data extraction process. Two reviewers are independently performing the quality and bias assessments. Discrepancies will be resolved through discussions between the reviewers. If a consensus is not reached, the final decision will be made by the project leader. No studies will be excluded based on their quality assessment or risk of bias observations. Studies not conforming to the JBI quality assessment items or with observations of biases will be reported in the study tables. These shortcomings will be specified in the data analysis and will be referenced in the discussion section of the reviews.

Data Analysis and Synthesis

The synthesis will be a narrative synthesis. Owing to the heterogeneity of the study populations and outcome measurements, we anticipate that a meta-analysis will be inappropriate. If sufficient studies are identified as comparable either during the baseline review or for updated reviews, we will develop an additional protocol for a meta-analysis and will add it to the review.

The narrative syntheses will have four components. The first will be the findings organized by the study design. The second will be a summary of descriptive statistics for the participants and intervention characteristics. The third will group the findings based on the tests performed, physiological functions, and disease outcomes. The final synthesis will tally studies that have been found to demonstrate quality issues or biases.

Three subgroup analyses of testing and disease outcomes will be conducted for (1) concurrent users of cigarettes (dual users), (2) populations with prior respiratory or cardiovascular diseases, and (3) ENDS use of a duration of 1 year or longer.

Sensitivity analyses will be performed to explore the influence of the risk of bias on the findings. One will be to rerun the third analysis by excluding all studies assessed at a high risk of bias. A set of sensitivity analyses will be performed on groups of studies based on the following types of funding sources and author affiliations: ENDS or tobacco industry, pharmaceutical affiliations, and philanthropic or medical organization affiliations or funding. Publication bias will be assessed using a funnel plot for the test results and disease outcomes.

The certainty evidence for each reviews' findings will be evaluated with the Grading of Recommendations Assessment, Development, and Evaluation framework [48,49].

Update Plan

Updating the Study Search

A literature search will be conducted at 3-month intervals to retrieve newly published studies. Searches were conducted using the same databases and keywords as the baseline review. Newly published papers will be checked for studies that meet the inclusion criteria. The searches will apply appropriate date limiters to include only those records added to the database subsequent to the last search, allowing for indexing lag time [31,32]. Searches will be maintained in an EndNote library that will record all the search results over the lifetime of the review. Notes about each new search and the inclusion or exclusion decision for each study will be recorded. The newly included studies will be checked for references. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram will be updated accordingly.

The first update search will be conducted on or shortly before April 30, 2021. The retrieved studies will be incorporated into the baseline review so that it will be updated when published.

The updating search can result in 3 scenarios: (1) no new studies are identified (highly unlikely), (2) new studies are retrieved but the evidence has no impact on the review's findings, or (3) new studies are found with evidence that significantly impacts the review's findings. This third scenario will trigger an immediate update of the review [31,32]. In evaluating the impact of new evidence, we will consider whether it causes a change in the Grading of Recommendations Assessment, Development, and Evaluation certainty rating or introduces previously unreported interventions, populations, serious adverse events, or other clinically meaningful findings [32,50]. Any of these conditions will trigger an updated review.

Updating the Review

Because a large volume of new studies is expected, we will update the review every 6 months if no studies prompt an earlier revision of the review. Narrative descriptions of the newly included studies and new study table listings were produced by merging them with the baseline review studies. All data analyses will be conducted using the procedures used for the baseline

review. Conclusions and recommendations are revised to reflect the addition of new studies.

In addition, the search methods will be reviewed annually, or sooner if substantial changes occur that impact the search methodology, such as new search terms or sources. Possible changes to the frequency of the searches will be considered. We will verify that the scope of the review (ie, population, intervention, comparator, and outcomes components) is reflected in the inclusion of adequate thesaurus terms or changes to database search syntax. Other methodological aspects such as the use of technology enablers will also be reviewed annually.

One addition to the scope of this review has been made for the COVID-19 pandemic. As tobacco smoking may be a risk factor for more severe COVID-19 disease outcomes, we will include in the reviews any clinical studies on the impact of ENDS substitution for smoking on patients with COVID-19, particularly with regard to *long COVID*. No studies in this area have been retrieved from the initial search.

Transition Out of Living Mode

The review will be transitioned out of living mode if the research question no longer meets all the 3 criteria justifying the living approach. At that time, we will examine article-level metrics, knowledge translation activities, and the output of new research studies. A practical factor that could result in the end of the living mode is reaching the end of our funding in September 2023. After this period, new funding will be sought to maintain the living mode. If funding is not acquired, we will ask if at least two members of the review team are available as volunteers for 1 year of updates, followed by a final revision of the review. If both of these strategies fail, the review will be transitioned into a traditional systematic review for final publication at the end of the project.

Results

The goal of these reviews is to assemble all the available human studies on the respiratory and cardiovascular effects of ENDS in people who smoke. Furthermore, the reviews will assess the quality and potential biases of the studies to foreground the best available evidence. The reviews will identify those studies that demonstrate reporting bias so that the misrepresentation of ENDS health effects can be addressed in the contentious debate around tobacco harm reduction. The living systematic review methodology will keep the evidence current and complete as opposed to a static systematic review that quickly becomes out-of-date due to the rapid pace of publication of ENDS studies.

As of March 11, 2021, the literature search has been completed except for the review of the study selection by experts, with 27 studies included in the cardiovascular outcomes review and 19 studies in the respiratory outcomes review. Training on data extraction, quality assessment, and bias assessment processes has been completed. The data extraction process has commenced. The target date for the completion of the reviews is July 2021.

Discussion

Few protocols contain substantive planning for dissemination or knowledge translation activities beyond the publication of the review in a peer-reviewed journal and conference presentations. Of course, the reviews will be disseminated through these traditional avenues. This protocol has been published as a preprint on medRxiv. Pending acceptance, the project protocol will be published in the *Journal of Medical Internet Research Protocols*. The baseline and updated reviews will be published in a peer-reviewed journal that agrees to work with the living format for updated editions of the review. The abstracts for the reviews will be translated into as many languages as possible. Announcements of these publications will be sent out on social media platforms (Twitter, Facebook, etc).

In addition, we will write white papers to make the findings of the reviews accessible to clinicians and current or potential ENDS users. The reviews and white papers will be made available for downloading on a dedicated website. The reviews and white papers will be added as references to the relevant Wikipedia pages.

For clinicians, a white paper will spell out the treatment considerations of ENDS use drawn from both the cardiovascular and respiratory outcomes from the reviews. As most physicians and health care providers hold erroneous beliefs about the health effects of nicotine itself [51-53], the white paper will include a section on nicotine. The white paper will be translated into as many languages as possible and sent to medical associations, distributed at conferences, and published on a website for downloading.

For current and potential ENDS users, a white paper with infographics will explain the health effects found in the reviews. The public also hold misperceptions about the health effects of nicotine [11,54], so this white paper will have a section on nicotine. The white paper will be sent to the International Network of Nicotine Consumer Organizations, vapor product magazines, the Cochrane Consumer Network, Consumers United for Evidence-Based Healthcare, and patient advocacy organizations concerned with smoking-related diseases. We will explore producing short videos for YouTube and TEDx based on the white paper.

Our goal with these actions is to achieve a wide dissemination of the findings of the reviews to a wide audience. Standard review publication practices would fail to reach the stakeholders who will benefit from having the evidence presented in a format that is accessible and readily understood.

The terrible toll of death and disease from cigarette smoking calls for every effort to stem the tobacco epidemic. The substitution of ENDS for cigarettes is one way to potentially reduce the risks associated with smoking. Clinicians and their patients who smoke need to understand the benefits of substituting ENDS for cigarettes. They also need to be aware of the risks because "research toward uncovering the risks of e-cigarette use is aligned with optimizing harm reduction" [55]. Our living systematic reviews seek to highlight the best and

most up-to-date evidence in this highly contentious and fast-moving field of research.

Acknowledgments

Authors' Contributions

RO and RP conceptualized the reviews. RO conducted the database search, and RWMV and DCO conducted the gray literature search. RO, MAQ, GRMLR, RWMV, and DCO contributed to the manuscript. RO revised the manuscript. RP and GB reviewed the initial draft and the final manuscript for accuracy and completeness. All authors have read and approved the final manuscript.

Conflicts of Interest

RO is supported by a contract with ECLAT, Srl, and ECLAT has received funding from the Foundation for a Smoke-Free World. RO declares no conflicts of interest. MAQ has a grant from the Foundation for a Smoke-Free World, outside the submitted work, for the project Pakistan Tobacco Economics Research and Dissemination. MAQ declares no conflicts of interest. GRMLR, RWMV, DCO, and GB declare no conflicts of interest. RP has received lecture fees and research funding from Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, MSD, Boehringer Ingelheim, Novartis, Duska Therapeutics, and Forest Laboratories. He has served as a consultant for Pfizer, Global Health Alliance for treatment of tobacco dependence, CV Therapeutics, Boehringer Ingelheim, Novartis, Duska Therapeutics (Electronic Cigarette Industry Trade Association, United Kingdom), Arbi Group Srl, and Health Diplomats. He has served on the Medical and Scientific Advisory Board of Cordex Pharma, Inc, CV Therapeutics, Duska Therapeutics Inc, Pfizer, and PharmaCielo. Lecture fees from a number of European electronic cigarette industry and trade associations (including Féderation Interprofessionnelle de la Vape in France and Federazione Italiana Esercenti Svapo Elettronico in Italy) were directly donated to vapor advocacy nonprofit organizations. RP is the founder of the Center for Tobacco Prevention and Treatment at the University of Catania and the Center of Excellence for the Acceleration of Harm Reduction at the same university and has received support from the Foundation for a Smoke-Free World to conduct eight independent investigator-initiated research projects on harm reduction. RP is currently involved in the following pro bono activities: scientific advisor for Lega Italiana Anti Fumo (Italian Anti-Smoking League), Consumer Advocates for Smoke-free Alternatives and the International Network of Nicotine Consumers Organizations, and Chair of the European Technical Committee for standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4).

Multimedia Appendix 1
Supplementary materials.
[DOCX File , 58 KB - resprot_v10i5e29084_app1.docx]

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Abbreviations

ENDS: electronic nicotine delivery systems
EVALI: e-cigarette or vaping product use–associated lung injury
NASEM: National Academies of Sciences, Engineering, and Medicine
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols

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<u>Protocol</u>

Predicting Risk of Hospital Admission in Patients With Suspected COVID-19 in a Community Setting: Protocol for Development and Validation of a Multivariate Risk Prediction Tool

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Abstract

Background: During the pandemic, remote consultations have become the norm for assessing patients with signs and symptoms of COVID-19 to decrease the risk of transmission. This has intensified the clinical uncertainty already experienced by primary care clinicians when assessing patients with suspected COVID-19 and has prompted the use of risk prediction scores, such as the National Early Warning Score (NEWS2), to assess severity and guide treatment. However, the risk prediction tools available have not been validated in a community setting and are not designed to capture the idiosyncrasies of COVID-19 infection.

Objective: The objective of this study is to produce a multivariate risk prediction tool, RECAP-V1 (Remote COVID-19 Assessment in Primary Care), to support primary care clinicians in the identification of those patients with COVID-19 that are at higher risk of deterioration and facilitate the early escalation of their treatment with the aim of improving patient outcomes.

Methods: The study follows a prospective cohort observational design, whereby patients presenting in primary care with signs and symptoms suggestive of COVID-19 will be followed and their data linked to hospital outcomes (hospital admission and death). Data collection will be carried out by primary care clinicians in four arms: North West London Clinical Commissioning Groups (NWL CCGs), Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC), Covid Clinical Assessment Service (CCAS), and South East London CCGs (Doctaly platform). The study involves the use of an electronic template that incorporates a list of items (known as RECAP-V0) thought to be associated with disease outcome according to previous qualitative work. Data collected will be linked to patient outcomes in highly secure environments. We will then use multivariate logistic regression analyses for model development and validation.

Results: Recruitment of participants started in October 2020. Initially, only the NWL CCGs and RCGP RSC arms were active. As of March 24, 2021, we have recruited a combined sample of 3827 participants in these two arms. CCAS and Doctaly joined the study in February 2021, with CCAS starting the recruitment process on March 15, 2021. The first part of the analysis (RECAP-V1 model development) is planned to start in April 2021 using the first half of the NWL CCGs and RCGP RSC combined data set. Posteriorly, the model will be validated with the rest of the NWL CCGs and RCGP RSC data as well as the CCAS and Doctaly data sets. The study was approved by the Research Ethics Committee on May 27, 2020 (Integrated Research Application

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System number: 283024, Research Ethics Committee reference number: 20/NW/0266) and badged as National Institute of Health Research Urgent Public Health Study on October 14, 2020.

Conclusions: We believe the validated RECAP-V1 early warning score will be a valuable tool for the assessment of severity in patients with suspected COVID-19 in the community, either in face-to-face or remote consultations, and will facilitate the timely escalation of treatment with the potential to improve patient outcomes.

Trial Registration: ISRCTN registry ISRCTN13953727; https://www.isrctn.com/ISRCTN13953727

International Registered Report Identifier (IRRID): DERR1-10.2196/29072

Introduction

Overview

During 2020, it became clear that assessment of the severity of COVID-19 infection required clinical tools specific to the condition and that repurposing tools such as the National Early Warning Score (NEWS2), designed for the early diagnosis of sepsis, would not be safe clinical practice [1]. The management of COVID-19 by clinicians is challenged by uncertainty about the disease progression [2]. There is evidence that a small percentage of patients present a dramatic deterioration of clinical status around the 8th to 10th day of disease, often associated with unperceived low oxygen saturations (known as "silent hypoxia") that may require hospital and intensive care unit (ICU) admissions [3-5]. The inability to predict which patients will experience clinical deterioration adds an additional level of complexity to the clinical challenge and diagnostic uncertainty that general practitioners (GPs) have faced during the pandemic, particularly as most of the consultations are carried out remotely (usually by telephone and occasionally by video) to minimize the risk of transmission [6].

It was initially suggested that NEWS2 could be used to assess severity of patients with COVID-19 [7]. NEWS2 is calculated from patient's temperature, pulse rate, respiratory rate, systolic blood pressure, pulse oximetry reading, and presence of new onset of acute confusion [8]. It is commonly used in hospital settings and ambulance service prior to transfer to hospital to assess the risk of deterioration of a patient [9]. However, NEWS2 seems to be a late indicator of decompensation, typically triggering within the last 12 hours before a transfer to ICU is considered necessary and, therefore, this limits its application and validity in a primary care or community care setting where an earlier warning would be preferred [9,10].

The Roth score (originally developed as a measure of breathlessness in cardiopulmonary disease [11]) was briefly considered by the Royal College of General Practitioners (RCGP) as possibly useful in the assessment of breathlessness when assessing patients with signs and symptoms of COVID-19 [12]. However, a rapid literature review concluded that the Roth score might have a low sensitivity (ie, a normal score in patients with "silent hypoxia"), and therefore should not be used by GPs when assessing patients over the phone or in video consultations [13].

Justification and Study Objective

This new condition and the forced shift toward remote consultations during the pandemic have increased the challenges and uncertainty commonly faced in general practice [6]. Primary care clinicians need a tool to guide the management of patients with suspected COVID-19 to be able to identify those whom they can reassure, those that need monitoring, and those that require urgent further assessment or referral to hospital. Even though the validity of NEWS2 for this purpose was a subject of intense debate during the height of the first COVID-19 wave, the score is still being used by primary care clinicians to assess patients prior to transfer to hospital [9]. The use of NEWS2 outside the hospital setting has not been validated, and it was not designed to capture the idiosyncrasies of COVID-19 infection. Therefore, there is need to develop an early warning score that incorporates key features of acute COVID-19 and that can be safely used by GPs when assessing patients remotely [14].

We reviewed the literature on COVID-19 early warning scores, then conducted a series of focus groups with 72 primary care clinicians (mostly GPs and including advanced nurse practitioners and paramedics) to derive elements that might form part of a suitable score, value sets, and appropriate SNOMED terms [15]. This paper describes the process of quantitative development and validation of the Remote COVID-19 Assessment in Primary Care (RECAP) score. The objective was to produce a multivariate risk prediction tool to facilitate the early identification, by primary care physicians and other clinicians working in the community, of those patients with COVID-19 that are at higher risk of becoming severely ill and inform the early escalation of their treatment, while also reducing unnecessary referrals in low-risk patients, with the aim of improving patient outcomes.

Methods

Study Design

This primary care data linkage study follows a prospective cohort observational design, whereby patients presenting in primary or community care with signs and symptoms suggestive of COVID-19 will be followed and their data linked with hospital outcomes, particularly focusing on hospital admission, ICU admission, and death. For data collection purposes, the initial set of items identified in earlier qualitative work [15],

known as RECAP-V0, will be integrated into an electronic template to be used by primary care physicians (see Figure 1 for a summary of items included in RECAP-V0). This will enable the standardized recording of patients' signs and symptoms and subsequent linkage with hospital and mortality data. Data collected will be used to develop and validate a multivariate regression model to predict hospital admission, ICU admission, and death.

Figure 1. Summary of RECAP-V0 items. Source: [15]. RECAP: Remote COVID-19 Assessment in Primary Care.

Data Collection

Recruitment

The development of the RECAP score will require the use of primary and secondary data. The collection of patients' signs and symptoms as they present in primary care requires the involvement of primary care clinicians, who will be asked to assess those patients with a clinical diagnosis of suspected COVID-19 using the RECAP electronic template.

The recruitment of clinicians (study sites) and patients (study participants) will be carried out by four different arms depending on clinician and participant location and service used to seek medical care:

1. North West London (NWL) Clinical Commissioning Groups (CCGs) arm: this arm has its own integrated linked database (Whole Systems Integrated Care [WSIC]) and a secure environment (Imperial's Clinical Analytics, Research and Evaluation [iCARE] secure environment) to hold the data. Recruitment of practices will be facilitated by the NWL clinical research network (CRN). General practitioners will use EMIS [16] or TPP SystmOne [17] electronic health record systems to capture patients' data.

2. RCGP Research and Surveillance Centre (RSC) arm: this is a national network of practices within the RCGP developed to contribute with data for disease surveillance and research [18], which is held in the Oxford RCGP Clinical Informatics Digital Hub (ORCHID) secure environment [19]. Subject to the patient's consent, data from RSC network practices (collected from computerized medical record systems EMIS or TPP SystmOne, the United Kingdom's most used systems, using Ardens RECAP electronic templates [20]) will be pseudonymized and extracted via a Wellbeing Software extraction system and linked to outcomes.

3. Covid Clinical Assessment Service (CCAS) arm: this service is organized within the National Health Service (NHS) 111 Online service (managed by South Central Ambulance Service) for the clinical assessment and management of patients with a clinical diagnosis of suspected COVID-19. It is staffed by general practitioners and uses the Adastra electronic health record system [21]. Upon patients' consent, the data collected will be transferred to ORCHID and linked to hospital outcomes.

4. Doctaly arm: this private health care platform has been commissioned by South East London CCGs to provide a home monitoring service for patients with a diagnosis of COVID-19 (positive result in laboratory test) in South East London. Patients' medical history and assessment data are collected using a chatbot via the WhatsApp mobile app. The questions asked via the Doctaly chatbot were designed to reflect the same concepts as the RECAP-V0 set. Data collected will be also transferred to the Oxford secure environment and linked to outcome data.

Figure 2 below depicts study data sources and data flow. Primary care data collected by practices in NWL and held in iCARE are already linked to hospital outcomes (ie, hospital admission, ICU admission, and death). Data held in the University of Oxford secure environment (RCGP RSC, CCAS, and Doctaly data) will be linked to outcome data contained in the Hospital Episode Statistics (HES) and Office of National Statistics (ONS) databases using an encrypted NHS number. Hospital admission and mortality data are available in HES and ONS; however, ICU admission information is not available.

Figure 2. Data flowchart. CCG: Clinical Commissioning Group; NHS: National Health Service; NWL: North West London; ORCHID: Oxford RCGP Clinical Informatics Digital Hub; RCGP: Royal College of General Practitioners; RSC: Research and Surveillance Centre; SE: South East.
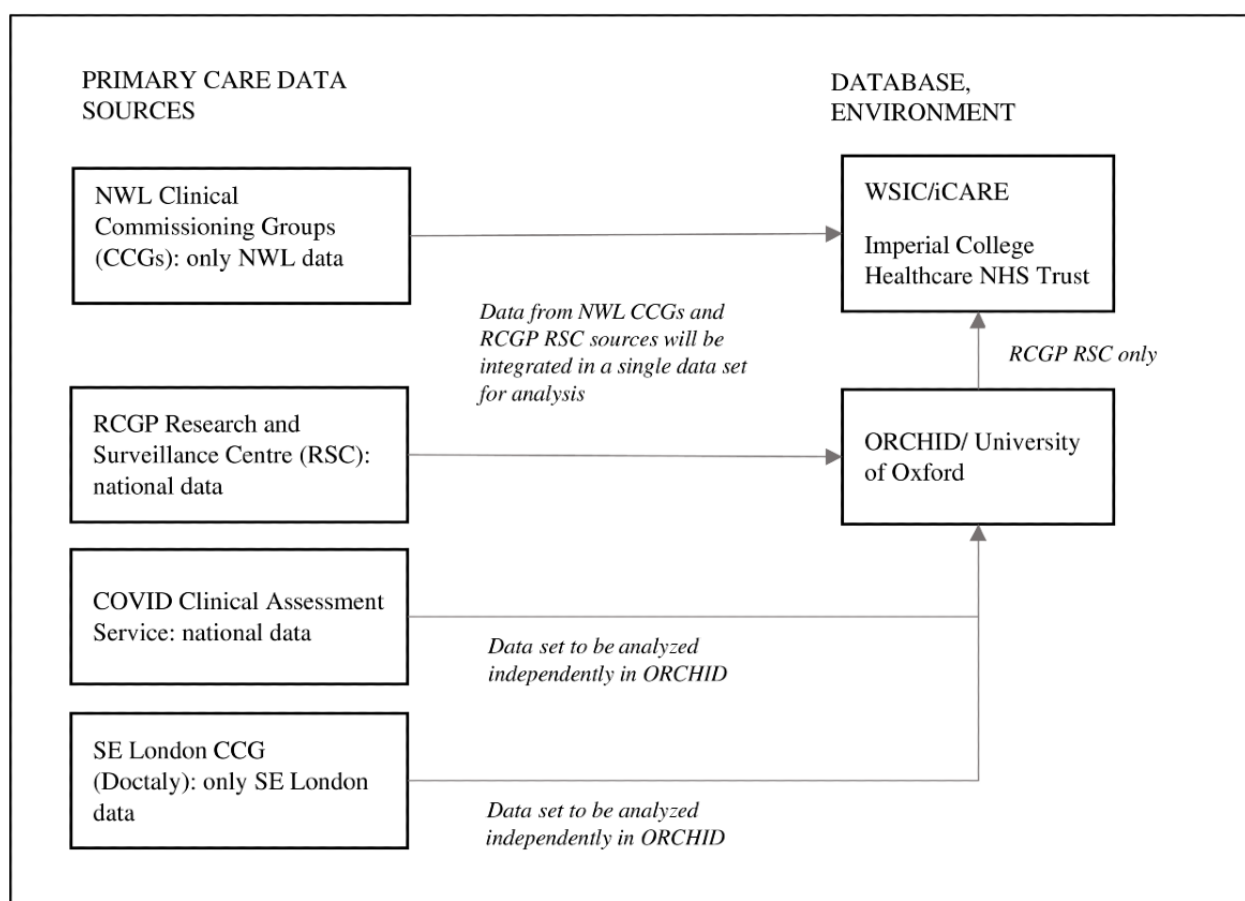
Selection Criteria

Our main cohort includes patients clinically diagnosed with COVID-19 that are being assessed and managed in primary care. Additional cohorts include patients with signs and symptoms suggestive of COVID-19 assessed by the NHS 111 CCAS and patients with established COVID-19 that are assessed as part of a primary care–led home monitoring service (Doctaly).

In the NWL, RCGP RSC, and CCAS arms, participants will be identified by primary care clinicians and enrolled in the study if they satisfy the following inclusion criteria:

1. The patient is willing and able to provide informed consent for data linkage (exceptions are described in detail in the Overview section of the Results)
2. The patient has signs and symptoms that are judged by the clinician to be suggestive of acute COVID-19 and time since onset of symptoms is ≤14 days.
3. The participant is 18 years of age or older.
4. The clinician is able to use the electronic template that contains the RECAP codes.
5. Data collected by the clinician can be linked to the following hospital outcomes: hospital admission, ICU admission (only for NWL CCGs arm data), and hospital outcome (either discharge or cause of death).

For data collected in South East London CCGs (Doctaly) arm, the selection criteria consist of participant age (ie, 18 years old or older) and having a data sharing or consent procedure in place, since the other criteria are already satisfied (ie, patients are offered home monitoring after receiving a positive result from a COVID-19 test and the monitoring tool was specifically designed to include RECAP codes).

Template Development

In order to collect primary data from primary care or community care settings, the RECAP-V0 items that captured patients' signs and symptoms along with other characteristics (sociodemographic information and comorbidities) are transferred into an electronic template using SNOMED and Read codes. These codes have been identified by the study team and collaborators and have been reviewed by NHSX, NHS England, and the UK Faculty of Clinical Informatics. The templates have been deployed for COVID-19 management via electronic health record systems—such as Ardens EMIS and SystmOne, TPP SystmOne, or Adastra—used by clinicians in GP practices, COVID-19 hubs, and CCAS, or via the patient-facing platform Doctaly. This will enable the collection of patients' signs and symptoms in large data sets that will be stored in two secure environments (ORCHID and iCARE secure environments).

Sample Size

A total of 2880 participants will be necessary to develop a model with a minimum 85% specificity, assuming 10% prevalence of hospital admission and 6% missing data. We will split the sample into two consecutive groups, taking the first 50% of participants' data for model development and the last 50% for model validation. CCAS will also collect 2880 participants as we wish to explore the hypothesis that, on account of case mix and spectrum bias, patients already triaged to the national service may require a separate model. We will then separately develop and validate a model for CCAS. Doctaly will provide an additional validation data set for RECAP-V1 score.

Data Analysis

Overview

A detailed statistical analysis plan (SAP) written before inspecting the data will be followed for analysis. The SAP provides a detailed description of data handling, RECAP-V1 model development and validation, and any planned secondary outcomes analysis. Given the complexity of issues to be addressed, including missing data not at random, potential correlations between clinical measurements; regression models and machine learning; and the relationships between the four different data sets, the SAP will be the subject of a separate article.

RECAP-V1 Early Warning Score Development and Validation

We will use multivariate logistic regressions to develop and validate the score. Table 1 contains a list of the items we included in the RECAP-V0 electronic template along with their SNOMED codes that will be used as inputs in the model.

The template has been designed to support the assessment of patients via both face-to-face and remote consultations; however, we anticipate that there are certain observations, such as respiratory rate or oxygen saturation, whose recording in remote consultations may be challenging. Therefore, we included information on patients' symptoms that could be used as a proxy of quantitative items if they were unavailable. The factors for the model (predictor variables) can then be summarized as follows: heart rate, respiratory rate or shortness of breath, trajectory of breathlessness, oxygen saturation or level of tiredness, temperature or feeling feverish, days from onset of symptoms, muscle aches, and cognitive decline. Moreover, we will extract other patient characteristics such as age, gender, body mass index, ethnicity, presence of comorbidities (eg, diabetes, hypertension, coronary heart disease, and chronic kidney disease), and whether the patient is or has been on a COVID-19 shielding list. During the conduct of the study, the QCOVID score [22] has been adopted as a measure of baseline risk and used to populate the COVID-19 shielding list in health record systems [23]. We expect that patient characteristics ought to be able to be represented by the shielding term and will test this hypothesis. Missing data will be handled with standard methodologies for the multiple imputation of missing data [24].

Regarding the outputs of the model, we are interested in hospital admission (defined as an overnight hospital stay within 28 days of onset of symptoms), ICU admission (only available in NWL's WSIC/iCARE database), and death (either at the hospital or at home within 28 days of onset of symptoms).

We will also conduct exploratory analyses, using machine learning algorithms for outcome prediction (nonlinear classifiers) including random forest, gradient boosting, and neural networks, alongside machine learning approaches for imputation of missing data.

Table 1. RECAP-V0 template items.

Variable name	Measurement level	Description/parameter	Concept ID
Heart rate	Continuous	• Heart rate measured at systemic artery (observable entity)	• 78564009
Respiratory Rate	Continuous	• Respiratory rate (observable entity)	• 86290005
Shortness of breath	Nominal	• No breathlessness (situation) • Breathless, moderate exertion (finding) • Breathless, mild exertion (finding) • Unable to complete a sentence in one breath (finding)	• 161938003 • 161939006 • 161940008 • 407588003
Trajectory of breathlessness	Nominal	• Patient condition improved (finding) • Patient condition unchanged (finding) • Patient condition deteriorating (finding) • Symptom very severe (finding)	• 268910001 • 359748005 • 275723000 • 162471005
Oxygen saturation (rest)	Continuous	• Peripheral blood oxygen saturation on room air at rest (observable entity)	• 866661000000106
Oxygen saturation (exertion)	Continuous	• Peripheral blood oxygen saturation on room air on exertion (observable entity)	• 866681000000102
Level of tiredness	Nominal	• Not tired (situation) • Fatigue (finding) • Unable to get on and off a bed (finding)	• 161869003 • 84229001 • 301663005
Temperature	Continuous	• Tympanic temperature (observable entity)	• 703421000
Feeling feverish	Nominal	• No temperature (situation) • Feeling hot (finding) • Rigor symptom (finding)	• 161851007 • 373904004 • 248457000
Date of onset of symptoms	Continuous	• Date of onset of symptoms (observable entity)	• 520191000000103
Muscle aches	Nominal	• Myalgia (finding)	• 68962001
Cognitive decline	Nominal	• Mentally alert (finding) • Clouded consciousness (finding) • Acute confusion (finding) • On examination, decreased level of consciousness (finding)	• 248234008 • 40917007 • 130987000 • 417473004
COVID-19 shielding list as defined using the QCOVID score [23]	Nominal	• High-risk category for developing complication from COVID-19 infection (finding)	• 1300561000000107
Age	Continuous	• Current chronological age (observable entity)	• 424144002
Body mass index	Continuous	• Body mass index (observable entity)	• 60621009
Patient sex	Nominal	• Patient sex (observable entity)	• 184100006
Diabetes	Nominal	• Diabetes (disorder)	• 73211009
Hypertension	Nominal	• Hypertension (disorder)	• 38341003
Coronary heart disease	Nominal	• Coronary heart disease (disorder)	• 53741008
Chronic kidney disease	Nominal	• Chronic kidney disease (disorder)	• 709044004
Ethnicity/related nationality data	Nominal	• Ethnicity/related nationality data (observable entity)	• 186034007
Participant's consent	Nominal	• Consent given to participate in research study (finding)	• 873771000000107

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Results

Overview

Recruitment started in October 2020. Initially, only the NWL CCGs and RCGP RSC arms were actively recruiting. In order to engage clinicians with the study and facilitate participation, we have run three webinars or training workshops where the study team described the study objectives and deadlines, and provided a detailed description of the RECAP template and how it would be used at the clinical front line. These webinars took place in October 2020 and January 2021. The study team has been in close contact with participating practices through the Imperial College London arm office, which has overall responsibility for the project and is directly in charge of data collection in North West London, and the University of Oxford arm office, which has direct responsibility for data collection from RCGP RSC practices. The CCAS and Doctaly platform arms joined the study in February 2021.

The initial data set to be used for model development will consist of RCGP RSC and NWL arms data and will be complete by the end of March 2021; this includes the primary care data on recruited patients' signs and symptoms collected by these two arms linked to outcomes 28 days later. Two stages of data extraction and analysis of this integrated data set have been identified: first, RECAP-V1 development using the first half of the data set will start in April 2021, and second, model validation using the second half of the data set will follow. As of March 24, 2021, we have recruited a combined sample of 3827 participants (173 active primary care practices enrolled) in these two arms. The CCAS arm started the recruitment process on March 15, 2021, and we expect to reach the desired sample size in this arm (2880 participants) by the end of May 2021. Data sharing agreements are being developed to access data that have already been collected from around 1400 participants by clinicians using the Doctaly platform. The CCAS and Doctaly platform data sets will be used to validate the RECAP-V1 model and will be analyzed independently. Once we have produced the model, and subject to findings, the RECAP-V1 score will be ready to be deployed and used by clinicians to guide the management of patients with suspected COVID-19 according to their predicted risk.

The study is sponsored by Imperial College London and ethical approval was granted by the North West-Greater Manchester East Research Ethics Committee and Health Research Authority on May 27, 2020 (Integrated Research Application System number: 283024, Research Ethics Committee reference number: 20/NW/0266). An amendment to include the CCAS and Doctaly arms was approved on February 1, 2021. Due to the low risk associated with participation in this study and the remote nature (telephone/video consultation) of most patient encounters, the review committee agreed that obtaining verbal consent for data linkage was acceptable.

To access and link retrospective data collected by the NHS 111 CCAS and Doctaly platforms in South East London (ie, data that have already been collected by the services prior to study participation) we requested the last ethics amendment submitted to be assessed under the Control of Patient Information (COPI) notice, data sharing provisions that allow public authorities and research bodies the use of COVID-19–relevant patient-level data without the need for patients' explicit consent [25]. For NHS 111 CCAS prospective data—that is, data from patients seeking medical care after the RECAP template has been installed in Adastra—we will apply the same mechanism to seek consent that has been followed in the NWL and RCGP RSC arms, and patients in the clinical queue will receive an SMS text message with information on the study and how to participate.

Data and all appropriate documentation will be stored in accordance with General Data Protection Regulation (Data Protection Act 2018) for a minimum of 10 years after the completion of the study, including the follow-up period. Participants can withdraw from the study at any point by informing their GP or a member of the study team. They will be asked whether the data obtained before withdrawal can be retained for analysis or they would like their data to be destroyed instead.

The study was included in the National Institute of Health Research (NIHR) Clinical Research Network Portfolio (CPMS number: 45890) on September 25, 2020, and badged as NIHR Urgent Public Health Study on October 14, 2020. These measures facilitate the rapid mobilization of resources from NIHR and clinical research networks toward study dissemination and participant recruitment and help ensure that high-quality data can be collected on a timely basis (trial registration number: ISRCTN13953727).

Dissemination Plan and Patient and Public Involvement

The RECAP-V0 template has already been disseminated nationally through CRNs facilitating the standardization of clinical records of patients with COVID-19. Its use has been encouraged through webinars and invited talks arranged by CRNs. Once the risk prediction tool has been developed and validated, we will seek endorsement for it to be incorporated into the electronic template to support clinical decision making when assessing patients with COVID-19. We expect to reach wide national and international dissemination of the RECAP-V1 risk prediction tool through submission to academic journals and international conferences.

Patient and public participation has been incorporated at different stages of the project. Patients were involved, along with primary care clinicians, in the qualitative study carried out to identify the set of elements to be included in the RECAP-V0 [15]. Once the RECAP-V1 tool has been developed and validated, public participation will be sought to coproduce project lay summaries, which will be valuable to disseminate the study findings to a wider audience.

Discussion

The RECAP-V1 early warning score will, we anticipate, facilitate the stratification of the severity of patients with COVID-19 and their appropriate management and escalation of treatment. This study also promotes the standardization of assessment of patients with COVID-19, of collection of medical

records, and record keeping thanks to the electronic templates developed, which can all have a positive impact in patients' care, continuity, and safety [26]. Moreover, since November 2020, NHS England and NHS Improvement have led the establishment of the COVID Oximetry @home pathway, offered to patients with symptomatic COVID-19 who are aged 65 years or older or who are clinically extremely vulnerable to COVID-19 [27]. This service is being delivered by general practice, with referrals from NHS 111, CCAS, and hospital emergency departments, and involves an initial face-to-face or remote clinical assessment followed by monitoring of home oximetry readings for 14 days, to aid early recognition of deterioration.

Items in the RECAP-V1 risk prediction tool in development are consistent with suggested clinical markers for triage on this pathway, and we anticipate that the tool will provide a unified quantitative risk score that will fit the monitoring needs of the service. Finally, we would like to emphasize the value of the study as an example of a digital clinical study, whose practice has been upheld by national research institutions on the basis of its cost-effectiveness and patient-centeredness due to the potential to recruit participants and collect large amounts of data with minimum inconvenience for the patient [28]. This is an example of leveraging the power of the NHS as a learning health system [29].

Acknowledgments

Conflicts of Interest

SdL is the Director of the RCGP RSC. All other authors declare no conflicts.

Multimedia Appendix 1
Peer review document.
[PDF File (Adobe PDF File), 125 KB - resprot_v10i5e29072_app1.pdf]

Multimedia Appendix 2
Peer review comments.
[PDF File (Adobe PDF File), 217 KB - resprot_v10i5e29072_app2.pdf]

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Abbreviations

CCG: Clinical Commissioning Group
COPI: Control of Patient Information
CRN: clinical research network
GP: general practitioner
HES: Hospital Episode Statistics
iCARE: Imperial's Clinical Analytics, Research and Evaluation database
ICU: intensive care unit

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NEWS2: National Early Warning Score
NHS: National Health Service
NIHR: National Institute of Health Research
ONS: Office of National Statistics
ORCHID: Oxford RCGP Clinical Informatics Digital Hub
RCGP: Royal College of General Practitioners
RECAP: Remote COVID-19 Assessment in Primary Care
RSC: Research and Surveillance Centre
SAP: statistical analysis plan
WSIC: Whole Systems Integrated Care

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Protocol

Implementation of Wearable Sensors and Digital Alerting Systems in Secondary Care: Protocol for a Real-World Prospective Study Evaluating Clinical Outcomes

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Abstract

Background: Advancements in wearable sensors have caused a resurgence in their use, particularly because their miniaturization offers ambulatory advantages while performing continuous vital sign monitoring. Digital alerts can be generated following early recognition of clinical deterioration through breaches of set parameter thresholds, permitting earlier intervention. However, a systematic real-world evaluation of these alerting systems has yet to be conducted, and their efficacy remains unknown.

Objective: The aim of this study is to implement wearable sensors and digital alerting systems in acute general wards to evaluate the resultant clinical outcomes.

Methods: Participants on acute general wards will be screened and recruited into a trial with a pre-post implementation design. In the preimplementation phase, the SensiumVitals monitoring system, which continuously measures temperature, heart, and respiratory rates, will be used for monitoring alongside usual care. In the postimplementation phase, alerts will be generated from the SensiumVitals system when pre-established thresholds for vital parameters have been crossed, requiring acknowledgement from health care staff; subsequent clinical outcomes will be analyzed.

Results: Enrolment is currently underway, having started in September 2017, and is anticipated to end shortly. Data analysis is expected to be completed in 2021.

Conclusions: This study will offer insight into the implementation of digital health technologies within a health care trust and aims to describe the effectiveness of wearable sensors for ambulatory continuous monitoring and digital alerts on clinical outcomes in acute general ward settings.

Trial Registration: ClinicalTrials.gov NCT04638738; https://clinicaltrials.gov/ct2/show/NCT04638738.

International Registered Report Identifier (IRRID): DERR1-10.2196/26240

Introduction

Vital signs and their trends are crucial in recognizing clinical deterioration, with changes often occurring several hours prior to an adverse event [1-7]. Consequently, monitoring of these physiological parameters forms a fundamental component of providing effective clinical care. Despite this, patient deterioration can go undetected, resulting in adverse clinical outcomes such as late referrals to intensive care units, increased morbidity, and mortality [8-13].

Routinely measured vital signs include heart rate, respiratory rate, temperature, blood pressure, oxygen saturation (and supplemental oxygen), and level of consciousness. Individuals admitted to nonintensive (general) hospital wards undergo intermittent monitoring of these vital signs. A "track and trigger" early warning score (EWS) is recommended in the United Kingdom; the National Early Warning Score 2 (NEWS2) provides guidance on escalation protocols and the monitoring frequency of vital signs. Each vital parameter is individually scored according to severity and combined for a total NEWS score. Most frequently, observations are performed every 4-6 hours unless the patient is acutely unwell [14].

EWSs are predicated around the idea that hospital inpatients at high risk of deterioration are identified early through prodromal vital parameter alterations (eg, elevated respiratory rate), enabling early intervention [15]. Since their implementation, EWSs have shown good predictive value for deterioration and have improved clinical outcomes [16]. However, their intermittent nature is a critical limitation that enables acute deterioration between measurements to be easily missed [16].

Wearable sensors and digital alerting mechanisms offer a potential solution to this issue. Continuous monitoring through novel wearable sensors provides near real-time monitoring of vital signs without hindering ambulation. It is theorized that continuous monitoring will enable earlier detection of deterioration through a culmination of additional data points and reduced reliance on availability of medical personnel for performing observations [17]. Alerts are subsequently generated, informing health care professionals when pre-established thresholds for vital parameters, often tailorable, are breached. However, the evidence supporting the use of wearable sensors outside of intensive care settings remains mixed and limited [18,19]. The heterogeneity of study designs and complexity of interventions used, however, limit meaningful conclusions.

Here, we describe the design of our trial, in which we implement wearable sensors and digital alerting systems in acute general wards in a National Health Service hospital; we also describe the implementation strategy and the evaluation of the resultant clinical outcomes (eg, length of stay, mortality, need for intensive care).

Methods

Study Design

This is a single-center, pre-post design in which digital alerting systems are implemented on acute wards. The preimplementation phase dated from September 2017 to August 2019, and the postimplementation phase is currently underway.

The preimplementation phase involved using the SensiumVitals system in accordance with usual care. However, health care staff were not able to view the continuous vital sign monitoring data or the digital alerts generated for abnormal parameters. Usual care, in our institution, involves intermittent monitoring of vital signs in accordance with NEWS2.

In the postimplementation phase, alerting systems following recognition of abnormal parameters will be included. These alerts will be transmitted to mobile devices and central monitoring hubs, with alert acknowledgement required from health care staff.

All participants provided informed consent. Ethical approval for this study has been granted by a Research Ethics Committee (Integrated Research Application System: 222979). The trial will be performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Patient data will be anonymized to ensure privacy. Storage and handling of personal data will comply with the General Data Protection Regulation.

Intervention Protocol for Alerts

All alerts will be viewed by dedicated trained nursing staff covering the wards. Alerts will be generated when measured vital signs exceed pre-established thresholds for 10 consecutive minutes. These thresholds can be individually tailored but are initially programmed to trigger if the patient's temperature exceeds 38.1 ℃, respiratory rate is over 25 breaths per minute, and heart rate is over 131 beats per minute, in accordance with NEWS2 cutoffs [14]. All incoming alerts are deemed to be of potential clinical relevance, and potential outcomes include but are not limited to reviewing the individual, repeating observations, increased frequency of monitoring, and escalation to a responsible physician.

Stakeholder Engagement

Several stakeholders will continue to be engaged during the establishment of the project; permission from the Estates and Information Technology departments has been obtained. This permission ensured that bridges were installed by the hospital Estates department, enabling adherence with local policies. Monitoring software has been integrated with the hospital admissions data system, enabling consenting participants to be easily added to the system. Data will be stored and retained on hospital networks, alleviating data security concerns. Senior clinicians have been informed of the project through engagement meetings to drive recruitment and elucidate the aims of the study. Nursing staff have been trained directly to use the system; ad hoc refreshers will be available throughout the duration of the study.

Eligibility Criteria

Adults (aged over 18 years) admitted to general wards who are able to understand the participant information sheet are eligible for inclusion. Individuals with cardiac implantable electronic devices, who experience a skin reaction to the wearable sensor or its components, who have an open chest wound, or who withdraw consent will be excluded.

Recruitment will be aided by the responsible clinical team, who will deem individuals suitable to participate.

Data Collection

After enrolment, data will be routinely collected by two research nurses and a clinical fellow. Outcomes will be obtained from case note review, SensiumVitals data, and electronic health records, enabling prospective data collection.

Outcome Measures

Outcome measures will include hospital length of stay; critical NEWS (defined as 7 or over); number of admissions to intensive care; mortality; sepsis events; and time to antibiotics.

To understand the acceptability and usability of the SensiumVitals system by participants and health care staff, mixed methods analysis (semistructured interviews and questionnaires) will be undertaken in the postimplementation phase. For participants, these interviews and questionnaires will be administered 24 hours after the SensiumVitals sensor has been applied, enabling familiarity with the sensor and maximizing of data capture before potential hospital discharge. Due to the nature of the shift patterns, a set time point has not been chosen for health care staff; however, the studies will only be conducted once familiarity with the system has been established. All key stakeholders will also be invited to take part in semistructured interviews to determine barriers and facilitators to implementing wearable sensors and alerting mechanisms within the hospital.

The questionnaires consist of 5-point Likert scale responses (strongly disagree to strongly agree), with elements adapted from the validated System Usability Scale [20].

Face-to-face interviews will be conducted by the lead researcher (FI) using a predetermined topic guide. Data collection will be an iterative process; emerging recurring concepts were incorporated into the interview guide for further exploration with remaining participants. Interviews will be recorded, anonymized, transcribed, and entered into NVivo 12 (QSR International) for analysis.

Statistical Analysis

The Shapiro-Wilk test will be used to check variables for Gaussian distribution. Data sets will be presented as absolute numbers of patients with the respective percentage per group or as parameter mean and standard deviation or median and range, depending on distribution. Descriptive statistics will describe the baseline characteristics of the participants, alerting frequencies, and events.

For comparisons of interval-scaled variables between the two groups, 2-tailed, unpaired t tests will be performed. Nonparametric between-group testing will be undertaken with 2-tailed Mann-Whitney U tests. Additionally, the chi-square test or Fisher exact test will be applied to nominal scale data.

Propensity score matching will be performed for differences among baseline demographics between pre-post phases, reducing bias from confounding variables. Analyses will be performed in SPSS (IBM Corporation), Stata (StataCorp LLC), and GraphPad (GraphPad Software Inc).

Mixed methods analysis will be undertaken for the questionnaire and semistructured interview data. Frequency distributions will be generated for Likert scale responses. Interview transcripts will be analyzed using thematic analysis [21]. The results will be discussed until consensus is reached.

Power Calculations

Formal power calculations are not possible on any of the outcomes, given the lack of surrounding data. However, Downey et al [22] estimated sample sizes of 325-625 for time to antibiotics after the first evidence of sepsis using the SensiumVitals sensor. A total of 226 participants were randomized; 140 had the sensor applied, and the remaining participants underwent usual care. All outcome measurements in this study demonstrated nonsignificant results. Therefore, we aim to recruit a minimum of 600 individuals, with approximately half in the preimplementation phase and the remaining participants in the postimplementation phase.

Data Monitoring

Overall, there is a low level of concern for patient safety with the SensiumVitals sensor, given previous use [22]. Furthermore, participants are at very low risk for adverse events; should any occur, they will be logged systematically and reported to ClinicalTrials.gov. Adverse events not related to the sensor will be reported to the responsible clinical team.

Results

Enrolment is currently underway, having started in September 2017; it is anticipated to end shortly. Data analysis is expected to be completed in 2021.

Discussion

This trial has the potential to detect earlier early clinical deterioration using the SensiumVitals sensor, which may improve clinical outcomes. This disposable, lightweight, waterproof, wearable wireless patch is attached to a participant's chest with two adhesive electrocardiogram electrodes and records the participant's temperature, heart rate, and respiratory rate every 2 minutes, transmitting data to a central monitoring hub through radiofrequency and dedicated intranet hotspots (bridges) installed on wards, viewable through a secured web browser or mobile device. This continuous monitoring enables alerting systems to inform health care staff of individuals whose condition is deteriorating, allowing for earlier intervention.

Acceptability and practicability of continuous monitoring using wearable sensors on general surgical and medical wards has been demonstrated in the United Kingdom and the Netherlands [22,23]. However, these studies focused primarily on feasibility rather than on implementation strategy and clinical outcome measures, such as hospital length of stay, mortality, and intensive care transfers, which remain untested. Furthermore, our use of semistructured interviews to capture stakeholder perceptions will yield pertinent considerations for pragmatic implementation of novel digital technologies.

As a trial designed to test real-world applicability, its design presents inherent limitations. The observational nature of this trial cannot establish cause-effect relationships. However, a prospective evaluation lends itself to describing practical issues that need to be overcome for successful implementation with evolving workflows in health care trusts. Moreover, pre-post

designs can be influenced by longitudinal changes in health care delivery, which are a potential source of bias.

In conclusion, the results of our study could offer data to demonstrate the effectiveness of using continuous vital sign monitoring through wearable sensors and digital alerts to improve clinical outcomes in acute general ward settings. We may offer a methodology for successful implementation that can be adopted more widely in various health care trusts.

Authors' Contributions

FMI drafted the manuscript. Significant amendments were made by MJ, SK, HA, and AD. All authors approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

EWS: early warning score
NEWS2: National Early Warning Score 2

<u>Protocol</u>

Expressed Symptoms and Attitudes Toward Using Twitter for Health Care Engagement Among Patients With Lupus on Social Media: Protocol for a Mixed Methods Study

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Abstract

Background: Lupus is a complex autoimmune disease that is difficult to diagnose and treat. It is estimated that at least 5 million Americans have lupus, with more than 16,000 new cases of lupus being reported annually in the United States. Social media provides a platform for patients to find rheumatologists and peers and build awareness of the condition. Researchers have suggested that the social network Twitter may serve as a rich avenue for exploring how patients communicate about their health issues. However, there is a lack of research about the characteristics of lupus patients on Twitter and their attitudes toward using Twitter for engaging them with their health care.

Objective: This study has two objectives: (1) to conduct a content analysis of Twitter data published by users (in English) in the United States between September 1, 2017 and October 31, 2018 to identify patients who publicly discuss their lupus condition and to assess their expressed health themes and (2) to conduct a cross-sectional survey among these lupus patients on Twitter to study their attitudes toward using Twitter for engaging them with their health care.

Methods: This is a mixed methods study that analyzes retrospective Twitter data and conducts a cross-sectional survey among lupus patients on Twitter. We used Symplur Signals, a health care social media analytics platform, to access the Twitter data and analyze user-generated posts that include keywords related to lupus. We will use descriptive statistics to analyze the data and identify the most prevalent topics in the Twitter content among lupus patients. We will further conduct self-report surveys via Twitter by inviting all identified lupus patients who discuss their lupus condition on Twitter. The goal of the survey is to collect data about the characteristics of lupus patients (eg, gender, race/ethnicity, educational level) and their attitudes toward using Twitter for engaging them with their health care.

Results: This study has been funded by the National Center for Advancing Translational Science through a Clinical and Translational Science Award. The institutional review board at the University of Southern California (HS-19-00048) approved the study. Data extraction and cleaning are complete. We obtained 47,715 Twitter posts containing terms related to "lupus" from users in the United States published in English between September 1, 2017 and October 31, 2018. We included 40,885 posts in the analysis. Data analysis was completed in Fall 2020.

Conclusions: The data obtained in this pilot study will shed light on whether Twitter provides a promising data source for garnering health-related attitudes among lupus patients. The data will also help to determine whether Twitter might serve as a potential outreach platform for raising awareness of lupus among patients and implementing related health education interventions.

International Registered Report Identifier (IRRID):   DERR1-10.2196/15716

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Introduction

Background and Rationale

Lupus is a chronic disease characterized by an autoimmune response that can range in its frequency and affect any part of the body (skin, joints, and organs). It is estimated that at least 5 million Americans have lupus, with more than 16,000 new cases of lupus being reported annually in the United States [1]. The condition strikes mostly women of childbearing age, while women of color are 2-3 times more likely to develop lupus than Caucasian women. However, the disease can present in men and children as well.

Lupus is a difficult disease to diagnose as its symptoms can often mimic those of other diseases [2]. Systemic lupus erythematosus (SLE), the most common form of lupus, has been reported to remain undiagnosed in some populations for an average of 6 years [2]. SLE tends to present more abruptly and cause more damage in patients of color. This often comes in the form of a spike in disease activity called a "flare" and without treatment, can lead to organ damage and failure. Therefore, early diagnosis is essential for patients with lupus [3].

As most people with lupus develop the disease between the ages of 15 years and 44 years, we hypothesize that social media provides a potentially promising tool for raising awareness and supporting early diagnosis and management of lupus. This study aims to shed light on the use of Twitter among patients who publicly discuss their lupus condition on the platform and to assess their attitudes toward using Twitter to engage them with their health care.

Social Media

The term "social media" describes widely accessible web-based and mobile technologies that allow users to view, create, and share information online and to participate in social networking [4-6]. Social media provides both a unique data source for data mining of health concerns and related attitudes [7,8] and an unprecedented opportunity for delivering information to reach large segments of the population [9] as well as hard-to-reach subpopulations [10,11]. Today, more than 70% of American adults use at least some type of social media [12].

The Social Network Twitter

The social network Twitter is used by 23% of American adults, and users are diverse, including Hispanics (25%), Blacks (24%), and Whites (21%) [12]. Twitter users can post short messages (tweets) that are limited to 280 characters. They can search for any public message and engage with tweets (ie, they can "like," reply, and "retweet" [share] them). By default, Twitter account information such as the profile name, description, and location is public unless a user decides to opt out and make an account private [13,14]. Previous research has suggested that Twitter provides a "rich and promising avenue for exploring how patients conceptualize and communicate about their health issues" [15]. The increasing use of Twitter among members of disease communities is further evidenced by the abundance of disease and health topic hashtags used in the messages [16-21]. A hashtag is a word or phrase preceded by a hash or pound sign (#) and used to identify messages on a specific topic (eg, #lupus, #spoonies). However, there is little information about the use of social media among lupus patients as well as their attitudes toward using Twitter for engaging them with their health care [22].

Previous Research on Social Media and Lupus

The emergence of social media has created new sources of analyzable data [8] and led to new research fields (ie, infodemiology and infoveillance) [7,23]. The data social media users generate through their online activities are referred to as their digital footprint [24] or social mediome [25]. On Twitter, for example, health surveillance researchers have used this data to gain insight into public perspectives on a variety of diseases and health topics such as influenza, autism, schizophrenia, smoking, and HIV/AIDS [26-31]. In some cases, social media user data demonstrated a correlation between disease prevalence and frequency with which Twitter users discussed a disease [32]. The investigators are not aware of lupus-related surveillance research that involved the social network Twitter.

However, previous research examined user-generated content about lupus on Facebook [33]. The authors looked at the representation of health conditions and found that lupus-related pages ranked the highest for patient support [33]. Additionally, a patient commentary highlighted the use of social media, in particular Twitter, among lupus patients to find rheumatologists, specialist care, and peers and to build awareness of their health needs and experiences [34]. To our knowledge, there are no studies that have leveraged Twitter to improve the understanding of attitudes among patients with lupus.

Study Objective and Research Questions

This study has two objectives: (1) to conduct a content analysis of Twitter data published by users (in English) in the United States between September 1, 2017 and October 31, 2018 to identify patients who publicly discuss their lupus condition and to assess their expressed health themes and (2) to conduct a cross-sectional survey among the lupus patients on Twitter to study their attitudes toward using Twitter for engaging them with their health care.

Our findings will shed light on whether Twitter provides a promising data source for garnering insights and attitudes about lupus expressed among patients. The findings will help to determine whether Twitter might serve as a potential outreach platform for raising awareness of lupus among patients and implementing related health education interventions.

Methods

This is a mixed methods study that analyzes retrospective Twitter data and conducts a cross-sectional survey among lupus patients on Twitter.

Data Collection

This study will analyze user-generated posts in English that include keywords related to "lupus" (Multimedia Appendix 1) from the social network Twitter and were published between September 1, 2017 and October 31, 2018. To access public Twitter user data, we used Symplur Signals [35], a health care social media analytics platform. We limited the dataset to posts from users with locations in the United States.

Search Filters

Twitter posts containing terms related to "lupus" (Multimedia Appendix 1) were obtained for the range between September 1, 2017 and October 31, 2018. We applied the approach suggested by Kim et al [36] to develop the search filters. These terms can appear in the post or in an accompanying hashtag, for example, Lupus or #LupusChat. We selected keywords and hashtags based on expert knowledge (clinicians, social media experts) and used a systematic search of topic-related language based on data in Symplur Signals.

Data Cleaning and Debiasing

The following types of irrelevant tweets were excluded: (1) non-English language tweets identified using the Liu method [37], (2) retweets (ie, messages shared by Twitter users that other users composed), and (3) messages that originated from outside the United States. Locating users in the United States was accomplished using a mapped location filter provided by Twitter GNIP through the "Profile Geo Enrichment" algorithm (formerly known as GNIP's Profile Geo 2.0, which was acquired by Twitter) [38]. This Twitter data service is among the most commonly used data sources in academic Twitter surveillance research [39]. To determine a user's location, the algorithm uses a number of data points including the self-reported "Bio Location" in the Twitter user profile and geotracking data if available. The Profile Geo service adds "structured geodata relevant to the user location value by geocoding and normalizing location strings where possible" [38]. Research using a similar multi-indicator method to infer the location of the user showed the capability of locating 92% of all tweets [40]. However, the Profile Geo service attempts to determine the best choice for the geographic place described in the profile location string. We acknowledge that the results may not be accurate in all cases due to factors such as multiple places with similar names or ambiguous names. If a value is not provided in a user's profile location field, the Profile Geo service does not provide a classification.

As we attempt to understand attitudes, we relied on machine learning to identify Twitter posts by social bots or marketing-oriented accounts that could possibly influence the results and introduce bias [41,42]. We used the program BotOrNot [43] to identify those Twitter accounts. Messages from these accounts were removed from the dataset to focus on analyzing patient perspective data. The program BotOrNot scores a detection accuracy above 95% [43].

Data Collection and Confidentiality

Database

Study data were collected using the system REDCap (Research Electronic Data Capture) at the University of Southern California (USC). REDCap is a secure, web-based application designed to support data capture for research studies [44]. All analyses will adhere to the terms and conditions, terms of use, and privacy policies of Twitter.

Twitter Data

Any identifying and personal health information was redacted from the dataset by the coders. Since the "Tweet ID," "Tweet URL," "Profile thumbnail URL," "Username," and "Display Name" in the dataset can potentially identify the person directly, we removed these from the initial data collection sheet and used a unique code identifier instead. We maintained the link between the unique code and the identifiable elements in a separate file. We retained the data only for use in this project and destroyed the identifiable (Tweet ID, Tweet URL, Profile thumbnail URL, Username, and Display Name) information prior to the data analysis as requested by the local IRB.

Survey Data

The data will be retained in a secure database called REDCap at USC. The anonymous data will be kept for future research. Individuals are informed that they should not participate in the study if they do not want their data kept.

Survey Study

Study Population

The proposed survey study involves contacting lupus patients in the United States who discuss their health in English on Twitter. Eligible survey respondents will be patients with lupus 18 years of age and older. To focus on feasibility, we will limit this pilot to lupus patients who discuss their health on Twitter. Other individuals who talk about how the condition affects a family member or friend (eg, parents, siblings) will be excluded from this study.

Survey Development

The goal of the survey is to collect data about the characteristics of lupus patients (eg, gender, race/ethnicity, educational level) and their attitudes toward using Twitter for health care engagement among lupus patients (eg, How concerned are you about researchers using Twitter user information to identify patients with lupus? How interested are you in getting information related to lupus via Twitter? How interested are you in receiving personalized information about ongoing research and clinical research opportunities on Twitter?). The full survey is included in Multimedia Appendix 2.

Recruiting Patients With Lupus via Twitter

We will conduct self-report surveys via Twitter by inviting all identified lupus patients who discuss their health on Twitter. We will recruit via the project Twitter account using a personalized message package approach (Multimedia Appendix

3) and replying to a user's most recent Twitter message where they mention their lupus condition. Sending multiple messages will allow us to introduce the research project and research team ensuring investigator transparency, ask recipients to follow the project Twitter account, and remind them of the privacy risks of using Twitter. Via the URL link in the message, interested users will be directed to a webpage (Multimedia Appendix 4) that includes more information about the study [45]. The page will be hosted by the USC Clinical Studies Directory, a public tool that allows anyone to search for clinical research studies at USC. Only those recipients who decide to follow the project account will be able to receive the link to the survey via a private, direct message. The survey will be available in English and can be completed on any computer, tablet, or smartphone. In the case of no response, reminders will be sent up to 4 weeks after the initial contact.

Consent Procedures

Eligible lupus patients who are 18 years and older will proceed to the information sheet form and access the survey once they give consent via a check box in the survey form.

Compensation

Survey participants will be able to enter a raffle to win one of three US $100 gift cards after they complete the survey.

Data Analysis

Coding

We will use a standard coding approach for characterizing the Twitter messages and users. Two independent team members will use a range of text classifiers (Multimedia Appendix 5) to identify a priori and emergent code categories in the Twitter posts. We will further characterize the user of the Twitter accounts who generated the posts (Multimedia Appendix 6) based on information available in a user's Twitter profile (ie, username, description, profile image). Cohen Kappa will be calculated for each code category to assess interrater reliability [46,47]. Average Cohen Kappa greater than 0.8 for all categories will be considered substantial for this research. The project principal investigators will help to build consensus for instances where coders disagree.

Statistical Analysis

The analyses will rely on public, anonymized data, adhered to the terms and conditions, terms of use, and privacy policies of Twitter. This study was performed under IRB approval from the authors' university. No Twitter posts will be reported verbatim in the report of the findings to protect the privacy of the users. Representative examples of tweets within each category will be selected to illustrate additional themes and will be shown as paraphrased quotes.

We will use descriptive statistics to analyze the data and identify the most prevalent topics in the Twitter content. Units of analysis will be unique terms in posts as well as the number of Twitter messages and users. For each analysis, we will present findings in a confusion matrix where the diagonal line indicates the prevalence of a topic and the off-diagonal lines indicate topic overlap. The number of posts containing 2 or more topics is found at the intersection of the matrix for these topics. We will

further describe the patient characteristics such as age, gender, race/ethnicity, and other characteristics and survey responses. We will use multiple regression to assess which variables (eg, demographics) are significantly associated with acceptance of using Twitter for health care engagement. Analyses will be performed in SPSS (v.24), using P=.05 for statistical tests.

Sample Size Calculation

The sample size estimate (and survey protocol) is based on previous similar research that demonstrated the usefulness of user data to identify and engage cancer patients on Twitter [48].

Twitter data from users in Los Angeles County posted over the course of 12 months were used to identify 134 cancer patients who had discussed their cancer condition on Twitter. Nearly one-quarter (33/134, 24.63%) of them responded positively to the outreach on Twitter that was focused on clinical trial recruitment. As the prevalence of SLE is lower in the United States, with 20-150 reported cases per 100,000 [49], compared to the cancer incidence, which is 439 per 100,000 men and women per year (based on 2011-2015 cases) [50], we anticipate a lower number of people who discuss their lupus condition on Twitter. In this pilot study, we anticipate identifying around 100-300 Twitter accounts of lupus patients across the United States. We expect that at least 25% of these lupus patients, who we will contact to participate in the survey study, will complete the survey.

Risk Analysis

This study presents minimal-risk research. We will use public data from the social network Twitter. We will de-identify any subject's names or Twitter handles, and they will not appear in the analysis dataset. We have implemented a number of measures to ensure data security and confidentiality (see Data Collection and Confidentiality section). We will further abide by USC IRB regulations and the USC Privacy of Personal Information policy. In general, all data will be entered into a computer and database that are password protected. The data will be stored using appropriate, secure computer software and encrypted computers.

Dissemination of Study Findings

The study authors plan to publish the study findings in a peer-reviewed journal and at topic-related conferences (to be determined at a later date). All listed authors or contributors are compliant with guidelines outlined by the International Committee of Medical Journal Editors for author inclusion in a published work. Furthermore, to support research transparency and reproducibility, we will share the de-identified research data after publication of the study results. We will share the de-identified data on Figshare, a repository where users can make all of their research outputs available in a citable, shareable, and discoverable manner.

Results

This study was approved by the IRB at USC (Protocol HS-19-00048; Multimedia Appendix 7). Data extraction and cleaning are complete. The detailed data extraction and cleaning flow chart is included in Multimedia Appendix 8. We obtained

47,715 Twitter posts containing terms related to "lupus" from users in the United States published in English between September 1, 2017 and October 31, 2018. After removing duplicates, retweets, non-English tweets, and Twitter posts from commercial and bot-like accounts, 40,885 posts were included in the analysis. Data analysis was completed in Fall 2020.

Discussion

Limitations

The generalizability of the study is somewhat limited, and we recognize that the use of social media data could also lead to potential bias. Social media research and social media–based intervention favor those with internet access. Twitter users tend to be younger (38% are 18-29 years of age), college graduates (32%), and located in urban areas (26%) [12]. Nonetheless, it is worth mentioning that social media users have grown more representative of the broader population; for example, they include the Black population (24%) as well as Whites (21%) and Hispanics (25%) [12]. Additionally, Twitter messages from locations outside the United States and messages in other, non-English languages such as Spanish will not be included. It is also possible that fewer lupus patients discuss their health on Twitter than we anticipate. We addressed this issue by searching Twitter data from users across the United States. However, even if we identify lupus patients on Twitter, it is possible that a lower number of them will engage and take the survey. To incentivize survey completion, participants who complete the survey will be able to enter a raffle to win one of 10 US $100 gift cards.

Finally, we will take several steps to reduce the chance of fraudulent survey responses on Twitter, including sharing the survey link only via private messages on Twitter once a user has followed the project account on Twitter. In the case that the majority of users seems reluctant to follow the Twitter account, we will send reminder messages with the personalized link to the survey via a public reply message on Twitter to increase the survey response rate.

Practical Significance

This pilot project will provide preliminary data and practical insight into the application of publicly available Twitter data to gain a better understanding of lupus patients who publicly discuss their condition on Twitter and their attitudes toward using the platform to engage them with their health care. The data will also help to determine whether Twitter might serve as a potential outreach platform for raising awareness of lupus and implementing related health interventions.

Conflicts of Interest

The authors have no conflicts of interest to report and will not be rewarded in any way, either financially or other by Symplur.com. Members of the Symplur.com team are neither included in the data analysis nor in the interpretation of the study findings.

Multimedia Appendix 1
Lupus-related keywords and hashtags used for the Twitter search. The selection is based on data from Symplur Signals.
[PDF File (Adobe PDF File), 80 KB - resprot_v10i5e15716_app1.pdf]

Multimedia Appendix 2
Survey.
[PDF File (Adobe PDF File), 86 KB - resprot_v10i5e15716_app2.pdf]

Multimedia Appendix 3
Twitter recruitment messages.
[PDF File (Adobe PDF File), 48 KB - resprot_v10i5e15716_app3.pdf]

Multimedia Appendix 4
Study information page.
[PNG File , 726 KB - resprot_v10i5e15716_app4.png]

Multimedia Appendix 5
Coding table used for identifying main themes in lupus-related Twitter posts.
[PDF File (Adobe PDF File), 55 KB - resprot_v10i5e15716_app5.pdf]

Multimedia Appendix 6
Code categories to classify Twitter users.
[PDF File (Adobe PDF File), 42 KB - resprot_v10i5e15716_app6.pdf]

Multimedia Appendix 7
IRB approval notice.
[PDF File (Adobe PDF File), 1140 KB - resprot_v10i5e15716_app7.pdf]

Multimedia Appendix 8
Data extraction and cleaning flow diagram.
[PDF File (Adobe PDF File), 54 KB - resprot_v10i5e15716_app8.pdf]

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Abbreviations

IRB: institutional review board
NCATS: National Center for Advancing Translational Sciences
NIH: National Institutes of Health
REDCap: Research Electronic Data Capture
SLE: systemic lupus erythematosus
USC: University of Southern California

Protocol

The Smartphone App haMSter for Tracking Patient-Reported Outcomes in People With Multiple Sclerosis: Protocol for a Pilot Study

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Abstract

Background: Treatment and monitoring decisions in people with multiple sclerosis (MS) are based commonly on clinician-reported outcomes. These reflect physical and radiological disease activity and are the most relevant endpoints in clinical trials. Over the past few years, the number of studies evaluating so-called patient-reported outcomes (PROs) has been increasing. PROs are reports from patients concerning their own health perception. They are typically obtained by means of questionnaires and aim to quantify symptoms such as fatigue, depression, and sexual dysfunction. The emergence of PROs has made a tremendous contribution to understanding the individual impact of disease in people with MS and their health-related quality of life. However, the assessment of PROs consumes resources, including time and personnel. Thus, useful ways to conveniently introduce PROs into clinical practice are needed.

Objective: We aim to provide a rationale and pilot study protocol for a mobile health (mHealth) solution named "haMSter" that allows for remote monitoring of PROs in people with MS.

Methods: The core function of haMSter is to provide three scientifically validated PRO questionnaires relevant to MS for patients to fill out at home once a month. Thereby, longitudinal and remote documentation of PROs is enabled. A scoring algorithm graphically plots PRO scores over time and makes them available at the next visit.

Results: The pilot study is currently ongoing and will evaluate adherence to this mHealth solution in 50 patients over a period of 6 months. Results from the haMSter pilot study are expected in 2021.

Conclusions: haMSter is a novel mHealth-based solution for modern PRO research, which may constitute the first step in achieving the ability to integrate PROs in clinical practice. This allows for a more problem-oriented approach in monitoring visits, which addresses patient needs and ultimately saves time.

Trial Registration: ClinicalTrials.gov NCT04555863; https://clinicaltrials.gov/ct2/show/NCT04555863

International Registered Report Identifier (IRRID): DERR1-10.2196/25011

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Introduction

Multiple Sclerosis and Patient-Reported Outcomes

Multiple sclerosis (MS) is a chronic neurological disease associated with inflammation and neurodegeneration. Its worldwide prevalence is estimated at 2.5 million people affected, and it is the most common cause of disability in young adults, aside from trauma [1-3]. Disease monitoring in people with MS encompasses continuous evaluation of the following three major components: clinical disease activity, radiological disease activity, and, albeit mostly for research purposes, biomarkers [4,5]. These outcomes can be summarized as clinician-reported outcomes. They represent the mainstay in determining the disease course and treatment response in routine MS care and are also the main endpoints in clinical trials. Complementary to clinician-reported outcomes, so-called patient-reported outcomes (PROs) are reports from patients concerning their own health perception, quantifying either specific symptoms that are hard to objectify, such as fatigue, depression, and sexual dysfunction, or more general parameters, such as quality of life, working abilities, treatment adherence, and treatment satisfaction. Over the past few years, PROs have contributed to displaying the disease burden in MS and its impact on health-related quality of life. So far, several PRO measures (PROMs) for MS have been validated and established, such as scores for quality of life, fatigue, and sexual functioning [6,7].

While garnering information about a patient's subjective impairment to health through PROs would theoretically have a palpable benefit, application in routine care is greatly hindered. Currently, filling out and evaluating paper-based PRO questionnaires are consuming a considerable amount of resources in terms of time and personnel. Thus, useful ways to conveniently introduce PROs into clinical practice are needed.

Mobile Health and Multiple Sclerosis

The use of mobile health (mHealth) may offer strategies for easily administered PRO questionnaires. This could facilitate research and advance the focus from merely reporting disease parameters to understanding an individual's impairment caused by disease. So far, a recognizable effort has been made to offer mHealth technologies for managing MS. These solutions can be summarized as elements of (1) screening and assessment, (2) treatment and rehabilitation, (3) advice and education, and (4) disease monitoring and management [8]. However, only a handful of these tools focus on integrating validated PROs into clinical practice. One smartphone app, for example, offers remote and active testing of *surrogate* markers for dexterity and mobility that correlated well with on-site administered tests [9]. Another study investigated an on-site tablet-based method

for evaluating bladder control [10]. The most prominent mHealth solution for remote patient monitoring in people with MS is probably the Multiple Sclerosis Performance Test. It is a tablet-based tool designed to measure physical disability, and it has spurred a lot of interest and subsequent adaptions [11,12]. Nevertheless, solutions that allow remote tracking of well-established PROMs in MS have not yet been reported.

Study Aim

The aim of this report is to introduce *haMSter* as an mHealth-based solution for tracking PROs in people with MS remotely. Through the use of the haMSter app, patients are offered an opportunity to fill out PRO questionnaires anywhere and anytime they feel comfortable. The scoring algorithm of haMSter provides neurologists a unique opportunity to visualize the longitudinal course of their patients' PROs. A pilot study evaluating the feasibility of the haMSter protocol is currently ongoing.

Methods

Study Design

This study protocol will be used in an uncontrolled pilot trial evaluating adherence to the haMSter app in 50 people with MS. Upon informed consent to participate in this study, eligible patients will be able to download the app on their smartphones during a regular visit to our MS clinic and use it at home over a period of 6 months.

Study Setting

This is a monocentric study at the MS Clinic of the Department of Neurology, Medical University of Vienna, Austria. An outline of the study protocol is shown in Figure 1 [13]. Patients are instructed to fill out three specific PRO questionnaires ("haMStercare") on their smartphone once every 30 days. In addition, patients are introduced to two other features of haMSter, which are available at their own convenience. These are a reminder for taking their medication ("haMSterreminder") and a diary ("haMSterdiary"). At the follow-up visit, a Bluetooth printer in the exam room will allow the patient to print out a PRO score sheet that graphically shows the score for each PRO over the course of the study. This illustration is intended as a base for discussing symptoms and the patient's individual health perception. The study concludes with the administration of a paper-based satisfaction questionnaire including a validated outcome measure for satisfaction with telemedicine (Telemedicine Perception Questionnaire [TMPQ] [14]) and an empirical questionnaire. The latter collects user feedback regarding technical implementation, design, handling, and possibilities for further improvement of the app's utility.

Figure 1. Overview of study enrollment, interventions, and assessments over the course of the haMSter pilot trial (Standard Protocol Items: Recommendations for Interventional Trials [SPIRIT] checklist). MS: multiple sclerosis; PRO: patient-reported outcome.

	Enrollment	STUDY PERIOD						Close-out
		Postallocation						
TIMEPOINT	*Baseline visit*	*Home use of haMSter over 6 months*						*Follow-up visit (6 months)*
ENROLLMENT:								
Eligibility screen	X							
Informed consent	X							
Download of the haMSter app	X							
Allocation of a unique study ID	X							
INTERVENTIONS:								
haMStercare		X	X	X	X	X	X	
haMSterreminder		per individual convenience						
haMSterdiary		per individual convenience						
ASSESSMENTS:								
Sociodemographic information	X							
MS disease characteristics	X							X
PRO score sheet from haMStercare								X
Satisfaction questionnaire								X

haMSter Smartphone App

haMStercare: PRO Questionnaires

The core function of haMSter is the provision of three validated and well-established PROMs in MS. After obtaining written consent from the respective PRO proprietor, we included three different questionnaires that are commonly used in MS research and for which a German version is available. The first is the Hospital Anxiety and Depression Scale (HADS), which is a widely used screening tool for depression and anxiety [15]. It reports two separate scores for depression and anxiety. The second is the Multiple Sclerosis Impact Scale (MSIS-29), which is a survey of quality of life measures in people with MS that provides subscores for physical and psychological impairment in context with MS [16]. The third is the Fatigue Scale for Motor and Cognitive Functions (FSMC), which is an MS-specific scale that quantifies motor and cognitive fatigue. The haMStercare feature is programmed to provide a pop-up message to remind patients every 30 days to fill out the questionnaires. Figure 2 illustrates the login screen, the main menu that navigates through the three haMSter features, and an example question from the HADS.

Figure 2. Screenshots of the the login screen (A), main menu screen (B), and a sample patient-reported outcome (PRO) question (C). The screenshots provided here have been translated from German to English for the purpose of this article. The lower end of the log-in screen reads "Programming of this app was funded by" and lists the corporate logos of pharmaceutical companies that provided funding for programming the haMSter app.
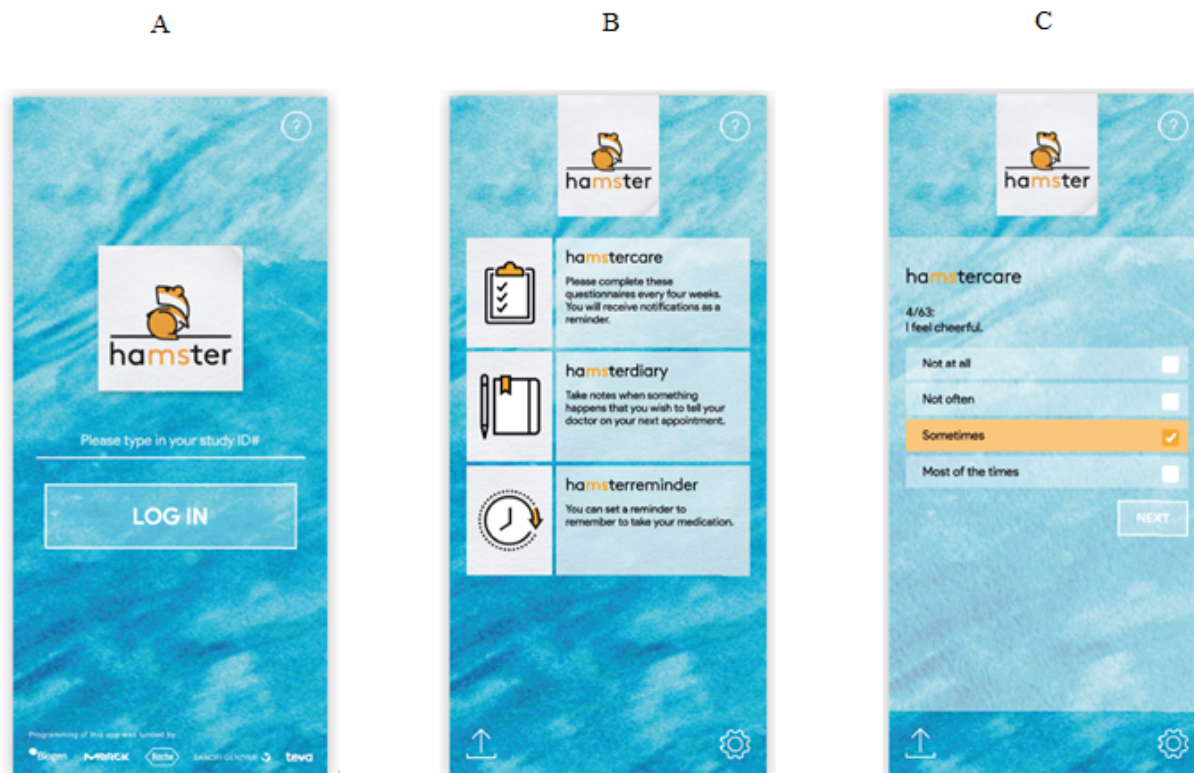
haMSterreminder: Reminder for Medication

The haMSter app allows participants to set a reminder for their medication. All medications approved for the treatment of MS in Austria as of April 1, 2019 (when the app was programmed) can be selected by the user. These include alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, interferon-beta preparations, natalizumab, ocrelizumab, and teriflunomide. The reminder's time algorithm is based on the fixed dosing regimen for these medications. Patients are made aware that this reminder does not intend to replace their own responsibility for adhering to their medication.

haMSterdiary: Diary Entries for Patients

Another feature of the haMSter app is a diary notepad (Figure 3). Patients can type in any matter concerning their lives with MS, such as certain events or symptoms they wish to communicate to their doctors at the next visit. The haMSter diary saves these entries together with the current date.

Figure 3. Sample entry for haMSterdiary. The screenshot provided here has been translated from German to English for the purpose of this article.

Coding Process

The haMSter app was coded using the WebView-based Cordova app (Apache Software Foundation). The Cordova native API (application programming interface) served as the app's main framework. User input was programmed to not communicate with any server. Data entered into the haMSter app is stored as an HTML (hypertext markup language) web storage API using a JavaScript Object Notation (JSON; Oracle Corporation) based on the "JSON.parse" and "JSON.stringify" commands. Repeated testing for plausibility and reliability of the haMSter app's performance was implemented before release and over a period of 3 months. This was performed using the PhoneGap command-line interface version 9.0.0 (PhoneGap CLI; Apache Software Foundation) through a node package manager, the developer tool in google chrome (Google International LLC), and prototype devices operating on Android version 8.0.0 or

above (Google International LLC) and Apple iOS version 5.0.0 or above (Apple Inc).

Considerations of Data Protection

The pilot study using the haMSter protocol adheres to current data protection guidelines in Austria as of April 1, 2019. Patients are educated on these guidelines on the informed consent form, which has been approved by our local ethics review board. In short, the main considerations of data protection regarding the use of haMSter are (1) the app works exclusively offline, (2) no patient-specific data are entered into the app, and (3) data are stored nowhere else but on the patient's smartphone. The app itself only operates on a study identification number that is assigned upon enrollment.

Participants

Eligibility Criteria

The pilot study evaluating haMSter will enroll any patient fulfilling the current diagnostic criteria for MS [17], regardless of their age, disease phenotype, or medication. Inclusion is offered to patients owning a smartphone and expressing a will to participate. Exclusion criteria are obvious language barriers.

Recruitment Procedure

Patients will be informed about this study during any visit to our MS outpatient clinic. The study will be advertised as an investigation into the feasibility of a smartphone app determining patient-reported symptoms electronically and repeatedly over time. All patients expressing interest will receive a more detailed introduction to the app and its functions. Subsequently, the recruiting neurologist will accurately inform participants on relevant considerations regarding data protection (see above). Upon informed consent, patients can download the app on any device with an Apple or Android-based operating system. After successful download, the recruiting neurologist will enter relevant baseline characteristics (sociodemographic information and MS disease–specific characteristics) in a case report form on site.

Timeline

The idea for the haMSter app was conceived in November 2018. The coding process began in May 2019 and was finished in October 2019. After a period of beta testing and some delay due to the COVID-19 pandemic, the pilot study was launched in April 2020 ("first patient in"), and it is expected to end in April 2021 ("last patient out").

Results

Baseline and Sociodemographic Characteristics

To provide an overview of the patients participating in this pilot study, we will report typical baseline and sociodemographic characteristics documented at baseline and follow-up. The structure is provided in Textbox 1 [18].

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Textbox 1. Sociodemographic and clinical characteristics of patients to be determined in this pilot study.

Parameter

- Participants analyzed, n (%)

  Age (years), mean (SD)

- Sex, n (%)

  - Female

  - Male

- Disease phenotype, n (%)

  - Relapsing multiple sclerosis (MS)

  - Progressive MS

- Expanded Disability Status Scale

  - Median

  - 0-3.5

  - 4 or above

- Number of relapses

  - Last 12 months

- Disease duration (years), n (%)

- MS medication, n (%)

  - Moderately effective

  - Highly effective

  - No treatment

  - Other medication and comorbidities

- Family status, n (%)

  - Single

  - Relationship

  - Married

  - Number of children

- Education, n (%)

  - Nine or less years of schooling

  - Secondary schooling

  - College degree

Primary Outcome Measure

The primary outcome measure is the adherence to filling out the questionnaires once per month. Results will be displayed as the mean percentage of filled out questionnaires based on the PRO scoring sheet. Figure 4 illustrates a sample scoring sheet as viewed in the app and as a printout that is presented to the patient and discussed with the physician during the end of the study visit. We will investigate whether adherence decreases over time by using the Friedman test and Jonckheere-Terpstra test for monotonic trend.

Figure 4. Screenshots of the patient-reported outcome (PRO) scoring information on the smartphone (A) and a printed score sheet (B). The screenshots provided here have been translated from German to English for the purpose of this article.
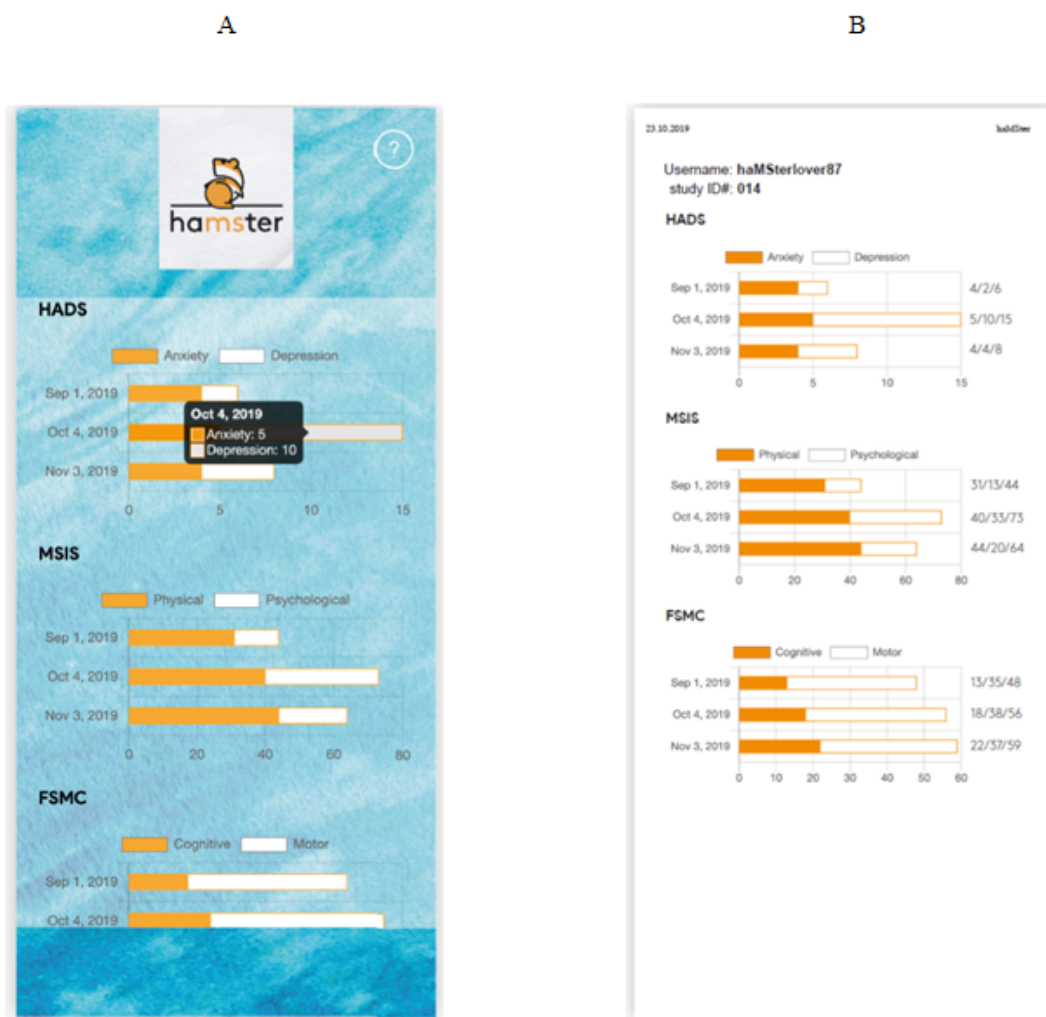
Exploratory Outcome Measures

Exploratory outcome measures include patient perceptions of this new mHealth method based on mean TMPQ values. There will also be a further exploratory analysis of PROs in conjunction with MS disease characteristics and of the empirical questionnaires with respect to the utility and design of haMSter. If reasonable, we will perform a subgroup analysis to identify patients with high (75th percentile) and low (25th percentile) satisfaction. Another secondary goal is group comparisons of adherence between patients with and those without upper extremity disability as defined by the Expanded Disability Status Scale (EDSS) score.

Statistical Considerations

Currently, there is no consensus on a significant threshold for adherence to mHealth methods. With respect to our main outcome measure, we regard a minimum adherence of 50% or higher as relevant (participants completed the three PRO questionnaires [a total of 63 questions] three times over a period of 6 months). As for the exploratory outcome measures, we aim to provide descriptive statistics (categorical variables expressed

as frequencies and percentages, and continuous variables tested for normal distribution by the Kolmogorow-Smirnow test and presented as mean and standard deviation or median and interquartile range as appropriate).

Ethics Review and Trial Registration

The ethics committee at the Medical University of Vienna, Austria, approved this study in September 2019 (EK1798/2019). Written informed consent will be obtained from each patient, and the study protocol follows the guidelines set by the Declaration of Helsinki. The trial has been registered at ClinicalTrials.gov (identifier: NCT04555863).

Discussion

This is the protocol for a pilot study testing a new smartphone app named haMSter. This mHealth-based approach enables continuous measurement of PROs in people with MS and uses scientifically validated questionnaires. Textbox 2 outlines the hypotheses regarding the possible future implications of haMSter and its use in patient care. We believe the haMSter app can save time during routine consultations and improve quality of

face-to-face visits with respect to targeting *patient-specific problems* rather than discussing a variety of *possible problems*. On a separate note, repeated questionnaires, such as the ones included in haMSter, may reflect the patients' everyday reality compared with a single assessment. Even so, since this is a pilot trial, the implementation of this app in real life may call for further adjustments.

Textbox 2. Future roles of haMSter in patient-centered care.

- haMSter makes monitoring of patient-reported outcomes (PROs) convenient and easy.

Advantage: Researchers do not have to resort to paper-based questionnaires anymore.

Future implication: PRO research can advance to a longitudinal dimension.

- haMSter demonstrates advances in modern PRO research.

Advantage: PRO research becomes accessible more easily.

Future implication: This may influence treatment considerations in the future.

- haMSter gives room to underrepresented symptoms.

Advantage: The haMSter protocol may unveil symptoms that were previously unnoticed.

Future implication: Health-related quality of life can improve further.

- haMSter is a solution to save resources in clinical care.

Advantage: Through a graphical illustration, PROs can easily be interpreted in context with time.

Future implication: Focus in routine care is diverted to a more patient-oriented discussion.

Results from the haMSter pilot study are expected in 2021. The primary endpoint is adherence to this new method based on the frequency of completed questionnaires over the study period. Furthermore, the utility of haMSter will be carefully assessed through the use of satisfaction questionnaires. The selection process for this study may introduce bias, as only patients with an a priori acceptance of this method would participate. However, we will report on the number of patients declining participation and their given reasons for it.

Taken together, this pilot study is set to lay the foundation for further advancement of haMSter as a digital solution with the ultimate goal of setting a new standard for modern and personalized patient care. Future possibilities of evolving this app further will be explored.

Authors' Contributions

PA owns the intellectual property of the haMSter app, established the study design, wrote the first draft of this article, will coordinate the pilot study, and was the recipient of the unrestricted grant that enabled the development of this protocol. WH programmed the haMSter app and provided continuous technical support. MP, BK, TM, TZ, KB, RL, and GZ contributed to general project development, administration, and optimization of the study protocol with respect to clinical relevance and utility. GB corrected and edited the manuscript. BK, FL, PSR, GB, and TB acted as supervisors, contributed a high amount of experience in treating people with MS, and will supervise the clinical study. All authors have read the manuscript.

Conflicts of Interest

There are no direct conflicts of interest with respect to the establishment of this protocol. PA has participated in meetings sponsored by and received speaker honoraria or travel funding from Biogen, Merck, Roche, Sanofi-Genzyme, and Teva, and has received honoraria for consulting from Biogen. He received a research grant from Quanterix International and received funding for the development of the haMSter app from Biogen, Merck, Roche, Sanofi-Genzyme, and Teva. WH has nothing to declare. FL has participated in meetings sponsored by or received honoraria for acting as an advisor/speaker for Bayer, Biogen, Celgene, MedDay, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. MP has nothing to declare. TM has participated in meetings sponsored by or received travel funding from Biogen, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. TZ has participated in meetings sponsored by or received travel funding from Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. GZ has nothing to declare. BK has received speaking honoraria or travel support from Biogen, Celgene, Merck, Novartis, Roche,

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Abbreviations

EDSS: Expanded Disability Status Scale
FSMC: Fatigue Scale for Motoric and Cognitive Fatigue
HADS: Hospital Anxiety and Depression Scale
MS: multiple sclerosis
MSIS-29: Multiple Sclerosis Impact Scale
PRO: patient-reported outcome
PROM: patient-reported outcome measure
TMPQ: Telemedicine Perception Questionnaire

Protocol

Immersive Virtual Reality to Improve Outcomes in Veterans With Stroke: Protocol for a Single-Arm Pilot Study

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Abstract

Background: Over the last decade, virtual reality (VR) has emerged as a cutting-edge technology in stroke rehabilitation. VR is defined as a type of computer-user interface that implements real-time simulation of an activity or environment allowing user interaction via multiple sensory modalities. In a stroke population, VR interventions have been shown to enhance motor, cognitive, and psychological recovery when utilized as a rehabilitation adjunct. VR has also demonstrated noninferiority to usual care therapies for stroke rehabilitation.

Objective: The proposed pilot study aims to (1) determine the feasibility and tolerability of using a therapeutic VR platform in an inpatient comprehensive stroke rehabilitation program and (2) estimate the initial clinical efficacy (effect size) associated with the VR platform using apps for pain distraction and upper extremity exercise for poststroke neurologic recovery.

Methods: This study will be conducted in the Comprehensive Integrated Inpatient Rehabilitation Program at the James A Haley Veterans' Hospital. Qualitative interviews will be conducted with 10 clinical staff members to assess the feasibility of the VR platform from the clinician perspective. A prospective within-subject pretest-posttest pilot design will be used to examine the tolerability of the VR platform and the clinical outcomes (ie, upper extremity neurologic recovery, hand dexterity, pain severity) in 10 veteran inpatients. A VR platform consisting of commercially available pain distraction and upper extremity apps will be available at the participants' bedside for daily use during their inpatient stay (approximately 4-6 weeks). Clinician interviews will be analyzed using qualitative descriptive analysis. Cohen d effect sizes with corresponding 95% CIs will be calculated for upper extremity neurologic recovery, hand dexterity, and pain. The proportion of participants who achieve minimal clinically important difference after using the VR platform will be calculated for each clinical outcome.

Results: This study was selected for funding in August 2020. Institutional review board approval was received in October 2020. The project start date was December 2020. The United States Department has issued a moratorium on in-person research activities secondary to COVID-19. Data collection will commence once this moratorium is lifted.

Conclusions: Our next step is to conduct a large multi-site clinical trial that will incorporate the lessons learned from this pilot feasibility study to test the efficacy of a VR intervention in inpatient rehabilitation and transition to home environments. When VR is used in patients' rooms, it serves to provide additional therapy and may reduce clinician burden. VR also presents an opportunity similar to home-based practice exercises. VR can be implemented in both clinical settings and people's own homes, where engagement in ongoing self-management approaches is often most challenging. This unique experience offers the potential for seamless transition from inpatient rehabilitation to the home.

International Registered Report Identifier (IRRID): PRR1-10.2196/26133

Introduction

Background

Over the last decade, virtual reality (VR) has emerged as a cutting-edge technology in stroke rehabilitation. VR is defined as a type of user-computer interface that implements real-time simulation of an activity or environment, allowing user interaction via multiple sensory modalities [1]. VR interventions can be characterized as immersive or nonimmersive. Immersion refers to the sensation of being inside a particular environment or world, for example, a 3D world [2]. Nonimmersive VR typically uses commercial video game systems developed by the entertainment industry for home use, although some researchers have developed rehabilitation-specific nonimmersive VR apps [3-5]. Nonimmersive VR uses 2D interfaces such as Nintendo Wii, Microsoft Xbox, and Sony PlayStation [6-8]. Immersive VR uses a 3D virtual environment with the intention of making the user feel a part of, inside, or immersed in the environment to the extent that they become unaware of their physical surroundings [2]. Immersive VR experiences typically involve the use of a head-mounted display (HMD), which creates a 3D image in all fields of view. We will use the most current VR technology, which at this time is a wireless immersive HMD app with hand controllers, the Oculus Quest 2.

Upper Limb VR Research

Upper limb deficits occur in up to 85% of stroke survivors and they significantly affect performance of activities of daily living [9]. The literature on the use of VR in stroke rehabilitation is fairly extensive, but is characterized by small, lesser quality studies with widely varying definitions of what constitutes a VR intervention. The stroke VR literature base has been criticized for lack of a control group, making it difficult to discern if positive effects were the result of the VR intervention itself or simply the result of extra therapy time, for example, when VR is used as an adjunct [10]. Studies on the use of VR for poststroke upper limb dysfunction have shown mixed results [2-8,11-15]. A Cochrane review published in 2017 [16] concluded that the overall effects of VR on upper extremity function were not significantly different when compared with those of conventional therapy (including both specialized VR systems designed for rehabilitation or commercial gaming consoles). However, when VR was utilized as an adjunct to standard care compared with no additional intervention

(increased overall therapy time), the VR group experienced statistically significant benefits in upper limb function (standardized mean difference 0.49, 95% CI 0.21-0.77). The overall quality of the trials included for upper limb function outcomes is low. The Cochrane review also found a small, yet statistically significant effect of VR on activities of daily living (standardized mean difference 0.25, 95% CI 0.06-0.43). Because of the heterogeneity in the outcomes used in the studies investigating the effect of VR on upper limb function after a stroke, 2 systematic reviews and meta-analyses [1,17] grouped outcomes by the International Classification of Function domains. For studies that used a virtual world environment approach to VR, medium effect sizes were found: body structure/function effect size of 0.43 [1] to 0.54 [17], activity effect size of 0.54 [1] to 0.62 [17], and participation effect size of 0.38 [17] to 0.56 [1]. Gains after the intervention were preserved at follow-up [17]. A limitation of both systematic reviews and meta-analyses was the variability in how VR was delivered in terms of intensity and duration [1,17] and lack of clarity regarding control group therapy.

Three recent randomized controlled trials (RCTs) [10,18,19] of nonimmersive VR interventions (using 2D interfaces) that included control groups dose matched for therapy time found mixed results. A single-center study [19] that compared 10 sessions of a self-administered upper extremity rehabilitation program, including 4 game apps on a smartphone and tablet with control therapy of 1 hour of conventional occupational therapy per day found a significant difference on the Fugl-Meyer Assessment of Motor Recovery after Stroke-Upper Extremity (FMA-UE) at 1-month follow-up in favor of the intervention group. In contrast, neither the efficacy and safety of nonimmersive VR exercising in stroke (EVREST) rehabilitation trial [10] that compared 10 sessions of commercial gaming with control recreational activities or the VR training for upper extremity in subacute stroke multi-center trial [18] that compared 16 sessions of VR designed for rehabilitation with conventional therapy found significant differences. The authors of the EVREST study did, however, speculate that utilizing an immersive VR system might have led to significant results. As VR becomes more immersive, more interactive, and less expensive, and because of its flexibility, studies of the use of VR in the inpatient environment [20] suggest that VR is efficacious, easy to use, safe, and contributes to high patient satisfaction.

VR and Pain

A recent multi-site study (N=546) found a 30% prevalence of pain across the acute, subacute, and chronic poststroke stages [21]. Cognitive factors (eg, attention) are important to pain perceptions, even when people are not engaged in specific tasks [22]. Theory suggests that VR directly or indirectly affects cognitive and attentional processes to attenuate pain. VR can be a distraction mechanism that consumes cognitive and attentional resources to limit pain-processing capabilities [23]. A randomized crossover study found a 56% reduction in time thinking about pain when using VR versus self-selected distraction (eg, meditation, smartphone; $P<.001$) [24]. VR may also create neurobiological interactions in the brain by regulating sensory stimulation to produce an analgesic effect [25]. Sense of immersion and presence are important to distraction and analgesia because distraction therapy is the most commonly used intervention in VR pain research [26]. A rapid evidence assessment of VR (20 studies, N=337) found strong evidence for short-term reduction in pain intensity and moderate evidence for pain analgesia [27]. A meta-analysis (14 studies, N=581) estimated a large, standardized effect (0.90, 95% CI 0.72-1.08) for VR pain distraction studies using between-group and mixed-model designs [28]. Thus, integration of VR during rehabilitation may have promising implications for poststroke pain.

Neuroplasticity

Decades of animal research and recent research in human subjects provide compelling evidence that the adult brain affected by stroke can reorganize itself in response to experience and training, with sufficient repetition playing a critical role [29-31]. In patients with subacute stroke, gains in the upper limb and hand dexterity (strength, range of motion, speed of movement) require more intensive repetitive task practice than gains in lower limb and mobility [31-33]. In addition, task motivation is essential for learning [29,30,34-36]. Immersive VR exposure is hypothesized to deliver the crucial impetus to drive lasting neural changes by providing a motivating environment for poststroke patients to retrain movement, range of motion, movement speed, fractionation (use of individual fingers), and force production [37]. In the proposed study, immersive VR will be utilized as adjunct therapy, allowing patients to increase their therapy dose and thereby engage in the repetition essential for motor learning.

Immersive VR

Nonimmersive VR environments are projected on 2D screens (eg, laptop). Nonimmersive VR can facilitate stroke symptom improvement [10,18,19], but it is lower on the immersion spectrum and less efficacious than immersive 3D VR [26,38]. Immersion and presence are theoretical mechanisms of change, which may facilitate greater learning within virtual environments [23,39]. Immersive VR interventions may be cost-effective and less resource-intensive than many traditional interventions with comparable efficacy [40].

Preliminary Studies

In a pilot study [41,42] in the James A Haley Veterans' Hospital (JAHVH) inpatient Chronic Pain Rehabilitation Program, our team found evidence for the feasibility of immersive VR within the chronic pain population as well as a decrease in fear of movement, pain interference with mobility, pain intensity, and pain catastrophizing. Veteran attendance (91%) and completion of attended 20-minute VR sessions was high (97%). Veterans typically rated 20-minute VR sessions as too short. According to the Department of Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI), in fiscal year 2018, there were more than 10,000 unique veteran inpatient admissions for stroke. The proposed study is an innovative treatment paradigm utilizing sophisticated immersive VR technology available at the bedside to increase therapy dosage. This cutting-edge technology has the potential to not only drive neurologic recovery by augmenting the brain's own intrinsic repair capacity in response to a stroke insult (neuroplasticity) but also improve veterans' quality of life by diminishing pain and enhancing self-efficacy. Immersive VR could ultimately become a new standard of care in acute inpatient rehabilitation, allowing unlimited rehabilitation experiences for patients with stroke. In addition, there is strong potential for seamless transition to home, as immersive VR technology rapidly becomes more sophisticated and less costly. Finally, the proposed research supports modernization of the veterans' health administration by incorporating technology-assisted rehabilitation, addresses the VA Rehabilitation Research and Development (RR&D) goal of maximizing functional recovery, and focuses on VA Office of Research and Development priorities, including access to care, mental health, health care value, and pain.

Aims and Research Questions

The proposed feasibility pilot project will address the RR&D goal of maximizing functional recovery by pilot testing an immersive VR intervention designed to increase exercise dosage for the upper limb and decrease pain for inpatient veterans after stroke without increasing therapist time [43]. The VR intervention will use an HMD, more commonly known as goggles, to which selected apps can be uploaded. Apps and goggles are commercially available and have been selected based on the following criteria: (1) address the treatment goals of overall upper extremity neurologic recovery, hand dexterity, and pain reduction, (2) utilized while patient lying in bed, (3) provide no stimulation to move legs or reach outside of bed area, (4) simple to use (require no technological expertise), (5) involve graded head, neck, upper extremity movement, and distraction to reduce pain, and (6) cognitive burden ranges from minimal to moderate. The VR intervention will be administered at bedside for two 30-minute therapy sessions per day for 4 weeks. The primary objective of this study is to determine the effectiveness of using VR as an adjunct to usual care therapy to enhance upper extremity neurologic recovery and hand dexterity and to decrease pain. Findings from this study will inform a larger multi-site RCT.

Our proposal is innovative in 4 distinct ways. First, we will use immersive 3D rather than the more typically used 2D VR. Immersion and the resulting "presence" within the virtual environment are thought to be the principal mechanisms of positive change [23,32]. Second, we will assess pain reduction after stroke by using VR apps, which is not well represented in the literature. Third, we are using VR as an adjunct

therapy—adding additional therapy time with less burden on clinicians than is required in traditional therapy. Finally, VR when used in patients' rooms presents an opportunity similar to home-based practice exercises. Our targeted enrollment is 10 clinical staff (research question [RQ] 1.1) and 10 inpatient veterans being treated for stroke (aim 2).

Specific aim 1: Determine the feasibility and tolerability of using a therapeutic VR platform in an inpatient comprehensive stroke rehabilitation program.

RQ 1.1: What is the feasibility of using the VR platform from the clinician perspective?

RQ 1.2: What is the tolerability for poststroke inpatients using the VR platform?

Specific aim 2: Estimate the initial clinical efficacy or effect size associated with the VR platform using apps for distraction and upper extremity exercise for veterans after the stroke.

RQ 2.1: What are the estimated effect sizes and degree of precision for the outcomes of upper extremity neurologic recovery, hand dexterity, and pain?

RQ 2.2: How clinically responsive are dexterity and upper extremity neurologic recovery (primary) outcomes to early stroke rehabilitation using a therapeutic VR platform?

Methods

Design

Our methodological framework is based on the work by the Virtual Reality Clinical Outcomes Research Experts committee [38]. We will use their VR2 clinical study design: conducting early prospective testing with a focus on feasibility and tolerability (aim 1) and initial efficacy (aim 2). Per Virtual Reality Clinical Outcomes Research Experts guidelines, we will use a single group so that we may optimize recruitment to represent the breadth and depth of our target patients.

Population

There are 2 populations for the proposed project. The first population consists of veterans (n=10) who have been diagnosed with an acute ischemic or hemorrhagic stroke and are admitted to JAHVH inpatient rehabilitation after a stroke. Inclusion criteria are as follows: (1) age 18-80 years and (2) stroke diagnosis verified by brain imaging. Exclusion criteria are as follows: (1) unable to follow instructions or participate in immersive VR therapy due to significant cognitive impairment and (2) history of seizures. The second population consists of occupational therapists and rehabilitation nurses (clinician champions) working in the Comprehensive Interdisciplinary Inpatient Rehabilitation Program, who will provide data on the feasibility of using VR in an inpatient environment (RQ 1.1).

Recruitment

All patients admitted to the Comprehensive Interdisciplinary Inpatient Rehabilitation Program at JAHVH (a designated Primary Stroke Center) with a diagnosis of acute ischemic or hemorrhagic stroke will be considered for inclusion in the study. A minimum of 5 beds will be designated for study participants. The Comprehensive Interdisciplinary Inpatient Rehabilitation Program admits 3.5 stroke patients per month, that is, 42 per year. We feel this is a sufficient subject pool from which to enroll the target sample size of 10 patients (16% of the patients admitted over the 18-month enrollment period). We have found that the technology is motivating for patients, which will help retention [42].

Procedure

VR Intervention

The VR intervention uses off-the-shelf technology: Oculus Quest HMD and commercially available apps specifically developed or adapted for Oculus Quest (Figure 1). App selection for individual patients will be guided by the motor difficulty of the apps (Figure 2). For example, patients will begin with the green-coded apps, which is the easiest activity level in the toolkit. These apps primarily address pain via distraction with minimal head and neck movement, but no hand movement, required. As tolerated, patients will advance to more difficult apps that require hand and finger movement, with high-level apps requiring controlled movement. Apps are commercially available and have been selected based on the following criteria: (1) address the treatment goals of overall upper extremity neurologic recovery, hand dexterity, and pain reduction; (2) can be utilized while patient is lying on bed; (3) provide no stimulation to move legs or reach outside of bed area; (4) are simple to use (require no technological expertise); (5) involve graded head, neck, upper extremity movement and distraction to reduce pain; and (6) cognitive burden ranges from minimal to moderate. Because hand-tracking app technology is developing/improving at a rapid pace, upon notice of funding, it is likely that we will need to update the VR toolkit (Figure 2).

Figure 1. Virtual reality intervention.

Figure 2. Apps in the virtual reality toolkit for Oculus Quest.

Outcome[a]			App name	Source	Description	Hand controller use		
						None	Min	Mod
Neurologic recovery	Hand dexterity	Pain						
			Ocean Rift	Oculus	Distraction (nature, music)	✓		
			Within	With.in	Distraction (cinematic)	✓		
			Nature Treks	Sidequestvr	Distraction (nature)		✓[b]	
			National Geographic Explore	Oculus	Distraction (nature)		✓[b]	
			Mr. Scribbles	Oculus	Hand, finger movement	✓		
			Virtual Piano	Sidequestvr	Play piano by moving hands up and down	✓		
			Cubism	Sidequestvr	Grab shapes with hand and put in container	✓		
			Virtual Reality Fishing	Oculus	Holding fishing rod, coordination			✓

[a]Level of difficulty: green=passive minimal movement, blue=moderate movement, and pink=controlled movement.
[b]Hand controller used to select view; intact extremity can be used.

Prior to beginning the intervention, clinician champions (occupational therapists and nurses) and the project manager will be instructed with regard to the use of the HMD and VR apps by our technologist. Staff will have the opportunity to practice with the HMD and apps for 2 weeks prior to using the apps with patients. Following institutional review board approval and funding on site, potential subjects will be identified by the admitting physician, principal investigator, or the project manager in the absence of the principal investigator. The project manager will use a Health Insurance Portability and Accountability Act waiver to check the inclusion and exclusion criteria.

Week 1: Baseline and Preintervention Data Collection

Once patients are enrolled, the project manager will collect the baseline data and administer the preintervention outcome measures (Table 1). Further, the principal investigator/Dr Tran, occupational therapists, project manager, and the technologists will select apps from the VR toolkit (Figure 2) that best address the individual patient's treatment goals based on his/her current functional level.

Table 1. Outcome variables and covariates.

Variable	Definition
Outcomes[a]	
Hand dexterity (primary measure)	Action Research Arm Test (MCID[b]: chronic=5.7, acute=12)
Neurologic recovery (primary measure)	Fugl-Meyer Assessment of Motor Recovery after Stroke-Upper Extremity (MCID 4-7)
Pain (secondary measure)	Pain Outcomes Questionnaire-Veterans Affairs, initial, item 12 and discharge, item 2 (pain numeric rating scale) (effect size 0.85, medium effect, standard error of measurement 0.79)
Demographic and clinical[c]	
Age	Age on date of baseline data collection
Sex	Male/female
Race/ethnicity	Caucasian, African American, Hispanic, other
Time since index stroke	In days: index event – baseline data collection
Type of stroke	Ischemic=0, hemorrhagic=1

[a]Source of information from clinical assessment and self-report.

[b]MCID: minimal clinically important difference.

[c]Source of information from computerized patient record system.

Weeks 2-4: VR Intervention

Patients will be instructed in the use of the HMD with VR apps by a project occupational therapist. It is anticipated that subjects may need 1-3 sessions of instruction. VR dosage will be 2 half-hour sessions per therapy day, facilitated by an occupational therapist and clinician champions, overseen by the principal investigator. The timing of VR sessions will vary based on the patient's therapy schedule. During the VR session, the patient will be reclining or seated in bed with both bed rails raised. The clinician champions will bring the VR HMD to the bedside and assist the patient with donning the device. Once the patient is comfortable using the HMD with VR apps, the clinician champion will begin each session by setting the patient up and making sure that they are successfully engaging with the app. The clinician champion will return 30 minutes later to remove the VR HMD from the room. This process will be repeated a second time each therapy day. Patients can initiate the use of a more challenging app (blue category) that gradually includes hand/arm movement. Some patients may progress to the pink category in which hand/arm coordination is required.

Week 4: Postintervention Data Collection

The average length of stay in the acute inpatient rehabilitation unit at JAHVH is 4-6 weeks. Accordingly, postintervention data will be collected at week 5 or at the end of week 4 if the veteran is being discharged. RQ 1.2 tolerability data will be collected throughout the subjects' participation in the study.

End of Data Collection

Once all veterans have completed the study, RQ 1.1 feasibility data will be collected from clinician champions.

Outcomes

Aim 1

Feasibility is the degree to which the VR treatment can be successfully integrated within the flow of usual care [13]. Feasibility will be measured with a 6-item survey based on the Consolidated Implementation Framework [44] that will be administered to 10 clinical staff using Research Electronic Data Capture (REDCap). Tolerability refers to the prevalence of patient-reported physical (eg, vertigo, nausea, cybersickness) and emotional (eg, fear, anxiety) adverse effects of the VR treatment, along with any discomfort or inconvenience related to the VR equipment (eg, ill-fitting headset, facial discomfort, inability to explore the 3D environment fully due to limited mobility) [32,38]. Tolerability data (complaints and adverse events frequencies) will be extracted from detailed meeting minutes where such events are reported and discussed.

Aim 2

Primary Measures

Hand dexterity will be measured using the Action Research Arm Test [45,46]. The 19-item Action Research Arm Test is a validated assessment of upper extremity limitations across 4 activity subdomains as rated by a clinician: grasp, grip, gross movement, and pinch [45]. Items are summed for each subscale with higher scores indicating more normal levels of functioning. The minimal clinically important difference (MCID) for chronic pain is a 5.7-point reduction from baseline [45,46]. Neurologic recovery will be measured using the FMA-UE [47]. The FMA-UE is a clinician-administered assessment of impairment in upper extremity motor functioning across multiple domains, including upper extremity, wrist, hand, and coordination/speed.

Items are summed for each subscale with higher scores indicating greater improvement in functioning. The MCID for the FMA-UE subscales is 4.25-7.25–point reduction from the baseline [47].

Secondary Measures

The Intake and Discharge Questionnaires from the Pain Outcomes Questionnaire-VA (POQ-VA) will be utilized to assess pain-related treatment outcomes [48]. Specifically, we will use a pain numeric rating (intake item 12, discharge item 2) scale of 0 (no pain at all) to 10 (worst possible pain). Identical pain numeric rating scales are well-validated in the literature, but we were unable to identify the MCID for pain within a poststroke population.

Analyses

A data set was used during the first month of the study by using Microsoft Excel software as Excel is easily imported into the statistical analysis system for analysis. We have chosen to use Excel on our local research server rather than VINCI because this is a prospective cohort of new admissions and a relatively small sample. Data will be collected and entered into the database by the project manager. Data entry will be verified by the principal investigator. Data will be stored on the secure JAHVH Research Service R-drive. With the proposed pilot study design, the overall analytic goals are to (1) determine the feasibility and tolerability of using a therapeutic VR platform in an inpatient comprehensive stroke rehabilitation program and to (2) estimate, with reasonable precision, the effect sizes of upper extremity neurologic recovery, hand dexterity, and pain reduction outcomes.

Aim 1

Qualitative descriptive analyses [49] will be used to address RQ 1.1 (feasibility) and RQ 1.2 (tolerability). For RQ 1.1, responses will be downloaded from REDCap. The 6 survey items address 3 feasibility constructs: adaptability, patient need, and staff comments. Responses for each construct will be pasted into an excel spreadsheet—one tab for each construct. Responses will then be grouped by similar content. Results will be reported as themes and subthemes. Similarly, for RQ 1.2, patient concerns, complaints, and adverse events associated with use of the VR platform will be abstracted from the research team meeting notes and will be tabulated. Responses will then be grouped by similar content. Results will be reported as themes and subthemes. Note that all adverse events will be immediately reported per VA and institutional review board policy. The analyses described here are for dissemination purposes.

Aim 2

For RQ 2.1, the primary outcomes will consist of preintervention to postintervention changes on 2 physical measures of stroke recovery: the Action Research Arm Test [45] and the FMA-UE [47]. Both of these measures are scored on a continuous scale,

as is the outcome of pain, as listed in Table 1. Therefore, the initial step will be to examine the distributions of each outcome measure, including the distribution in the change of scores from preintervention to postintervention. To estimate effect sizes over 4 weeks with the use of the VR platform, standardized effect sizes and 95% CIs will be calculated using the within-group pretest/posttest design described by Morris and DeShon [50] and Kadel and Kip [51]. Considering that this is a pilot study design, which can have a potential type I error due to multiple outcomes evaluated, the confidence intervals for the 2 coequal primary outcomes will be evaluated with a type I error rate of 0.025 (ie, to determine if the confidence interval for the outcome difference scores includes the null effect size value of 0); secondary outcomes will be evaluated with a type I error rate of 0.01. The above confidence interval approach parallels the use of a paired two-sided t test to determine statistical significance.

For RQ 2.1, since the effect sizes to be calculated are standardized measures, corresponding results across these outcomes will be directly comparable. However, these metrics do not necessarily translate to meaningful clinical differences (improvements). Therefore, for those outcome measures with published metrics for MCID [52], results of the VR platform will be compared across outcomes. As listed in Table 1, the measures of dexterity and neurologic recovery have published references for MCID, whereas we are unaware of a published MCID for POQ-VA. Therefore, for POQ-VA, we will first determine the change (prescores versus postscores) in standard deviation units (from the baseline value) that denotes MCID for the measures of dexterity and neurologic recovery. We will then average these 2 calculations of standard deviation units to estimate the magnitude of change in prescores to postscores on the POQ-VA that may approximate MCID on this measure. Thus, in addition to the comparison of standardized effect sizes across the 3 outcomes measures, all 3 measures will be compared in terms of proportion of subjects who experience MCID.

Results

This study was selected for funding by VA RR&D in August 2020. The approval for the study from the University of South Florida Institutional Review Board and the JAHVH R&D Committee (Protocol STUDY001075) was received in October 2020. The project start date was December 2020. All VR equipment for this study has been purchased and inventoried. Clinical staff are currently being trained to use the VR equipment in the clinic. The United States Veterans Health Administration has issued a moratorium on all in-person VA research activities secondary to COVID-19. Data collection will commence once this moratorium is lifted and will follow the projected study timeline presented in Figure 3.

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Figure 3. Study timeline.

Task	Person(s) responsible		Year 1				Year 2			
			Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Institutional review board, research and development	T, PM	▓								
Train staff	T, PM, K, F	▓	▓							
Enroll subjects	T, PM, RT		▓	▓						
Train patients	PM, RT		▓	▓						
Data collection/intervention	T, PM, RT		▓	▓	▓	▓	▓	▓	▓	
Analyze data	M, F, W									▓
Disseminate findings	T, W, F, RT									▓

T: Dr. Tran; F: Dr. Fowler; W: Dr. Winkler; K: Mr. Kaplan; M: Marszalek; PM: project manager; RT: research team.

Discussion

Overview of This Study

If the aims of this research are achieved, VR will be used in combination with established pain management strategies to improve neurologic recovery and hand dexterity and to decrease pain. The short-term goal of this project is to determine the feasibility of conducting an RCT to determine the effectiveness of using VR as an adjunct to usual care therapy to enhance upper extremity neurologic recovery and hand dexterity and to decrease pain. Our long-term goal is to provide veterans with an exercise and pain reduction modality that can serve as an adjunct to scheduled therapy and assist with the clinic to home transition. VR has the advantage of being easily implemented both within VA health care settings as well as veterans' own residences, where engagement in ongoing self-management approaches is often most challenging [32,42].

Potential Limitations and Strategies

As this pilot study will employ a within-subject design to evaluate the magnitude of stroke rehabilitation over 3 weeks with the use of VR technology, there will be no control condition to judge rehabilitation results to that which might be expected from time alone and natural history of stroke recovery. Therefore, as described for RQ 2.1, we will place a premium on evaluating rehabilitation results by using MCID, which is highly relevant to patients and generally would not be expected to be achieved simply from time alone (4 weeks).

Dissemination

Dissemination will be led by the principal investigator. Channels for dissemination include (1) annual progress and final summary reports to VA RR&D service, (2) bulleted briefings to our Program Partner, (3) presenting findings at national and local research meetings/conferences and VA cyberseminars and Military Health System Speaker series, and (4) submitting manuscripts to relevant peer-reviewed journals.

Conclusion

Examining the feasibility of this immersive VR intervention will be beneficial for veterans, clinicians, and policy makers. The health care market size of extended reality (ie, VR, augmented reality) technology utilization is projected to grow from nearly US $2.1 billion in 2019 to roughly US $8-11 billion by 2026-27 [53,54]. Despite this exceptional growth, published VR research to date often does not extend beyond pilot trials and case studies. Given the lack of large-scale RCTs examining the clinical effectiveness of immersive VR for poststroke rehabilitation, evidence from this pilot trial presents a key step to inform a larger multi-site trial.

Conflicts of Interest

None declared.

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Abbreviations

EVREST: Efficacy and safety of nonimmersive Virtual Reality Exercising in Stroke
FMA-UE: Fugl-Meyer Assessment of Motor Recovery after Stroke-Upper Extremity
HMD: head-mounted display
JAHVH: James A Haley Veterans' Hospital
MCID: minimal clinically important difference
POQ-VA: Pain Outcomes Questionnaire-Veterans Affairs
RCT: randomized controlled trial
REDCap: research electronic data capture
RQ: research question
RR&D: rehabilitation research and development
VA: Veterans Affairs
VINCI: Veterans Affairs Informatics and Computing Infrastructure
VR: virtual reality

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<u>Protocol</u>

Improving Medication Adherence Through Adaptive Digital Interventions (iMedA) in Patients With Hypertension: Protocol for an Interrupted Time Series Study

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Abstract

Background: There is a strong need to improve medication adherence (MA) for individuals with hypertension in order to reduce long-term hospitalization costs. We believe this can be achieved through an artificial intelligence agent that helps the patient in understanding key individual adherence risk factors and designing an appropriate intervention plan. The incidence of hypertension in Sweden is estimated at approximately 27%. Although blood pressure control has increased in Sweden, barely half of the treated patients achieved adequate blood pressure levels. It is a major risk factor for coronary heart disease and stroke as well as heart failure. MA is a key factor for good clinical outcomes in persons with hypertension.

Objective: The overall aim of this study is to design, develop, test, and evaluate an adaptive digital intervention called iMedA, delivered via a mobile app to improve MA, self-care management, and blood pressure control for persons with hypertension.

Methods: The study design is an interrupted time series. We will collect data on a daily basis, 14 days before, during 6 months of delivering digital interventions through the mobile app, and 14 days after. The effect will be analyzed using segmented regression analysis. The participants will be recruited in Region Halland, Sweden. The design of the digital interventions follows the just-in-time adaptive intervention framework. The primary (distal) outcome is MA, and the secondary outcome is blood pressure. The design of the digital intervention is developed based on a needs assessment process including a systematic review, focus group interviews, and a pilot study, before conducting the longitudinal interrupted time series study.

Results: The focus groups of persons with hypertension have been conducted to perform the needs assessment in a Swedish context. The design and development of digital interventions are in progress, and the interventions are planned to be ready in November 2020. Then, the 2-week pilot study for usability evaluation will start, and the interrupted time series study, which we plan to start in February 2021, will follow it.

Conclusions: We hypothesize that iMedA will improve medication adherence and self-care management. This study could illustrate how self-care management tools can be an additional (digital) treatment support to a clinical one without increasing burden on health care staff.

Trial Registration: ClinicalTrials.gov NCT04413500; https://clinicaltrials.gov/ct2/show/NCT04413500

International Registered Report Identifier (IRRID): DERR1-10.2196/24494

KEYWORDS

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Introduction

Overview

Hypertension is a common, dangerous, and treatable but undertreated condition worldwide and has a prevalence of approximately 30% in adults [1]. It becomes more common in more advanced ages, and the prevalence increases to 60% in persons over 60 years of age [2]. However, about 33% of persons with hypertension are unaware of their condition [2-4]. The incidence of hypertension in Sweden is estimated at approximately 27% [5]. Although blood pressure (BP) control has increased in Sweden, barely half of the treated patients achieved adequate BP levels [6].

Hypertension causes increased mortality and morbidity, most often by congestive heart failure, ischemic heart disease, and ischemic and hemorrhagic cerebrovascular insults [7]. Hypertension is also associated with increased occurrence of peripheral vascular disease and chronic kidney disease [8,9].

According to the National Board of Health and Welfare in Sweden [10], support and motivation for lifestyle changes as well as for self-care management are the first options when a person is diagnosed with hypertension, that is, having a systolic BP >140 mm Hg and diastolic BP >90 mm Hg measured repeatedly several times (3-6) over weeks or months, after 5 minutes of rest, while sitting with the right arm at heart level [10-12].

Lifestyle changes such as reducing weight, quitting smoking, reducing alcohol, and increasing physical activity are usually supported by visits to the district nurses individually or in groups in order to lower the BP. The support consists of educational and behavioral strategies to motivate and facilitate the person to conduct lifestyle changes in daily life [10]. If the lifestyle changes do not give results in lowering the person's BP, medication treatment is required.

Low Adherence to Medication

The World Health Organization defines adherence to long-term therapy as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds to agreed recommendations from a health care provider" [13]. In this work, we focus specifically on adherence to a medication regimen to improve BP control.

Although there are several effective medications that prevent cardiovascular events, persons can have poorly regulated BP. The main reasons for poor regulation of BP include patients' lack of adherence to treatment and a lack of monitoring and intervention on the part of the doctor [2,14,15].

Adherence to the medication has been shown to be deficient. As an example, an analysis of pharmacy records has demonstrated that less than 50% of the study population had collected prescribed medications intended for hypertension [2]. Adherence to treatment is affected by many factors, including polypharmacy (ie, the number of tablets prescribed for hypertension), practical difficulties (eg, managing treatment costs, forgetfulness), and personal impressions affecting adherence (eg, side effects of medications) [16].

Factors Affecting Adherence

Previous studies have linked both intrinsic and external factors to low or poor medication adherence (MA). Intrinsic factors include demographics such as age and income [17,18]. Psychological determinants include perceived susceptibility [19,20] and trust in the care provider [21,22], and behavioral factors include forgetfulness [19,23], employment, and travel [23]. External factors include the number of medications prescribed [18], availability of prescribed medication [23], and family support [18].

Intervention Strategies That Improve Medication Adherence

A person's adherence can be improved by affecting the person's habit patterns in concurrence with the medication administration [24]. With BP monitoring at home, provision of adequate feedback, and improvement of cooperation between the person and health care personnel, the likelihood of the person retrieving their medication at the pharmacy increases [25].

There are several recommended approaches to address MA. Education strategies directed to the person have been shown to be of great importance [26]. Several studies have reported that health literacy levels may predict MA [27-29]. Behavioral strategies are important interventions to improve adherence to medications [26,30]. These strategies can vary and include unit-dose packaging, self-monitoring of medication, self-monitoring of symptoms or side effects, reminders, and other cues to action such as associating medication-taking with other daily activities.

Educational and behavioral strategies are highlighted in guidelines but are lacking in how to support the persons to improve MA [30]. In general, interventions successful in improving BP control and increasing MA are ones that improve awareness of and involvement in the treatment [31].

Digital Interventions for Medication Adherence

Modern technologies make it possible to reach a vast number of persons using few personnel resources. With the widespread use in Sweden of the Internet and smartphones (93.1% internet penetration [32]), there are opportunities to use digital interventions, in specific to support people with hypertension on a wide scale and at low cost.

The authors have performed a systematic review recently on studies that applied digital interventions in order to improve BP and MA during the past decade [33]. The results show that digital interventions were effective in that regard, and the main targeted behaviors to change were lifestyle management, medication intake, self-measurement, and patient-provider interaction.

Problem Formulation

Despite the availability of effective medications and the prior success of digital interventions, nonadherence to medications still remains a problem for some persons with hypertension. One of the common limitations of digital interventions is that they may be effective in changing the user's current behavior but cannot adapt to the user's changing needs over time. Most of the existing digital interventions provide a general solution

for their users, and the user himself or herself is responsible for finding the right information or intervention. These digital interventions generally do not consider the barriers causing patients' nonadherence (and other related behaviors) and their needs over time.

In a previous paper [33], the authors revealed the need to design a multifaceted digital intervention that can be personalized according to one or more patient behaviors that need to be changed to overcome the key determinant or determinants of low adherence to medication or uncontrolled BP among patients with hypertension, considering different levels including patient and health care team and system involvement.

The aim of this study is to design, develop, test, and evaluate a tailored digital intervention, to be delivered through a mobile app, to increase MA and self-care management for persons with hypertension.

Methods

Study Design

The design of the study is influenced by the intervention mapping technique [34], which is used for the design and development of health promotion programs. We decided to accomplish such a big study in smaller steps, as follows.

Systematic Review

We first conducted a systematic review in order to detect the determinants, behaviors to change, and implemented digital strategies in previous studies [33]. The literature review included key determinants for MA among persons with hypertension. From this review, we have extracted a list of target behaviors and psychological determinants to create an encompassing Matrix of Change Objectives. It reviews digital interventions for persons with hypertension in order to determine which intervention strategies have been employed previously for each combination of behavior and determinant in the Matrix.

Focus Groups

We conducted focus groups to ascertain the needs of persons with hypertension in a Swedish context and in relation to the findings of the conducted systematic literature review. The focus groups helped us to determine whether literature findings are applicable to our target population in a Swedish context, whether some key factors must be added or removed from our Matrix of Change, and whether the identified intervention options are applicable and in which order of preference. We will also conduct focus groups after the pilot study to verify the participants' comprehension of the 16-item Maastrict Utrecht Adherence in Hypertension (MUAH-16) questionnaire regarding MA for hypertension (see Distal Outcomes), translated to Swedish, and also to perform the usability test for the mobile app.

App Design

Through what has been learned with the above findings, adaptive digital interventions are designed and developed to be delivered via mobile app.

Pilot Study

The pilot intervention will be conducted in order to evaluate the feasibility and usability of the proposed app for 2 weeks with the same group that attended the focus groups.

Longitudinal Study

The longitudinal study is designed to assess the effect of the proposed adaptive digital interventions delivered through the mobile app with individuals with hypertension for 6 months. The design is proposed to be an interrupted time series approach, which is considered to be the strongest quasi-experimental design that can be used to evaluate the effectiveness of an intervention [35,36]. The interrupted time series designs start to collect outcome measures before, during, and after intervention steps. Therefore, they are supposed to capture the level and any trend changes of one or more outcomes through time.

We will keep track of multiple variables for each participant through time and try to deliver the right intervention to the right person through patient-reported measures and app usage.

Two arms are considered in this design: One arm receives digital intervention. We will also add a nonequivalent no-treatment arm. This control group will be picked out of the group of patients who fulfilled the inclusion criteria and for whom the only criteria that are available for comparison is the primary MA (ie, pickups from the pharmacy). The reason to add this control group is to be able to address the internal validity threat [37]. By adding the control group, the effect of history is mitigated, and the study is strengthened against other threats to internal validity such as maturation (does the MA improvement occur naturally over time?).

Recruitment

The study will be performed in Region Halland, Sweden, as it is a collaborative project between Halmstad University and Region Halland. The organization of the health care system in Sweden is designed so that primary care centers are the main actors and there are district nurses to take care of people with high BP registered in each primary care center. There is an integrated electronic health data system available in Region Halland that facilitates the recruitment process.

First, the primary care centers are strategically chosen, and the responsible heads of the primary care centers receive information regarding the project. Through access to the integrated medical data given the ethical approval, we will select the potential pseudonymized persons with hypertension according to the inclusion criteria described below. Then, staff at Region Halland with authority and access to the integrated medical data will reveal their identities. The contact information will be sent to a district nurse working in this study, who will send invitation letters to each eligible person. The letter will contain information about the purpose, that the research objective is to develop an interactive app for persons with hypertension, methodology for the project, instructions explaining how to join, and the informed consent. It will be clearly stated in the invitation letter that participating in the

project is voluntary and does not affect the process of treatment in the primary care center.

A week after, the nurse contacts them by telephone regarding participation in the project. The eligible persons are asked to join the project for the first step of the project (focus groups) and will also be invited to join the second step of the project (pilot intervention) and, if wanted, (only) the third step (longitudinal study). Furthermore, being able to speak and understand Swedish and having their own smartphone will also be inclusion criteria that is checked by the nurse.

Inclusion Criteria

The inclusion criteria are as follows: (1) aged 40-70 years; (2) have hypertension diagnosis (ie, International Classification of Diseases, Tenth Revision [ICD-10] codes from I10 to I16 in the person's medical history) for 1 year or more and have prescribed medications; (3) know Swedish, both spoken and written; and (4) have own smartphone.

Exclusion Criteria

In order to alleviate the factors that might affect MA and make it hard to see the effect of the intervention, the following exclusion criteria were applied based on experts' knowledge: (1) receiving medication with unit-dose packaging (Apodos); (2) previous stroke; (3) myocardial infarction; (4) psychological disorder or cognitive impairment (ie, ICD-10 codes F01 to F99); (5) pregnancy-induced hypertension; (6) insulin treatment; or (7) kidney disease defined as glomerular filtration rate <60 mL/min.

Apodos directly affects MA, especially for the patients with polypharmacy. Psychological disorders or cognitive impairments also affect MA directly due to forgetfulness and other factors related to their disease. We believe this type of patient needs specific types of interventions and should not be included in this study. Patients with psychological disorders (ICD-10 F01-F99) will first be excluded based on their medical health records. Patients with any occurrence of these diagnoses, anywhere in their histories, will be excluded. Additionally, though, there might be some cases of psychological disorders that are not registered in electronic health records as diagnoses. Hence, after the interested participants show up, we will also contact the district nurse at the included primary care centers to detect and exclude if such cases exist in the interested participants. Pregnancy-induced hypertension is partially excluded already, since we included only patients who already have at least 1 year of hypertension. The other exclusion criteria (ie, previous stroke, myocardial infarction, insulin treatment, and kidney disorders) were suggested by clinicians to exclude due to having other complications and treatment plans that might

interfere with MA. Excluding all, we have around 12,000 individuals with hypertension in Region Halland who may be interested in participating.

Data Collection and Analysis

Focus Groups

In the focus groups (both the ones conducted for needs assessment and the ones for testing the usability and the translated MUAH-16 questionnaire), approximately 6-8 persons with hypertension per group are included in a total of 4-5 groups. The focus groups last approximately 2 hours. Focus groups are chosen to generate a deeper meaning with varying views through group discussions [38]. Due to the outbreak of COVID-19, the possibility of conducting online or telephone focus groups with 2-4 participants is also considered to avoid any possible infection threat in face-to-face focus groups. In order to measure and describe the participants' acceptability and usability testing and app usage, a semistructured interview guide will be developed based on a mobile health app usability questionnaire [39] (with 3 subscales: ease of use, interface and satisfaction, usefulness). The data from the focus groups will be analyzed with qualitative content analysis and a manifest approach [40].

Longitudinal Study

The data from the participants in the study are sent through their mobile app to the server, where all the participants' data is stored. All the data from the participants are collected via self-reports and their hypertension-relevant information in the aggregated health database. The only item that we measure without the participants' engagement is if they have seen the intervention and how long it took to answer the questions. This information is used to measure the user's fatigue and intervention retention and will be used to adapt the interventions.

The effect of the intervention is analyzed statistically using segmented regression analysis, testing for changes in both the level and the trend of the outcome.

Intervention Design

The design of the digital intervention module is considered to follow the just in-time adaptive intervention framework (JITAI). JITAI is an intervention design aiming to provide the right type and amount of support at the right time by adapting to an individual's context [41]. It has potential for promoting health behavior change, which in our study is supposed to be MA. The conceptual model of JITAI, including all its components, is shown in Figure 1 (borrowed from Nahum-Shani et al [41]). We explain the details of the intervention design following the JITAI conceptual model.

Figure 1. Conceptual model of just-in-time adaptive intervention components.
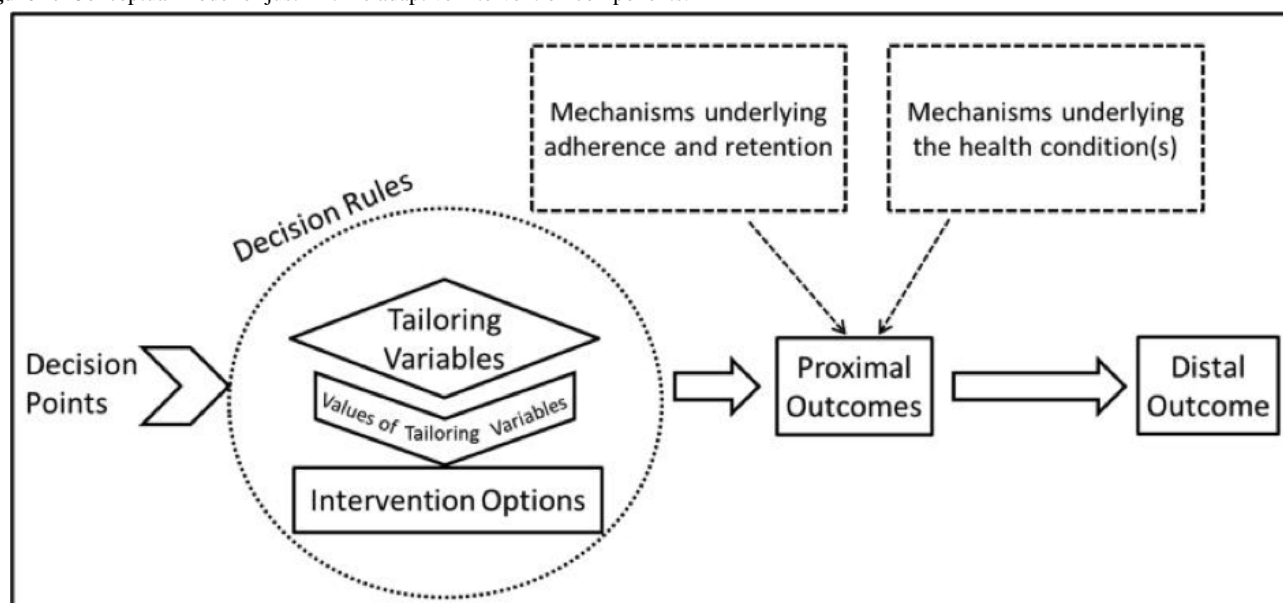
Intervention Options

Intervention options are a set of possible interventions that are going to be delivered at decision points. In JITAI, intervention options can be various types of support (information, advice, feedback, etc), source of support (mobile, nurse, physician, etc), amounts of support (intensity, dose, etc), and type of media or channel (phone call, SMS text messaging, etc).

From the conducted literature review, we summarized all types of digital interventions delivered to individuals with hypertension as follows: (1) reminders for medication intake (daily or several times per day depending on the antihypertensive medication plan), reminders for BP measurement (every 3 months), and reminders for physical activity (biweekly); (2) informational contents regarding hypertension and all its facts, consequences, treatments, risks, medications and side effects, lifestyle, and so on (text, videos, etc)—the prepared interventions will be based on health care professional advice plus the reference of webpages for further readings; (3) trends on medication intake, physical activity, etc in a feedback motivational message—based on the recent activity of the user, a feedback motivational message is sent biweekly; and (4) motivational messages—the relevant messages are phrased in a motivated manner (eg, regarding smoking, a message like "Treatment of high blood pressure has a much better effect if you do not smoke.").

Distal Outcomes

Distal outcome is the ultimate goal that the intervention is trying to achieve. In iMedA, we considered primary and secondary distal outcomes. Primarily, we aim at improving MA. Then, in the long term, BP is considered as a secondary distal outcome along with increased quality of life [42], assessment of the lifestyle behavior (smoking, alcohol consumption, physical activity, and food intake) [10], and communicative and critical health literacy [43].

In order to measure MA, we consider the following:

1. Self-reported medication intake through the mobile app is supposed to be collected every day.
2. MUAH-16 [44] is measured before and after the intervention. It is a MA questionnaire for hypertension. It consists of 16 items with four factors: (1) positive attitude towards health care and medication, (2) lack of discipline, (3) aversion toward medication, and (4) active coping with health problems. The items are on a 7-point Likert scale (1=completely disagree to 7=completely agree). A previous study [44] had found correlations between adherence and the MUAH-16 score. Specifically, they found that higher scores in subscale 1 correlated positively with adherence, and higher scores on subscale 2 correlated negatively with adherence.
3. Pickups from pharmacies will be collected after the intervention is finished.

BP is to be measured once before the start of the intervention, at 3 months, and then at 6 months by the recruited nurse.

Health literacy will be measured by the Swedish Communicative and Critical Health Literacy scale. It consists of 5 items with a 5-point Likert scale [43]. Health status will be measured by EQ-5D (EuroQol 5-Dimension questionnaire). It consists of 5 areas for covering health, with 5 response alternatives and 1 overall question regarding health (EQ-VAS [EuroQol visual analogue scale] with score range of 0 to 100) [42]. Both will be measured before and after the intervention.

Proximal Outcomes

Proximal outcomes are the short-term goals of the interventions. They can be mediators, intermediate measures, or both for the distal outcomes. The medication intake is considered to be the main proximal outcome, which is measured daily. The physical activity rate, which is measured weekly, is another proximal outcome.

Since most of the contents are educational, and they try to increase the hypertension knowledge of the participants, we will add a proximal outcome to measure how much their

knowledge has increased. We consider two methods to measure it. First, after showing the content, we will ask "Did you know...?". Second, we will design simple gamification tests to be presented to the participants biweekly.

To prevent poor adherence to the interventions, it is recommended to define a few proximal outcomes related to intervention engagement and fatigue. Therefore, we consider the number of clicked interventions, dwell time, number of watched videos, and like/dislike feedbacks for each intervention as proximal outcomes related to intervention adherence and retention.

Tailoring Variables

Tailoring variables are information about the participant that is used to decide when to provide which intervention. In other words, they are used to personalize the interventions and make them adaptive to the individual's circumstances. All proximal outcomes can serve as tailoring variables. They can be measured actively, passively, or both. Active assessments require an individual's engagement in measuring, for example through self-reports, while passive assessments require minimal or no individual engagement, for example through a mobile phone's sensors.

From baseline information, we can select a few tailoring variables, including alcohol consumption, smoking, specific diet, age, and gender, in order to personalize the interventions. These are considered to be hard-pruning because, with the help of these baseline tailoring variables, a set of intervention options are ruled out from the beginning. As an example, if the person is a nonsmoker, there is no need to motivate him or her to quit smoking.

From the MUAH-16 questionnaire, we start to learn more about an individual's beliefs, barriers, and behavior about MA. It has 4 subscales regarding (1) positive attitude toward health care and medication, (2) lack of discipline, (3) aversion toward medication, and (4) active coping with health problems. Each subscale contains 4 questions. At the beginning of the intervention, MUAH-16 questions are used as tailoring variables. Then, during the intervention period, and based on the previously delivered informational contents to the individual, the answers to "Did you know...?" questions will be used as tailoring variables.

Decision Rules

Decision rules are the adaptation engine of JITAIs. They are used to determine which intervention option to deliver to whom and when. They are the links between intervention options and tailoring variables. Operationally, a JITAI includes a sequence of decision rules (ie, treatment policies) that take the individual's current context as input and specify whether an intervention should be delivered now and what intervention should be delivered [45].

Decision rules in iMedA will be probabilistic rules from experts modified by "suggestions" from reinforcement learning [46]. Reinforcement learning is used to continuously learn and optimize the treatment policy in JITAI as the individual experiences the interventions. It automatically "discovers" which interventions are most successful for which patients by using statistical machine learning methods.

Since we are using an interrupted time series design, we will consider the first 14 days after the app installation to be the preintervention phase (ie, data collection). Figure 2 shows the flowchart of these initial 14 days in more detail.

Figure 2. An illustration of the preintervention step (ie, the first 14 days). HL: health literacy; MUAH-16: 16-item Maastricht Utrecht Adherence in Hypertension; QoL: quality of life.
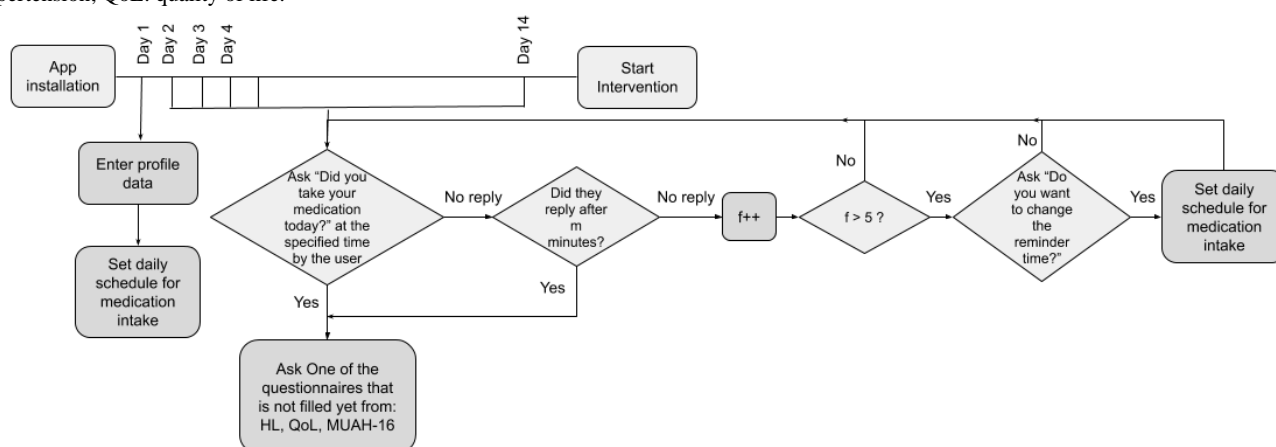
At the beginning of the intervention delivery, the JITAIs will be delivered based on expert suggestions, taking into account the answers to the initial questionnaires, to provide baseline data that a reinforcement learning agent can use to improve upon without the necessity for a warm-up period characterized by random interventions. To allow the agent to learn effectively from collected data, the expert decision rules will be defined in a probabilistic manner, allowing off-policy evaluation. The agent will be built upon a contextual bandit framework that uses tailoring variables to adaptively suggest interventions to improve proximal outcomes and, ultimately, distal outcomes. The agent will optimize the decision rules on a biweekly basis, allowing evaluation before deployment, as illustrated in Figure 3.

Figure 3. An illustration of the intervention phase. PA: physical activity; RL: reinforcement learning; RP: random policy.
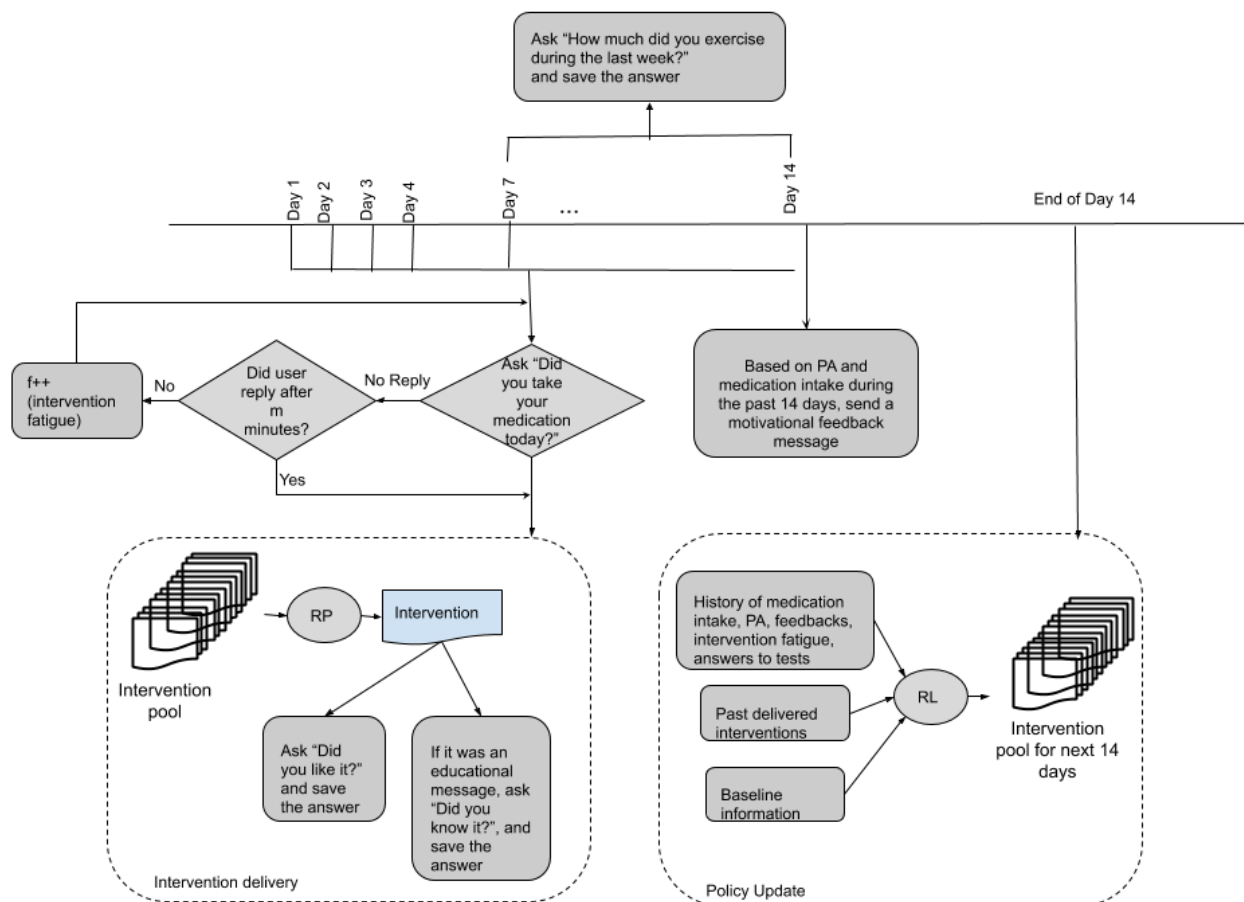
Contextual Bandit Formulation

The decision rules update is scheduled every 14 days, and the policy (decision rules) remains unchanged during the 2 weeks between each update. With the previous data (tailoring variables, interventions, query-responses) collected, the agent's policy is updated to personalize interventions for individual patients. We formulate the learning of an optimal policy for a given patient as a stochastic contextual bandit problem. Traditionally, the problem is specified by a tuple (S, A, R) where S is the context space (tailoring variables), A is the finite action-space (number of interventions), and R is the rewards (query-responses). Only rewards of the chosen action are known to the agent at a decision point; rewards of other actions are unknown. Through interactions with the patient, at every decision point at time t, the agent has a sequence of tuples $D = \{(S_0, A_0, R_0), (S_1, A_1 R_1), \ldots, (S_{t-1}, A_{t-1}, R_{t-1})\}$ available to make decisions. D is known as the interaction history, containing the context and actions (interventions) chosen by the agent as well as reward received up until $t-1$.

We make several simplifying assumptions necessary for optimal learning:

Assumption 1

The stochastic bandit formulation assumes identically and independently distributed contexts, therefore action A_t does not affect the distribution of future contexts S_τ for $\tau > t + 1$.

In simpler terms, the agent does not affect the contexts (tailoring variables) we observe from patients. The effect of each intervention is limited in time, such that we can adjust to changes in behavior gradually.

Assumption 2

The expected reward (query-responses) of an action (intervention) can be modeled by an arbitrary (often linear) function $f: S \times A \rightarrow R$ for all t such that the expected (average) reward for an action in a particular context can be predicted as:

In our formulation, we assume that the context allows an informative mapping from contexts and actions to reward (ie, the reward we would receive for an intervention can be predicted and therefore allows the optimal action to be selected for a particular context).

We cast the learning of function $f(\cdot)$ as a binary classification problem where the probability outputs directly correspond to the expected reward given context S_t and action A_t. At every decision point t, the agent follows a greedy action selection strategy, that is, the agent selects action A_i with the highest predicted reward $f(S_t, A_i)$ given the current context:

$$A_t = \pi_B(S_t) \ (2),$$

where π_B is greedy policy, defined as .

To facilitate occasional exploration, action A_t is chosen by an ε-greedy strategy that randomizes action selection irrespective of current context with probability $ε ∈ (0,1]$. At each time step, either a random action (with probability ε) or the action with the maximum predicted reward (with probability 1−ε) is chosen.

Policy Update

The policy $π_B$ is updated every 14 days using the data collected by the agent thus far by estimating the parameters of function $f(S, A)$. To evaluate new and better policies before deployment, we use importance sampling in combination with the updated reward predictor $f(S, A)$ to estimate the expected reward under the new policies. More formally, given a policy $π_B$ used to collect the past data D and the current tuple (S_t, A_t, R_t) forming data set $S = D ∪ (S_t, A_t, R_t)$, we estimate the expected reward of target policy $π_T$ in combination with the updated reward predictor $f(S, A)$, using the doubly robust estimator [47]:

$$\boxed{\times}$$

where $I(π_T(S) = A)$ is an indicator function, being 1 if action A is chosen under target policy $π_T$ and 0 otherwise. $\boxed{\times}$ is the probability of choosing an action under the old policy $π_B$, which is known. For a set of policies $Π$, we choose the policy that maximizes the average policy reward $\boxed{\times}$:

$$\boxed{\times}$$

The new policy $π_{new}$ is then deployed with the ε-greedy strategy.

Decision Points

A decision point is a time when an intervention decision is made. Considering the nature of JITAIs that are delivered through mobile devices, decision points occur much more rapidly than in standard interventions.

In iMedA, every day the intervention is delivered accompanied by the time of medication intake question (ie, "It is time to take your medication <medication name>. Did you take it today?"). If the patient has >1 antihypertensive dose per day, then the decision point will happen in only one of those reminders.

These daily interventions are chosen from a 14-day intervention list that the reinforcement learning agent has picked. However, the decision rules are updated every 2 weeks, meaning that the reinforcement learning agent will optimize the decision rules to be adapted to the patient's needs after 14 days of looking into the patient's behavior.

Sample Size

As a rule of thumb for an interrupted time series, 10 measurement points before and 10 measurements after an intervention provide 80% power to detect a change in level of 5 standard deviations (of the pre-data) only if the autocorrelation (ie, the extent to which data collected close together in time are correlated with each other) is greater than 0.4 [48].

According to simulations done in Liu et al [49], considering the trend change B3=0.1 (B2 + B3 = 0.25), where negative values for the parameters indicate a "decrease" (either level, trend, or both) after intervention, and positive values indicate an "increase" after intervention; autocorrelation >0.4; the Poisson time series; power >0.80; and statistical significance level of 0.05, we need at least 32 participants in the intervention group. Our plan is to recruit 100 participants to the longitudinal study, 50 in each arm due to attrition rate, specifically during the COVID-19 outbreak.

Results

We have started the focus groups, although the COVID-19 outbreak is a big roadblock at the moment. The design of the digital interventions is in progress, and the mobile app will be ready in November 2020. Then, we are planning to run the pilot study. After fixing all the probable modifications due to the pilot evaluations, the longitudinal study will then start in February 2021. We expect to publish the results of the analysis in mid-2021.

Discussion

Overview

This study plans to design, develop, test, and evaluate a mobile app that is personalized and adapted to persons with hypertension-specific needs and behavior in order to increase MA. To do so, it is essential that it is based on theoretical knowledge as well as in contextual settings. Therefore, we start with a literature review to identify these needs and focus groups with persons who will use it.

Conducting the focus groups in different ways, both face-to-face and digital (such as via Skype or telephone) due to the global COVID-19 situation, might create difficulties recruiting participants. Using digital means can also increase bias in the answers and therefore the data. The researchers will make an effort to encourage the participants to describe their experiences. When using digital means, fewer participants can be included each time, which can be positive for some, but it also has a risk of limited discussion [50]. Conversely, having large groups can have a negative impact on some participants' opportunities to speak [50]. However, using these digital means can also facilitate conducting the focus groups due to the COVID-19 situation.

Since MUAH-16 items have not been translated, tested, and used before in a Swedish context, we aim to perform the process of translation and adaption of this instrument following the World Health Organization guidelines [51]. The forward translation and expert panel back-translation steps have been performed. In order to run the pretesting and cognitive interviewing, to finalize the final version of MUAH-16, the focus groups will be conducted after the pilot study to discuss the items. During the pilot study, the participants are supposed to receive the MUAH-16 items and answer them via the mobile app.

Using focus groups both before and after, including persons with hypertension, will be a strength in the development of the content of the app. It has been stated in other focus groups with persons with hypertension that reminders in an app for MA could be of a positive nature, but on the other hand, their use

might cause anxiety [52]. This emphasizes the need to involve persons in the target group in order to develop a personalized app to strengthen self-care management.

Importance

The intended result of this study is to increase the knowledge of how an interactive app can support MA in persons with hypertension. With the increased limit of health care resources, it is important to use the rapidly growing digital technology to develop new ways of supporting this population as a complement to conventional care. Therefore, to design, develop, test, and evaluate an interactive app used for 6 months with different features is of interest to support persons with hypertension. With different features in an app that is formed as a personalized means of support, it can increase the users' MA as well as their likelihood to perform lifestyle changes. It is essential to develop features that are appropriate and feasible for the target population in order to conduct a larger study for evaluating the effect.

Ethical Considerations

This study has been split into smaller studies, for which ethical approval was given by the Swedish Ethical Review Authority (Etikprövningsmyndigheten) (2020/04399, 2019/04067, and 2018/294).

Conflicts of Interest

None declared.

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Abbreviations

BP: blood pressure
EQ-5D: EuroQol 5-Dimension questionnaire
EQ-VAS: EuroQol visual analogue scale
ICD-10: International Classification of Diseases, Tenth Revision
JITAI: just-in-time adaptive intervention
MA: medication adherence
MUAH-16: 16-item Maastrict Utrecht Adherence in Hypertension

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Protocol

Monitoring Health Care Workers at Risk for COVID-19 Using Wearable Sensors and Smartphone Technology: Protocol for an Observational mHealth Study

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Abstract

Background: Health care workers (HCWs) have been working on the front lines of the COVID-19 pandemic with high risks of viral exposure, infection, and transmission. Standard COVID-19 testing is insufficient to protect HCWs from these risks and prevent the spread of disease. Continuous monitoring of physiological data with wearable sensors, self-monitoring of symptoms, and asymptomatic COVID-19 testing may aid in the early detection of COVID-19 in HCWs and may help reduce further transmission among HCWs, patients, and families.

Objective: By using wearable sensors, smartphone-based symptom logging, and biospecimens, this project aims to assist HCWs in self-monitoring COVID-19.

Methods: We conducted a prospective, longitudinal study of HCWs at a single institution. The study duration was 1 year, wherein participants were instructed on the continuous use of two wearable sensors (Fitbit Charge 3 smartwatch and TempTraq temperature patches) for up to 30 days. Participants consented to provide biospecimens (ie, nasal swabs, saliva swabs, and blood) for up to 1 year from study entry. Using a smartphone app called Roadmap 2.0, participants entered a daily mood score, submitted daily COVID-19 symptoms, and completed demographic and health-related quality of life surveys at study entry and 30 days later. Semistructured qualitative interviews were also conducted at the end of the 30-day period, following completion of daily mood and symptoms reporting as well as continuous wearable sensor use.

Results: A total of 226 HCWs were enrolled between April 28 and December 7, 2020. The last participant completed the 30-day study procedures on January 16, 2021. Data collection will continue through January 2023, and data analyses are ongoing.

Conclusions: Using wearable sensors, smartphone-based symptom logging and survey completion, and biospecimen collections, this study will potentially provide data on the prevalence of COVID-19 infection among HCWs at a single institution. The study will also assess the feasibility of leveraging wearable sensors and self-monitoring of symptoms in an HCW population.

Trial Registration: ClinicalTrials.gov NCT04756869; https://clinicaltrials.gov/ct2/show/NCT04756869

International Registered Report Identifier (IRRID): DERR1-10.2196/29562

KEYWORDS

mobile health; app; mHealth; wearable; sensor; COVID-19; health care worker; frontline worker; smartphone; digital health

Introduction

Background

A novel coronavirus (SARS-CoV-2) causing severe respiratory illness (COVID-19) was first reported in a cluster of individuals in the city of Wuhan, Hubei Province, China on December 31, 2019 [1]. The cases quickly spread beyond Wuhan to other parts of China and to many other countries. In the United States, the first case of COVID-19 was confirmed in Washington State on January 19, 2020 [2]. By January 31, 2020, the World Health Organization declared the outbreak a Public Health Emergency of International Concern and a global pandemic by March 11, 2020. As of March 23, 2021, there were nearly 124.5 million confirmed cases worldwide and over 2.7 million deaths. More than 30.5 million cases and 556,000 deaths occurred in the United States alone [3].

COVID-19 is spread by human-to-human transmission via droplets or direct contact. The symptoms of COVID-19 infection appear after an incubation period of 5.5 days on average [4]. The most common symptoms at the onset of COVID-19 illness include fever, cough, and fatigue. In addition, muscle or body aches, headache, new loss of taste or smell, sore throat, and congestion have been commonly reported [5]. During the early months of the pandemic, much of the world's population faced government-mandated lockdowns to mitigate transmission. Social and behavioral science insights were being widely deployed in an effort to improve public health [6]. The most effective strategies to mitigate the spread of this novel viral respiratory illness were nonpharmaceutical—social distancing, quarantine, and isolation [7]. Indeed, data from the severe acute respiratory syndrome–related coronavirus outbreak in 2002 suggested that the psychosocial burden of these health measures including quarantine was wide-ranging, substantial, and long-lasting [8]. However, the magnitude of the COVID-19 pandemic was unlike any other in our lifetime, so the impact that these widespread lockdown strategies would have on health-related quality of life (HRQOL) was largely unknown [9].

Prior Work

Health care workers (HCWs) are at increased risk for many infections including COVID-19. A large-scale observational study from early in the pandemic found that HCWs were over 11 times more likely to report a positive COVID-19 test than the general population and still over three times more likely when that statistic was adjusted for increased testing frequency among HCWs [10]. Numerous studies have reported nosocomial outbreaks of COVID-19 affecting both patients and HCWs at hospitals and long-term care facilities throughout the United States [11-13]. Fortunately, health care facilities have implemented universal masking policies and increased their testing capacity as the pandemic has progressed; these practices have mitigated some of the risks of transmission to HCWs [14,15]. Despite these improvements, the efficacy of safety precautions is limited by compliance and availability of supplies, leaving HCWs at risk. Thus, monitoring HCWs for COVID-19 is critical for protecting HCWs themselves and for protecting their patients, their families, and the health care infrastructure overall.

In addition to the physical health consequences of COVID-19 infection, mental health consequences of the pandemic have been widespread. Stress, fear, and anxiety about novel contagious disease outbreaks, like COVID-19, can be immense among higher-risk groups, including HCWs and other frontline workers [16]. Being exposed to COVID-19 cases in hospitals while working, being quarantined and isolated, the death or illness of a relative or friend from COVID-19, and heightened self-perception of danger due to the lethality of the virus can all negatively impact the well-being and HRQOL of HCWs [4]. More research is needed on the best ways to support the physical and mental well-being of HCWs, particularly during a pandemic.

Study Purpose

Our research team recently developed the Roadmap 2.0 mobile health app, which includes positive psychology-based activities for users with the goal of enhancing well-being and HRQOL for family caregivers of patients undergoing hematopoietic cell transplantation (HCT) [17-19]. The mobile randomized trial in HCT caregivers is currently ongoing (ClinicalTrials.gov NCT04094844) [20]. The Roadmap 2.0 app is configured with the Fitbit application programming interface (API) [21], which enables the collection of continuous physiological data from a Fitbit watch. In addition to the Fitbit, our research team has been using a Food and Drug Administration–approved axillary temperature wearable sensor (TempTraq, BlueSpark Technologies Inc) for monitoring patients who are high risk for complications (eg, fever or cytokine release syndrome) during HCT and chimeric antigen receptor T-cell therapy (ClinicalTrials.gov NCT04051216). As the COVID-19 pandemic rapidly disrupted health care in the United States and worldwide, our research team adapted our technology, the Roadmap 2.0 app, to be used in the HCT and cellular therapy settings for the HCW population.

Herein, we provide a detailed description of the design for a longitudinal study to test the uptake and sustained use of the Roadmap 2.0 app with positive psychology–based activities over a 30-day period in HCWs (ClinicalTrials.gov NCT04756869). We postulated that simple and intentional pleasant activities combined with daily mood and symptom reporting and use of wearable sensors could be incorporated into routine HCW practices during the COVID-19 pandemic.

Methods

Study Design

Human Participants Approval

The first diagnosed COVID-19 case at Michigan Medicine—a large, tertiary academic health system in the Midwest—was on March 10, 2020. By March 13, 2020, Michigan Medicine modified its employment work schedules where only essential, frontline HCWs were allowed into its facilities. This study was approved by the Institutional Review Board (IRB) of Michigan Medicine (IRBMED HUM00180076) on April 20, 2020, and registered on ClinicalTrials.gov (NCT04756869). At the time, all clinical research studies underwent an initial review process by the University of Michigan Office of Research Committee.

Overview

This was a prospective study of HCWs at risk for COVID-19 at a single academic institution, Michigan Medicine. In this study, participants consented to wearing a Fitbit Charge 3 smartwatch and TempTraq temperature patches continuously for up to 30 days. They could also opt in to providing nasal swabs and saliva samples daily throughout the study period and blood samples up to 3 times throughout the year after study enrollment. Finally, they completed several surveys on the smartphone-based Roadmap 2.0 app; these surveys included a baseline survey, exit survey, daily mood surveys, and daily symptom surveys. After the 30-day study period, participants were asked to participate in a semistructured qualitative exit interview. Follow-up interviews are being conducted at 3, 6, 9, and 12 months after study completion (see Figure 1 for a schematic outline of the study procedures).

Figure 1. Study schematic. HCW: health care worker.
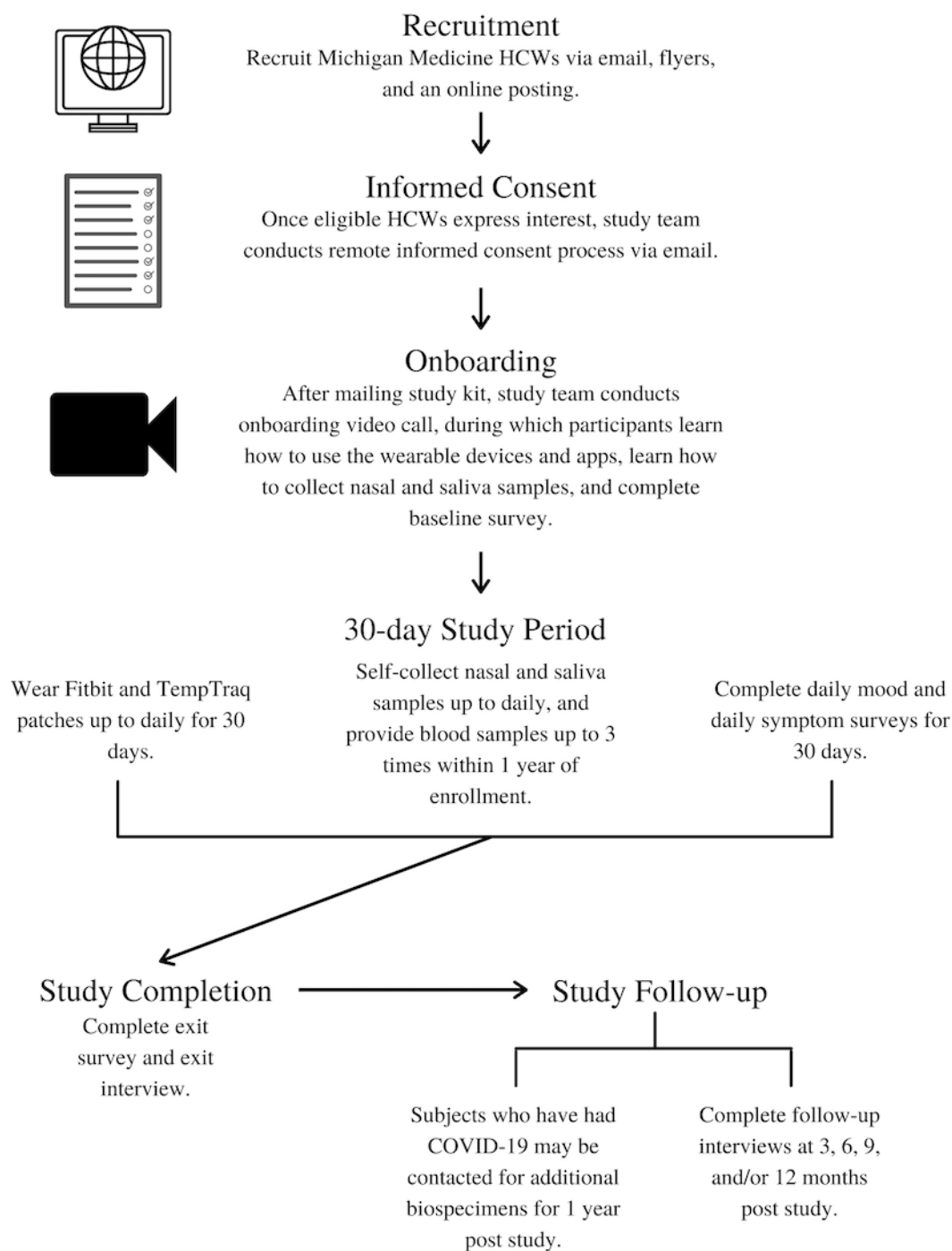
Objectives

The primary objective was to test the feasibility of using wearable devices in HCWs. Feasibility was defined as wearing the Fitbit Charge 3 at least 8 hours per day for at least 5 days per week (~40 hours/week or 160 hours/30 days) and wearing the TempTraq patch at least 8 hours per day for at least 5 days per week (~40 hours/week or 160 hours/30 days).

The secondary objective was to assess survey completion rate, estimating that at least 50% of participants would complete the baseline survey and exit survey, and at least 50% of participants would complete at least 50% of the daily symptom surveys.

The exploratory objective was to analyze continuous heart rate and temperature data from wearable devices alongside nasal swabs, saliva, and blood samples in HCWs to facilitate the eventual development of an early prediction and detection model for COVID-19 infections.

Participant Enrollment

Eligibility Criteria

Participants were required to be HCWs at Michigan Medicine who were aged at least 18 years at the time of enrollment. Additionally, they must have provided direct in-person patient care, or they must have worked in units where COVID-19 patient care occurred or was likely to occur (eg, medical assistants and custodial staff). The only exclusion criteria were unwilling or unable to comply with the study procedures or allow the study team access to health data.

Recruitment

The primary tools for recruitment were flyers, emails, and an online posting at UMHealthResearch.org. The study team distributed an IRB-approved recruitment flyer describing the study and providing the study team contact information. Emails containing this flyer were sent to relevant list servers, including House Officers (eg, residents and fellows). Finally, the team created an online posting at UMHealthResearch.org, through which many participants expressed interest in the study and communicated with the study coordinators.

Informed Consent Process

Due to COVID-19 restrictions at Michigan Medicine and other public health guidelines, informed consent was obtained remotely. Interested participants that contacted the study team received additional study information, including an IRB-approved electronic copy of the informed consent document via email. The study coordinators then provided real-time discussion of the consent via videoconference (eg, Zoom) or phone. After that discussion, the participant could sign the informed consent document and return it to the study team electronically via email.

Enrollment

Upon receipt of the signed informed consent document, the study coordinators assembled a study kit for the participant, including a Fitbit watch, TempTraq temperature patches, saliva kit, and nasal swab kit. They also included written instructions and shipping materials for collecting and returning the biospecimens. Finally, the study coordinators mailed study kits to participants via United Parcel Service.

After mailing study kits, study coordinators scheduled an *onboarding* video call with each participant. During the onboarding call, the study coordinators helped the participant download and log in to the study apps: Fitbit app, Roadmap 2.0 app, and TempTraq Patient app. Study coordinators reviewed how to use, charge, and sync the Fitbit watch, and how to use and place the TempTraq patches for accurate temperature readings. Study coordinators also reviewed nasal swab and saliva collection components. Finally, participants completed the initial 40-item baseline survey on their smartphones through the Roadmap 2.0 app during the onboarding video call.

Biospecimens

Nasal Swabs and Saliva Collections

The study team collected only one nasal and saliva sample from each participant. These samples were self-collected by the participants at home, using collection kits provided by the study team. We used Zymo DNA/RNA Shield Nasal Swab Collection Kits and Spectrum DNA Saliva Collection Kits [22,23]. Both of these kits have a preservative that not only preserves the RNA present in the sample but also inactivates any virus that may be present in the sample.

During the onboarding video call, study coordinators instructed participants on how to collect their nasal and saliva samples. For the nasal swab, coordinators instructed participants to insert the swab into each nostril until the tip was no longer visible. Participants were then instructed to twist the swab back and forth in each nostril. They were then to place the swab into a tube that contained a reagent to preserve the sample. For the saliva sample, coordinators first instructed the participant not to eat or drink for at least 30 minutes before collecting the sample. To collect the sample, participants were instructed to spit into the collection tube up to the fill line. They were then to pour a preservative into the collection tube and mix the solutions. Finally, participants were instructed to ship their samples to the Tewari Lab at Michigan Medicine within 24 hours of collecting their samples, using the provided biospecimen packaging and shipping supplies.

Blood Collections

Blood collections were an optional component of this study, and participants indicated their willingness to participate in during the consent. Blood draws could occur up to 3 times over the course of 1 year following study enrollment at any Michigan blood draw station in accordance with COVID-19 guidelines.

The primary goal of collecting blood samples was to determine antibody titers to SARS-CoV-2. The team was also interested in obtaining specimens for the measurement of other immunologic analytes (eg, immune cell profiles) and to do new biomarker discovery. We proposed to collect up to 50 mL of blood in ethylenediaminetetraacetic acid tubes, serum collection tubes, or in some cases tubes with specifically targeted preservatives (eg, Cell Preparation Tubes or Streck DNA or RNA tubes). Tubes would be stored and transported at room temperature for processing within the Tewari Lab.

Specimen Handling, Processing, and Storage

Because we did not know the COVID-19 status of participants in real time, we developed a standard operating procedure to ensure the safety of all lab members. In summary, lab staff wore personal protective equipment at all times while handling specimens (face mask, safety glasses, lab coat, and disposable gloves), and all work handling the sample's primary container was conducted in a biosafety cabinet. Lab surfaces were sprayed down with 70% ethanol, and UV light was turned on in the biosafety cabinet at the beginning of each day. For each sample received, the outside packaging was sprayed with 70% ethanol, and then the sample's primary container was sprayed with 70% ethanol as well. Decontaminated samples were labeled with a study ID and stored at –80 °C. At the end of each day, lab surfaces were again sprayed with ethanol, and UV light was turned on in the biosafety cabinet once more.

Wearable Devices

TempTraq Single Use Thermometer

TempTraq is a single use adhesive thermometer that continuously records axillary temperature data for 24 hours [24]. TempTraq has been tested to the American Society for Testing and Materials E1112-00 standard, which is required for all clinical digital thermometers. The temperature patch broadcasts continuous temperature data via Bluetooth 4.0 to the TempTraq mobile app. The current temperature is broadcast every 10 seconds, and the complete history of temperature data stored on the patch is broadcast every 2 minutes.

For this study, participants were asked to wear the patches continuously for up to 30 days. During the onboarding call, they were instructed on how to download and log in to the TempTraq Patient app, as well as how to properly apply the patches for accurate readings. Participants could view their temperature data in real time on their smartphone via the TempTraq Patient app. The complete TempTraq data is stored on the TempTraq Connect server for access by the study team using the TempTraq Clinician app.

Fitbit Charge 3

The Fitbit Charge 3 is a smartwatch fitness tracker that monitors various fitness metrics including steps, heart rate, and sleep. The Charge 3 device wirelessly connects to the patient's smartphone via Bluetooth Low Energy and uploads data to the Fitbit app every 15 minutes [25].

For this study, participants were asked to wear the Fitbit at least 40 hours per week for 30 days. During the onboarding call, they were instructed on how to download and log in to the Fitbit app. They were also instructed to connect their Fitbit to the Roadmap 2.0 app, which was used as an interface for the study team to access the participants' Fitbit data. The study team has access to the complete Fitbit data and can download it for analysis.

Surveys and Interviews

Surveys

All surveys were Qualtrics-based and were stored on Health Insurance Portability and Accountability Act (HIPAA)–compliant U-M secure servers through the Roadmap 2.0 app. Participants were not incentivized to complete the surveys; the only incentive for study participation was keeping the Fitbit watch. Certain survey items were only conditionally displayed based on responses to other items to reduce the number of the questions. Participants were not able to review or change their survey responses. Data collection from surveys is complete as of January 2021, and data analyses are ongoing.

During the onboarding video call, participants were provided with a unique access code that was required to enter the Roadmap 2.0 app. After entering the code, participants completed a 49-item baseline survey, distributed over five screens, that automatically was pushed to the Roadmap 2.0 app on their phones. Completion of the baseline survey was required to gain access to the rest of the Roadmap 2.0 app.

For 30 days following study onboarding, study participants received daily surveys through the Roadmap 2.0 app, including a 9-item daily symptom survey and a single-item mood questionnaire. Finally, at the end of the 30-day study period, participants received and completed an 8-item exit survey through the Roadmap 2.0 app. Participants were instructed and reminded to complete these follow-up surveys, but unlike the baseline survey, they were not required to use the rest of the Roadmap 2.0 app (see Multimedia Appendix 1 for a list of all questionnaire items and interview guides).

Exit Interview

Participants were asked to participate in a semistructured qualitative exit interview lasting about 10-20 minutes. The interviews were conducted via videoconference or phone, and permission was asked to audio record the interviews. The exit interview included questions about the HCWs' experiences with each of the study components and their experiences surrounding the COVID-19 pandemic.

Follow-up Interviews

Participants may be contacted by study coordinators to complete short follow-up semistructured interviews at the 3-, 6-, 9-, and 12-month time points after their 30-day study period was complete. These interviews included questions surrounding the participants' overall health and well-being; their experience of the study; and their beliefs and perceptions surrounding the COVID-19 pandemic, testing, and vaccination.

Roadmap 2.0 App

Study participants responded to all surveys on their smartphones through the Roadmap 2.0 app, which was also used to interface with the Fitbit data through an API [21]. This app was originally developed by author SWC and colleagues as part of a project funded by a National Heart, Lung, and Blood Institute (NHLBI) R01 grant, R01HL146354-01, and is currently being evaluated in a study of caregivers of HCT patients [17-19]. As an added potential benefit to the participants, the Roadmap 2.0 app included a set of positive psychology–based activities that participants could use if they desired, including positive piggy bank, gratitude diary, savoring, pleasant activity scheduling, random acts of kindness, signature strengths, love letter, and engaging with beauty. The app also had a chat forum where participants could anonymously post and comment about themes related to the positive psychology–based activities.

Study Completion

At the end of the initial 30-day study period, participants were asked to complete an exit survey and exit interview, in addition to follow-up interviews at 3, 6, 9, and 12 months post study. Participants were allowed to keep their Fitbits for personal use after study completion. Any Fitbit data that continues to be collected will be accessible by the study team for up to 1 year after study completion.

We proposed to collect additional nasal swabs and blood samples up to 1 year after study completion on any participants who are clinically diagnosed with COVID-19 while in the study. Participants could opt in or out on the informed consent document to allow for recontact by the study team.

Data Collection and Analysis

Data Storage and Security

Participant data were stored on the wearable sensor devices and transmitted to the relevant device's app on the participant's smartphone via Bluetooth or Wi-Fi. Participants and their data are deidentified using coded identifiers within the devices and apps. The study team maintained deidentified participant data on a HIPAA-compliant, password-protected drive on secure university encrypted servers maintained by the Health and Information Technology Services at Michigan Medicine to protect the confidentiality of the participants.

Data Collection and Sharing

In addition to the study data generated from the wearable devices and survey responses, participants provided consent to access a database of COVID-19 testing results maintained by Occupational Health Services at Michigan Medicine. This access would allow the study team to determine which of the participants developed COVID-19 illness or other respiratory infections, as well as antibody titer information if it becomes available in the future. The study team could also access participants' work schedules through hospital administrative data. Finally, the study team could access participants' electronic medical records during the study and up to 2 years after study completion to obtain additional clinical data to correlate with the wearable sensor data and symptom reporting data.

Participants' deidentified data and biospecimens could be shared with other researchers at the University of Michigan, around the world, and with companies. Deidentified participant data could also be used for future research studies without additional informed consent.

Data Analysis

Participant demographics, baseline characteristics, and daily symptom surveys will be summarized for all participants. Participant characteristics to be examined include age, gender, race, ethnicity, occupation, comorbidities, COVID-19 history, COVID-19 beliefs, and overall health and well-being.

Using computational techniques, we plan to assess the relationship between self-reported symptom data, wearable sensor data, and clinical diagnoses of respiratory illnesses, which may be COVID-19 or other types of infections. We will build on analytic approaches already developed in our other studies among oncology patients, including HCT patients who develop fevers and cell therapy patients who develop cytokine release syndrome.

We will take a multitiered approach to data analysis. This will involve initial quality control and data cleaning, data visualization, and descriptive statistics. Subsequent analyses will seek to calculate measures of correlation between the data themselves—temperature, heart rate, and symptoms data—and with clinical outcomes, particularly COVID-19 status. This aim is exploratory; we expect to obtain pilot data to power a larger subsequent study to test correlations between wearable sensor data, symptoms data, and clinical outcomes. If sufficient data are available, we may also undertake a machine learning–based analysis, such as the one we recently described for the analysis of continuous temperature data for graft-versus-host disease prediction in an animal model [26,27].

Results

This protocol was approved by the IRB of Michigan Medicine on April 24, 2020. The first participant was enrolled on April 28, 2020, and the last participant was enrolled on December 7, 2020. We enrolled 226 HCWs within that time period. All participants have now completed the 30-day study procedures and will remain on follow-up for 2 years after completing the study period. Data collection is ongoing. Analysis of demographic and baseline characteristics has begun, and the rest of the analysis is ongoing.

The COVID-19 pandemic affected the execution of this study in a number of ways. All recruitment, consenting, onboarding, and participant follow-up were conducted remotely via videoconference, phone, and email. Although we proposed to collect saliva and nasal samples daily and blood samples up to three times throughout the study, due to COVID-19 restrictions at the University of Michigan in conjunction with limited resources, we only collected one saliva sample, one nasal sample, and no blood samples from our participants. Finally, due to the ever-changing nature of the pandemic, the study was carried out in two segments. An initial cohort of 20 HCWs was enrolled in April and May 2020 and participated in the wearable device portion of the study, in addition to surveys and interviews. Informed consent for biospecimen collection was later added to the study, after which a second larger cohort of HCWs was enrolled between August and December 2020.

Discussion

In this study, HCWs wore a smartwatch and temperature patches, completed daily symptom surveys, and submitted biospecimens for analysis, with the aim of assisting HCWs in self-monitoring for COVID-19 infection. We enrolled 226 HCWs between April 28 and December 7, 2020. All participants have completed the 30-day study procedures, with the last participant reaching day 30 on January 16, 2021. Data collection will continue through January 2023. Data processing and analyses are ongoing at the time of writing this manuscript.

Studying the feasibility of wearable sensor use and daily smartphone-based symptom logging is timely, as the use of digital health technologies has surged during the COVID-19 pandemic [28,29]. One year since the start of the pandemic, the majority of HCWs have adjusted to social distancing and remote working and learning. A return to some sense of normalcy in the near future is anticipated with wide scale vaccine distribution efforts. However, it remains uncertain what the new normal may entail. It is imperative that the wellness and HRQOL of HCWs, their families, and their colleagues continue to be prioritized as health care systems navigate through the broad, sweeping changes that the pandemic has brought worldwide. Thus, the role of wearables and mobile health apps in health care is likely to continue growing in the coming years.

The COVID-19 pandemic has affected health care systems in many ways. In particular, the health care workforce has been

impacted by the relatively high incidence of COVID-19 among HCWs [10]. There have been wide-ranging physical and mental health implications for all HCWs working during the COVID-19 pandemic, including what is now described as the long-haul syndrome [30]. Psychological distress, fear, and burnout related to working during the COVID-19 pandemic are common among HCWs [31-34]. As such, many recent mobile health studies have targeted the mental health of HCWs during COVID-19—from telepsychiatry to mindfulness apps [35-38]. Our study builds upon this literature with the positive psychology–based activities included in the Roadmap 2.0 app. Additionally, the literature surrounding the use of wearable sensors to predict or detect COVID-19 is growing. Several studies have demonstrated that wearable sensor data and symptoms data may be useful for the early detection of COVID-19 [39-42]. However, research is limited on the utility of this kind of data for monitoring HCWs for infection.

At first glance, the movement toward digital health technologies seems apt to increase access to health care by increasing the ease and accessibility of consulting with a physician or monitoring one's health. Indeed, virtual visits tend to be more flexible in terms of time and location than in-person consultations. However, telemedicine and other forms of digital health technologies require internet access and knowledge of how to use the digital health platform. Research shows that lack of internet access and digital illiteracy are both correlated with low income, being a racial or ethnic minority, being older than 65 years, or speaking a primary language other than English [43]. Thus, the equitable distribution of digital health solutions is limited by digital access and digital literacy. Furthermore,

just as patients vary in this parameter, HCWs have varying levels of digital literacy. For this reason, mobile health interventions in both patients and HCWs need to consider these factors.

This study has several limitations. First, we did not address the digital divide. HCWs are a relatively highly educated group, which correlates with higher digital literacy. For this reason, the protocol may not be easily adapted to other populations outside of HCWs. Second, our study is subject to selection bias by which technologically savvy HCWs may have been more likely to enroll than those with lower digital literacy. Thus, results surrounding the feasibility of using the wearable sensors, which requires some technological expertise, may be positively skewed. Finally, this was a study of HCWs at a single institution, Michigan Medicine, which means unique institutional factors may influence our results. Future studies should focus on strategies to mitigate the digital divide and expand the reach of mobile health interventions.

This protocol will reveal key data on the feasibility of using wearable sensors and symptom reporting among HCWs. These data are important for evaluating the viability of this kind of intervention for monitoring HCWs for infection in the real world. Additionally, we hope that it will add valuable pilot data to the growing literature surrounding wearable sensor and symptoms data for the early detection of COVID-19 infection. With its unique combination of wearables data, symptoms data, and biospecimens, we anticipate that this study will illuminate effective HCW monitoring practices, which may be useful for future pandemic preparedness.

Authors' Contributions

CAC contributed toward writing the original draft, data curation, visualization, and review and editing. MD contributed toward review and editing, and data curation. MR contributed toward review and editing, study coordination, study recruitment, study consent, study onboarding, and data curation. KNG contributed toward review and editing, study coordination, study recruitment, study consent, study onboarding, and data curation. CRC contributed toward review and editing, study coordination, study recruitment, study consent, study onboarding, and data curation. JB contributed toward review and editing, study coordination, study recruitment, study consent, study onboarding, and data curation. ES contributed toward review and editing, sample processing, and data curation. MO contributed toward review and editing, sample processing, and data curation. CF contributed toward review and editing, methodology, and data curation. JT contributed toward review and editing, methodology, and data curation. CM contributed toward review and editing, methodology, and data curation. ES contributed toward investigation, methodology, and review and editing. TB contributed toward investigation, methodology, supervision, visualization, and review and editing. DBF contributed toward investigation, methodology, supervision, visualization, and review and editing. MT contributed toward data curation, investigation, methodology, resources, supervision, visualization, writing of original draft, and review and editing. SWC contributed toward data curation, investigation, methodology, resources, supervision, visualization, writing of original draft, and review and editing.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Survey measures.
[DOCX File , 20 KB - resprot_v10i5e29562_app1.docx]

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Abbreviations

API: application programming interface
HCT: hematopoietic cell transplantation
HCW: health care worker
HIPAA: Health Insurance Portability and Accountability Act
HRQOL: health-related quality of life
IRB: Institutional Review Board
NHLBI: National Heart, Lung, and Blood Institute

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Protocol

Using Biometric Sensor Data to Monitor Cancer Patients During Radiotherapy: Protocol for the OncoWatch Feasibility Study

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Abstract

Background: Patients with head and neck cancer (HNC) experience severe side effects during radiotherapy (RT). Ongoing technological advances in wearable biometric sensors allow for the collection of objective data (eg, physical activity and heart rate), which might, in the future, help detect and counter side effects before they become severe. A smartwatch such as the Apple Watch allows for objective data monitoring outside the hospital with minimal effort from the patient. To determine whether such tools can be implemented in the oncological setting, feasibility studies are needed.

Objective: This protocol describes the design of the OncoWatch 1.0 feasibility study that assesses the adherence of patients with HNC to an Apple Watch during RT.

Methods: A prospective, single-cohort trial will be conducted at the Department of Oncology, Rigshospitalet (Copenhagen, Denmark). Patients aged ≥18 years intended for primary or postoperative curatively intended RT for HNC will be recruited. Consenting patients will be asked to wear an Apple Watch on the wrist during and until 2 weeks after RT. The study will include 10 patients. Data on adherence, data acquisition, and biometric data will be collected. Demographic data, objective toxicity scores, and hospitalizations will be documented.

Results: The primary outcome is to determine if it is feasible for the patients to wear a smartwatch continuously (minimum 12 hours/day) during RT. Furthermore, we will explore how the heart rate and physical activity change over the treatment course.

Conclusions: The study will assess the feasibility of using the Apple Watch for home monitoring of patients with HNC. Our findings may provide novel insights into the patient's activity levels and variations in heart rate during the treatment course. The knowledge obtained from this study will be essential for further investigating how biometric data can be used as part of symptom monitoring for patients with HNC.

Trial Registration: ClinicalTrials.gov NCT04613232; https://clinicaltrials.gov/ct2/show/NCT04613232

International Registered Report Identifier (IRRID): PRR1-10.2196/26096

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Introduction

A promising type of patient-generated health data is biometric sensor data [1]. A "wearable" is a device that uses biometric sensors to monitor variables such as heart rate, blood glucose, and skin temperature [2-4]. One type of consumer wearables are smartwatches, which are also commonly used as fitness trackers [5].

In the oncological setting, most patients receive their treatment at outpatient clinics, which implies that they spend most of their time outside the hospital. The patients are instructed to contact the oncology department if they experience side effects or other alerting symptoms. If their symptoms deteriorate, they might need acute hospital admission. In the hospital, the patients are monitored with vital signs depending on their condition. Changes in vital signs can alert the health care professionals and can contribute to optimizing supportive treatment. In the outpatient clinics, the patients are seen at planned intervals. During regular consultations, side effects are discussed with the patient, and the patient's health status is evaluated.

The symptoms and side effects experienced by the patient during cancer treatment depend on the cancer type, treatment type, and comorbidity. Patients with head and neck cancer (HNC) experience severe acute side effects during radiotherapy (RT), including pain, dysphagia, and dehydration [6-8]. At the annual American Society of Clinical Oncology meeting in 2018, Peterson et al [9,10] presented the findings of their randomized clinical trial, which showed that patients undergoing RT for HNC experienced less severe symptoms if they sent their daily monitored weight and blood pressure to their clinician.

Systematic home monitoring with a sensor device may have the potential to detect symptoms such as dehydration and increased pain [11], and biometric sensors in consumer wearables such as a smartwatch have made it possible to obtain objective measures with minimal burden to the patient [12]. However, studies on wearable sensor devices for home monitoring in the health care setting are limited [13-15]. We have previously shown that in oncological clinical trials, wearable sensors have primarily been used to monitor physical activity and the circadian rhythm [16]. The most frequent cancer types in these studies were breast cancer, followed by gastrointestinal and lung cancer. Few studies focused on biometric sensor data as a supplement to symptom monitoring

[12,17-19]. Knowledge about the adherence to the wearable is important when introducing new technologies, and this is generally a lesser known area [16]. It remains unknown whether patients with a moderate-to-severe symptom burden, such as those with HNC undergoing RT, can adhere to the use of a wearable during treatment.

Here we describe the design of the OncoWatch 1.0 feasibility study. This study is aimed to determine the adherence to using an Apple Watch during curatively intended RT for HNC. Our findings may provide novel insights into the patients' activity levels and variations in the heart rate during their treatment course.

Methods

Patients and Recruitment

Ten patients from Denmark, who are aged ≥18 years and are intended for primary or postoperative curative RT (5-6 fractions/week/up to 34 fractions) for squamous cell carcinoma of the head and neck at the Department of Oncology, Rigshospitalet (Copenhagen, Denmark) will be enrolled. Other inclusion criteria are the ability to read and speak Danish, having no serious cognitive deficits, and providing written informed consent to participate in the study. Patients will be included consecutively at their initial visit at the Department of Oncology, Rigshospitalet.

Design

The trial is an explorative feasibility study investigating the adherence to the Apple Watch, changes in the heart rate and physical activity during RT for HNC. This trial has been registered on ClinicalTrials.gov (protocol# NCT04613232). The study will be performed in a public health care system, which implies that the patients will have access to the hospital free of charge. The research intervention is continuous monitoring of heart rate and physical activity (minimum 12 hours/day) with a smartwatch connected to a smartphone (Figure 1). The patients will be asked to wear the smartwatch from baseline until 14 days after the end of treatment. Patients will go off study when they have attended their control visit 2 weeks after the end of RT or if they no longer want to participate. Inclusion in the study will have no interference with their oncological treatment. The primary investigator will oversee that data are regularly transmitted to the database.

Figure 1. Overview of the OncoWatch feasibility study assessment times, tasks, and measures. RT: radiotherapy.

		Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	End of RT	14 days post RT
		Up to 10 days before RT	Day 1-7, day 1=1st day of RT	Day 8-14	Day 15-21	Day 22-28	Day 29-35	Day 36-42		
	Treatment		Radiotherapy (5-6 sessions/week) with or without weekly chemotherapy							
	Out-patient visits*	x	x	x	x	x	x	x	x	x
	Apple Watch monitoring	Continuous (minimum 12h/day)								
	Informed consent	x								
	Off study registration									x

*The specific number of control visits depends on the individual patient's treatment plan (8-10 planned visits)

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The study will follow the General Data Protection Regulation and is registered at the capital region of Denmark (ID. P-P-2019-797). In a Danish setting, the study does not need approval from the National Committee on Health Research Ethics. This study has been approved by the local division for information technology and medical technology in the capital region of Denmark. This study is a collaboration between the Department of Oncology, Rigshospitalet, and the Telemedical Knowledge Center at the capital region of Denmark. The Telemedical Knowledge Center supports and improves the use of telemedicine in in the capital region of Denmark.

Hardware

The wearable is an Apple Watch Series 5 worn on the wrist. The watch is connected to an iPhone 8 device.

The smartwatch and smartphone will be supplied by the hospital. The patients will return the devices at study termination. The patients will not be able to use their own device, neither phone nor smartwatch. Only the patient is allowed to wear the smartwatch during the study period. The watch and phone can only be operated with a unique password. The patients will be responsible for charging the watch and phone. The patients will not receive any rewards or financial support for participating in the study.

Software

ZiteLab ApS has developed the OncoWatch app, which collects data from the Apple HealthKit and sends it to a secure cloud server [20]. The primary investigator has access to the database. In this feasibility study, the patients are not supposed to interact with the smartwatch or the OncoWatch app.

The patients will be assigned an account before they can use the app (Figure 2).

Figure 2. Framework for the OncoWatch 1.0 feasibility study.
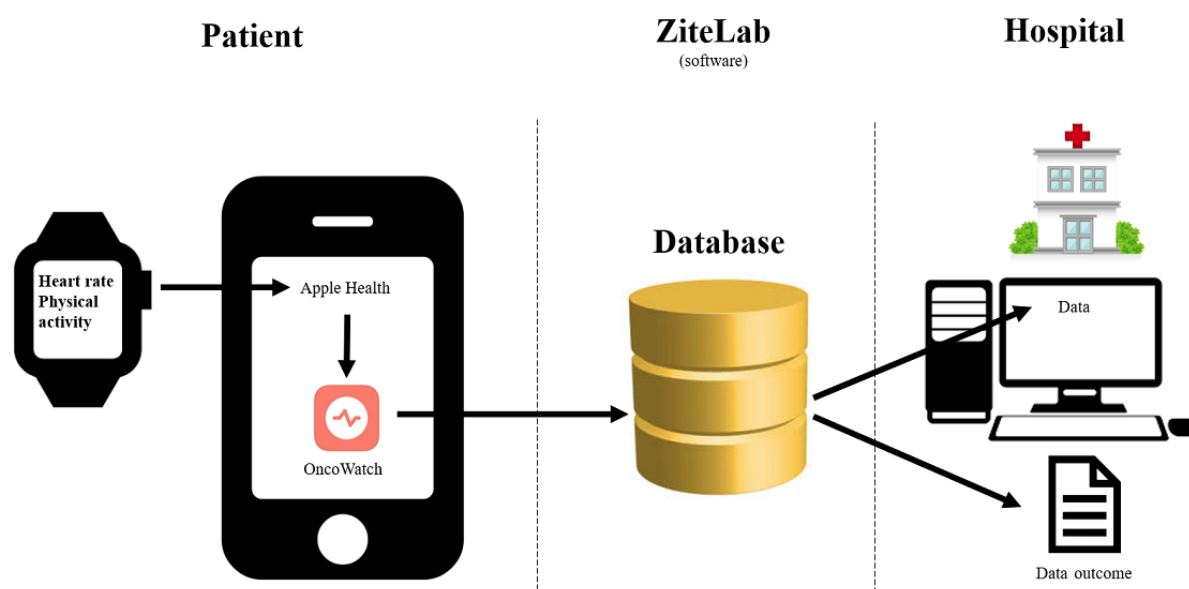
Statistical Analysis

Endpoints

To determine the feasibility and adherence to the smartwatch, the primary endpoint is number of patients who could wear the device minimum 12 hours/day during the study period (from baseline until 2 weeks after the end of RT). Secondary endpoints are the percentage of successful data acquisition events and variations in heart rate and physical activity. Heart rate at rest and the average heart rate during movement will be recorded. Physical activity, defined as steps per day, is registered.

Clinical data from all patients will be collected and will include age, stage, treatment regimen, information on hospital admissions, and toxicity score. The Danish Head and Neck cancer Study Group toxicity score is an objective grading of the patient's symptoms assigned by the clinician [21], which is determined using a categorical scale of 0-4 with 0="no or nothing" and 4="severe."

The statistical analysis will include descriptive statistics of the patients included in the study. Descriptive data will be collected and analyzed using SPSS Statistics (IBM Corp) or SAS (SAS Institute). Data will be captured in RedCap. Missing data will be described.

Power

This is a feasibility study and does not require a power calculation. The present study data will be used to calculate adequate sample sizes in future randomized clinical trials.

Ethical Considerations

The patients will receive verbal and written information and will be required to provide written informed consent, which they can withdraw at any time. The patient will be handed a phone and watch by the hospital.

Results

Patient recruitment was initiated in March 2021.

Discussion

This study will assess the feasibility of using the Apple Watch for home monitoring of patients with HNC. Our findings may provide novel insights into the patients' activity levels and variations in the heart rate during their treatment course. The knowledge obtained from this study will be essential for further investigating how biometric data can be used as part of symptom monitoring for patients with HNC.

Conflicts of Interest

IRV receives teaching and research contracts from Varian, ViewRay, and Brainlab. The other authors have no conflicts to declare.

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Abbreviations

HNC: head and neck cancer
RT: radiotherapy

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Protocol

Presenteeism Among Nurses in Switzerland and Portugal and Its Impact on Patient Safety and Quality of Care: Protocol for a Qualitative Study

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Abstract

Background: Nurses dispense direct care in a wide variety of settings and are considered the backbone of the health care system. They often work long hours, face emotional stress, and are at a high risk of psychosocial and somatic illnesses. Nurses sometimes fall sick but work regardless, leading to presenteeism and subsequent risks to quality of care and patient safety due to the increased likelihood of patients falling, medication errors, and staff-to-patient disease transmission.

Objective: This study aims to understand presenteeism among frontline nurses and nurse managers in acute, primary, and long-term health care settings and to contribute to the development of future interventional studies and recommendations.

Methods: A qualitative study based on online focus group discussions will explore the perceptions of, attitudes to, and experiences with presenteeism among frontline nurses and nurse managers. Using a pilot-tested interview guide, 8 focus group discussions will involve nurses working in acute care hospitals, primary care settings, and long-term residential care facilities in Switzerland's French-speaking region and Portugal's Center region. The data collected will be examined using a content analysis approach via NVivo 12 QSR International software.

Results: The University of Applied Sciences and Arts Western Switzerland's School of Health Sciences and the Polytechnic of Leiria's School of Health Sciences in Portugal have both approved funding for the study. The research protocol has been approved by ethics committees in both countries. Study recruitment commenced in February 2021. The results of the data analysis are expected by September 2021.

Conclusions: This present study aims to gain more insight into the dilemmas facing nurses as a result of all causes of presenteeism among frontline nurses and nurse managers in different health care settings. The researchers will prepare manuscripts on the study's findings, publish them in relevant peer-reviewed journals, exhibit them in poster presentations, and give oral presentations at appropriate academic and nonscientific conferences. Regarding further knowledge transfer, researchers will engage with stakeholders to craft messages focused on the needs of nurses and nurse managers and on disseminating our research findings to deal with the issue of nursing presenteeism.

International Registered Report Identifier (IRRID): PRR1-10.2196/27963

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Introduction

Rationale

According to the United Nation's 2030 Agenda for Sustainable Development, all countries should have a healthy, well-educated health care workforce with the knowledge and skills needed for productive, fulfilling work and full participation in society [1]. Inside health care systems, nurses are the primary providers of direct care, delivering vital services, and often considered the system's backbone [2,3]. Undeniably, the SARS-CoV-2 coronavirus has emphasized that many health care settings are also workplaces where nurses face particular risks from occupational exposure to diseases and stress [4]. A perfect illustration of organizational presenteeism was seen during the COVID-19 pandemic in Australia: Hospital staff infected with SARS-CoV-2 while at work continued working for up to 7 days, even with respiratory symptoms [4]. The International Council of Nursing has confirmed that more frontline nurses were affected by SARS-CoV-2 than all the other health care professions combined [5].

Nurses often face difficult work conditions, including working long hours, overtime, and emotional stress: They are at a high risk of developing psychosocial and somatic illnesses [6]. Despite these poor working conditions, much of the absenteeism previously noted among nurses has been replaced by presenteeism [7,8]. Presenteeism may be described as the act of a health care professional who continues to work while sick or suffering from another condition that results in their underperformance at work [3,9]. One frequently used definition of presenteeism in nursing is the "act of being physically present at work when one should not be there" [10]. However, numerous studies of presenteeism have included identified etiologies as conditional for this behavior, such as "a physical presence at work when one should not to be there due to one's health and well-being, a stressful work environment, a lack of work-life balance, or a sense of professional identity or obligation" [10-13].

Although it is widely recommended that nurses be in good health when providing health care to patients [1], in some cases and for numerous reasons, some sick nurses do not follow recommendations to stay at home and continue to work, leading to presenteeism [14]. The existence of presenteeism differs by sector, but it is more likely to occur among staff working in jobs with extensive interpersonal interactions with clients or patients [15]. There are many reasons why sick health care professionals might continue working. Nurses face pressures that contribute to presenteeism, including difficulties finding replacements due to workforce shortages, strong organizational-culture barriers, and professional-culture norms against taking sick leave [16]. Worries about presenteeism are not limited to potential loss of earnings; the lack of replacement staff; concerns about the resulting burdens on patients, clients, customers, co-workers; and a potential competitive disadvantage [14]. Presenteeism occurs not only when physically or mentally unwell nurses go to work but also when their level of awareness or responsiveness is compromised or when their emotional, behavioral, or cognitive engagement is diminished [11,12,17-20]. Nurses are 4 times more likely to exhibit presenteeism than other professions; yet, this threatens patient safety through increased falls, medication errors, and staff-to-patient disease transmission [21].

The Concept of Presenteeism in Nursing

The concept of presenteeism has been described across different professions, organizations, and work environments [9,17,22]. One multisector study of presenteeism found that nurses reported 3-4 times higher rates of presenteeism than employees in management positions, and they had the highest rate among the 42 occupational groups surveyed [17]. The concept of presenteeism in nursing has been related to the Quadruple Aim Framework (population health, patient experience, provider experience, and costs) linking optimizing nurses' performance and their own health to harmful patient outcomes and increased health care costs [23,24]. Unlike factors such as nurse staffing ratios and nursing shortages, which impact care and costs, nurses' behaviors are seen as potentially correctable in the short term and within organizations [19]. Figure 1 presents the conceptual model of presenteeism in nursing and the underlying relationships between presenteeism's antecedents, definition, and consequences, by Rainbow and Steeg [10].

Figure 1. Conceptual model of presenteeism in nursing developed by Rainbow and Steeg [10].
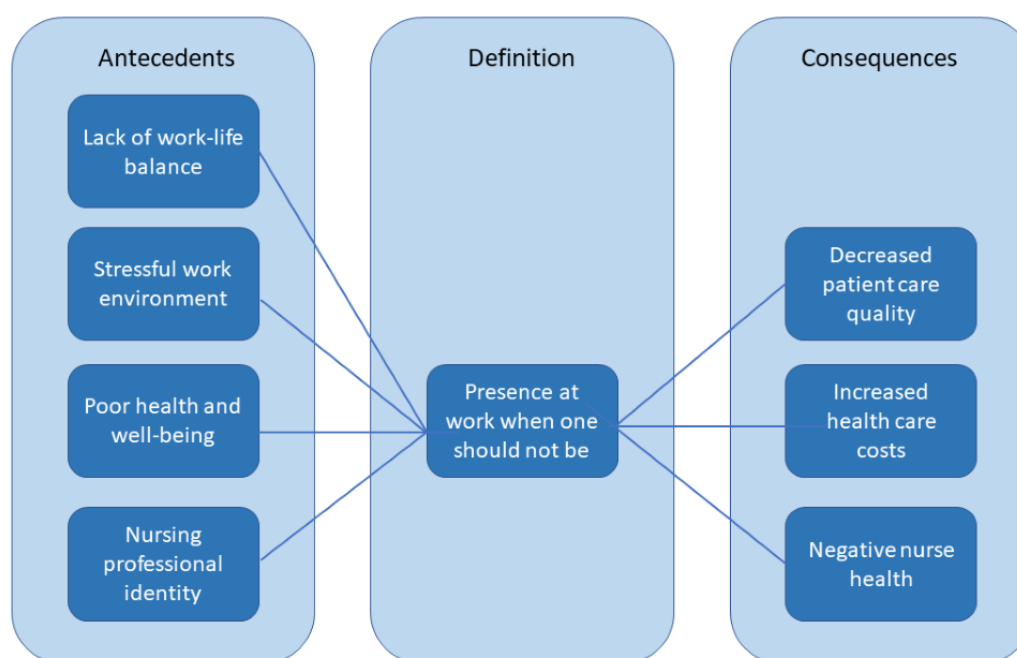
Prevalence of Presenteeism

In 2016, Barbosa [25] identified a prevalence of presenteeism among Portuguese nurses of 91.4% in the previous month, more related to psychological reasons than to physical ones. Meanwhile, 32.9% of professional care workers in 162 Swiss nursing homes reported their own presenteeism during at least one shift in the month before being surveyed [26]. A very broad range of other estimates was also reported in a systematic review, where self-reported presenteeism in relation to an infectious illness ranged from 37% to 97% in the health care sector [14]. Although these rates varied considerably, even the lower end of this range is troubling, as it would probably have resulted in increased rates of transmission of infection in the workplace [14]. The heterogeneity of prevalence rates should be considered in light of different variables: (1) the sample characteristics (population and response rate), (2) the type of presenteeism studied (sickness, nonsickness, overall), (3) the variation in presenteeism recall periods (ranging from 7 days to 1 year), (4) the frequency and experience of episodes of presenteeism, (5) the threshold for presenteeism's seriousness, and (6) the heterogeneity of measurement instruments [14].

Consequences of Presenteeism

Decreased Quality of Care and Patient Safety

Several studies have demonstrated that presenteeism affects nursing quality and patient care outcomes [23,24,27,28]. High-quality nursing is expensive, but poor-quality nursing can lead to higher health care costs via potential adverse events, whether detected or not; increased hospital or intensive care unit lengths of stay; and even earlier death [23,28,29]. Unlike factors such as nurse staffing ratios and nursing shortages, which affect care and costs, nurses' behaviors can be adjusted in the short term and within organizations [30-32].

Economic Costs

A systematic review by Kigozi et al [33] revealed that, on average, the cost of presenteeism comprised 52% of the total costs of the disease conditions investigated. The proportion of presenteeism was highest among employees suffering from rheumatoid arthritis, back pain, and insomnia. In 5 of the studies included in that review, the costs of presenteeism were greater than those for absenteeism, which was explained by the chronicity of the conditions investigated [33]. Although presenteeism has been associated with significant costs, losses from reduced productivity at work are rarely included in cost-effectiveness or cost-utility analyses. Ignoring these costs could significantly underestimate the true value of interventions that reduce nurses' limited functioning at work due to illness [34].

Reasons for Presenteeism

Most studies have reported similar types of reasons that can be grouped into 3 overarching themes: organizational factors and working conditions, job characteristics, and personal reasons [14].

The *organizational factors and working conditions* explaining presenteeism resulted from internal organizational policies and the suggestion that working while ill was due to employees not being protected by paid sick leave or having no more available sick leave entitlement [31,35]. A culture of presenteeism in certain organizations shed light on the fact that this could become a social norm, embedded in the organization's culture. Taking sick leave might even lead to disciplinary action [14,35,36]. Worries about losing a job were a major concern in many studies, whereas fears of getting into trouble, receiving a poor evaluation, being somehow penalized, and being anxious about job security were also reported [31,35,37]. Economic difficulties and the risk of unemployment may push nurses to

presenteeism when they are ill or accepting excessive overtime [34,38,39]. Depending on the health care system, regulations concerning salaries, employment rules, and working conditions can reduce absenteeism and instead increase the incidence of presenteeism [34]. Presenteeism eventually leads to more health problems and a loss of productivity due to excessive working hours and feelings of insecurity; it can also develop into normal employee behavior, installing a culture of not missing work and working to meet the hierarchy's service demands. The situation is worse among nurses who have chronic diseases and are more likely to practice presenteeism due to social pressures [40]. However, episodic conditions, such as allergic disorders, the common cold, and pregnancy, contribute to high levels of presenteeism among health care staff [41-43].

Some *job-related factors* also cause presenteeism. Nurses often have a strong work ethic and feel an obligation towards their patients and colleagues: Taking sick leave might jeopardize their reputations. A nurse's professional identity is built on maturity and self-esteem reflected in their self-image. The professional function of a nurse is characterized by an elevated level of psychological commitment and sometimes expressed as the "super nurse phenomenon" [44]. This can result in many nurses working in health care settings being apprehensive about being covered for by agency or bank nurses, when available, and therefore reluctant to go absent or on sick leave [45,46]. High workloads may influence presenteeism because tasks might be left undone during an absence, creating fears of falling behind with tasks and having to make up for lost time on returning to work [12,47].

Some studies have demonstrated *personal reasons* for presenteeism [14]. A major one is that nurses did not want to burden colleagues with the extra workload resulting from their absence, and they often felt guilty about asking colleagues to cover their duties. Some nurses feared that colleagues would perceive them as weak and irresponsible if they were absent from work [48]. Another personal reason concerned the *financial stress* felt by nurses: They could not afford the loss of earnings inherent in taking sick leave as they needed to support their family [49].

A common theme running through the reasons given for presenteeism was nurses feeling that their illness did not meet the *threshold* of seriousness for taking sick leave and that it did not influence their capacity to carry out their duties. If they believed their illnesses to be noninfectious, then they supposed that they were not a risk to colleagues or patients, and they therefore chose to attend work [50,51].

Relationships Between Sociodemographic and Professional Characteristics, Health Status, and Presenteeism

Sociodemographic and Professional Characteristics

Studies exploring *age* and *sex* as determinants of presenteeism have found no significant associations but should be considered inconclusive [14,52]. Nurses working in hospital settings had higher levels of presenteeism than those in long-term residential care settings, although without reaching the level for significance. No significant associations were found between

presenteeism, *professional experience*, the number of *working hours* per week, or the type of patients cared for. Likewise, *job satisfaction* and the amount of work left undone if absent showed no significant associations with presenteeism. Nurses' perceptions of the infection control measures in their health care settings were associated with presenteeism, with those who thought there was poorer control showing higher levels of presenteeism [14,53].

Nurses' Health Statuses

Nurses' health statuses and chronic conditions, such as asthma or diabetes, were not significantly associated with presenteeism. However, nurses whose otherwise healthy immune systems were weakened by illnesses such as cancer or immunosuppressant medication were more likely to report presenteeism. Numerous studies have found indications that presenteeism is associated with nurses' past and intended work behavior with regards to having influenza [54,55].

Measurement of Presenteeism

Presenteeism among nurses has been explored in numerous health care settings using quantitative, qualitative, and mixed methods research designs. The systematic review by Ospina et al [56] reported more than 20 self-administered presenteeism instruments usable for different professions and work settings. Based on the COSMIN methodology [57], the instruments providing the strongest level of evidence are the 6-item Stanford Presenteeism Scale, the Endicott Work Productivity Scale, and the Health and Work Questionnaire [56]. To the best of our knowledge, there is a scarcity of qualitative research into presenteeism [44]. Most studies of nurse presenteeism have focused on the consequences for patients, linking it to increased rates of patient falls, medication errors, missed care, and changes in patient safety error reporting [58,59]. It is also possible that the consequences of presenteeism in nursing are different from those found in other industries or the patient consequences associated with presenteeism among other health care professionals. Nurses have not previously been asked to describe presenteeism's consequences but have instead completed retrospective self‐reporting surveys. Asking nurses what they perceive to be the consequences of their presenteeism will expand this body of research.

Methods

Aims and Research Questions

The present study aims to understand presenteeism among frontline nurses and nurse managers in acute, primary, and long-term health care settings and to contribute to the development of future interventional studies and recommendations.

To address known concerns about presenteeism and its impact on the quality and safety of care, the planned investigation should attempt to provide well-developed answers to the following research questions: What are frontline nurses' and nurse managers' perceptions of, attitudes toward, and experiences with the personal, professional, and contextual or organizational factors that lead to presenteeism? What are frontline nurses' and nurse managers' perceptions of, attitudes

toward, and experiences with adverse health outcomes among patients resulting from nurse presenteeism? Are there different perceptions and attitudes about the reasons for presenteeism among frontline nurses and nurse managers?

Study Design and Conceptual Framework

To gain more insight into nurses' dilemmas resulting from all causes of presenteeism, our investigation will use a qualitative design and focus on participants' perceptions, attitudes, and experiences.

The study's conceptual framework is based on prior work published by Pit and Hansen [60]. As an adaptive behavior aimed at meeting the demands of work or performance criteria during periods of impaired capacity due to ill health, 3 precipitating factors give rise to presenteeism, namely (1) personal health resources, (2) occupational health factors, and (3) work and personal characteristics (Figure 2) [60].

Figure 2. The study's conceptual framework [60].
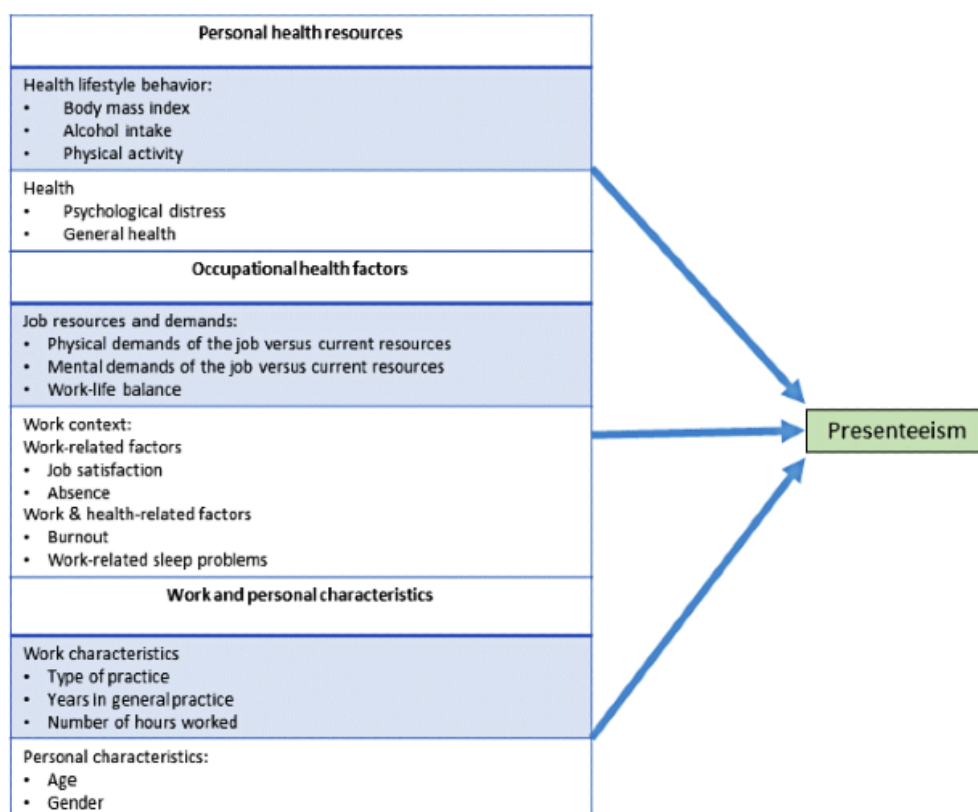
Population and Settings

The research population will be composed of frontline nurses and nurse managers working in acute care hospitals, primary care settings, and long-term residential care facilities in Portugal's Center region and Switzerland's French-speaking region.

Recruitment, Focus Group Discussion Procedures, and Data Collection

Participants

Eligible health care settings will be contacted by telephone or through a visit to determine their interest in participating in the study. A list of eligible nurses (frontline nurses and nurse managers) will be requested from the institution. Using a purposive sampling method, eligible participants will be recruited from the lists provided. A research team member will invite eligible participants to join the study. If the nurse agrees, an appointment will be arranged for them to respond to questions about a clinical vignette before participating in an online focus group discussion (FGD). The inclusion and exclusion criteria are listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Full-time frontline registered nurses with a bachelor's or master's degree or a PhD

- Full-time nurse managers

- Access to a computer, smartphone, or tablet with an internet connection

Exclusion criteria

- Less than 1 month's employment in their current health care setting

- Student nurses

Procedure for Focus Group Discussions

FGDs will take place via videoconferencing software, but only audio will be recorded. A key advantage of this type of software is its ability to record and store sessions securely without recourse to third-party software. This feature is particularly important in research where highly sensitive data require protection. Institutional servers in each country will be used to ensure data protection and secure storage. To ensure that online discussions are manageable, FGDs will only include 6-10 participants. Before commencing data collection, participants will be asked to sign a written informed consent form, and confidentiality will be guaranteed. Participants will fill out a questionnaire about their sociodemographic characteristics. A URL link will be sent to participants by email so they will not have to download the program onto their own computer or mobile phone.

A total of 8 FGDs will be planned and run in Portugal and Switzerland, in public and private health care settings, depending on data saturation. The FGDs are expected to last 60-90 minutes each. The Portuguese research team will conduct 4 FGDs in acute care hospital settings: 2 among frontline nurses active on acute care wards and 2 among nurse managers. The Swiss research team will conduct 4 FGDs: 2 in long-term residential care facilities (frontline nurses and nurse managers) and 2 in community health care settings (frontline nurses and nurse managers).

Data Collection

Data will be collected via FGDs and clinical vignettes.

FGDs will collect data to investigate similarities and differences in the perceptions, attitudes, and experiences of frontline nurses and nurse managers. FGDs can be defined as semistructured discussions with stakeholder groups of 6-10 people that aim to explore a specific set of questions. Moderators often start an FGD by asking questions of general interest before asking more specific ones. Although participants respond individually to the researcher's questions, they are encouraged to talk and interact with each other. This technique is based on the notion that group interaction encourages respondents to explore and clarify individual and shared points of view [47-49].

Each FGD will start by presenting a situationally and culturally adapted vignette about presenteeism. This will be followed by a semistructured interview about presenteeism and the quality and safety of care. The interview guide will include the following topics based on the study's framework: the management of presenteeism, the causes of presenteeism, its impact on the quality and safety of patient care, how colleagues deal with and perceive sickness presenteeism (practically, ethically, and socially), professional recognition by superiors and colleagues, and satisfaction with their professional quality of life. The semistructured interview guide for the FGDs will be pretested and refined in a pilot FGD involving 3-4 volunteers who meet our inclusion criteria (Multimedia Appendix 1).

The semistructured questionnaire and the clinical vignette have been built using the 3 concepts of personal health resources, occupational health factors, and job resources and demands [57].

To better understand the reasons for presenteeism among frontline nurses and nurse managers, each participant will receive an identical clinical vignette with open questions to see whether they understood the situation presented to them. A pretest phase is planned to test participants' understanding of the clinical vignette's content and the extent of the responses obtained from 3-4 volunteers meeting our inclusion criteria. The data collected during this phase will enable eventual modifications to be made to the vignette's content or the wording of the questions to make them more straightforward.

Data Analysis

Data will be analyzed according to good clinical research practices based on the dimensions included in the theoretical framework. Responses to the clinical vignette will be analyzed according to usual practices and respondents' responses to the open-ended questions concerning the situations described. Descriptive statistical analyses will be performed using SPSS, version 27 (IBM Corp, Armonk, NY). These will describe the sample and establish the typical profiles of participating nurses.

Analysis of the data collected during the FGDs will be carried out via a qualitative content analysis approach [51-53] using NVivo 12 QSR International software. This analysis will enable a thorough description and examination of the causes and predictors of presenteeism, as well as their impacts on the quality and safety of care. A transversal reading of the interviews can be done at the end of the category analysis. This reading will allow transversal themes to be updated (occurrence of significant themes identifiable in the interviews) even if they are not linked to the pre-established categories. The results will be presented by category, and occurrences will be illustrated with significant examples, including verbatim quotes from the interviews.

Following the analysis of each FGD, a second-stage analysis will compare findings across the groups. This will involve talks within the research team to refine the discussed themes and to develop higher-level themes, that is, grouping the open codes into meaningful conceptual categories.

To ensure study reliability, the researchers will be deeply involved in data handling (eg, transcribing, reading, and rereading the transcripts; conducting the inductive analysis) and will maintain transparency while they analyze the data subjectively. The research team includes 4 nurses involved in academic teaching and with expertise in clinical nursing practices (CL, HV, AQ, FP), as well as a research psychologist (MB). Data analysis will be guided by the COREQ guidelines [61].

Results

The University of Applied Sciences and Arts Western Switzerland's School of Health Sciences (HES-SO Valais/Wallis) and the Polytechnic of Leiria's School of Health Sciences in Portugal have both approved funding for the study. The research protocol has been submitted for approval by both institutions' ethics committees (Human Research Ethics Committee of the Canton of Vaud n° 2021-00071 and the Comissão de Ética do Politécnico de Leiria n° CE/IPLEIRIA/44/2020). At the time of writing, no participants had yet been recruited. Study recruitment commenced in February 2021, and the FGDs will be conducted from March 2021 to May 2021. The results of the data analysis are expected to be available by September 2021.

Discussion

The Study's Expected Impact

Nurses' services have been in increasing demand since the outbreak of the COVID-19 pandemic. It is vital to ensure that they have the resources to mitigate the impacts of this and new pandemics—when health care professionals face greater risks than usual. Forging closer working relationships between nurse managers and frontline nurses will also enhance their mutual understanding of risk factors and help to generate more effective ways of managing absences due to sickness and rehabilitation during a pandemic. This will require health care organizations to take a proactive approach to employee well-being and to make sure their policies encourage rest and recovery rather than promoting an "always on" or "work at all costs" culture.

We expect that the findings from our Swiss-Portuguese research partnership will contribute to a better understanding of where the thresholds for presenteeism lie. Our recommendations should lead to other multicenter studies aiming to develop effective measurement scales for presenteeism, as an essential first step

to designing interventions that improve the health and well-being of nurses in their workplaces.

The proposed study is relevant because, to the best of our knowledge, there have been few investigations of health care institutions' presenteeism prevention strategies. Indeed, these may not be well-developed at all because several studies have revealed that health care professionals are often the main victims of their own presenteeism (ie, it can compound their health problems), which can lead to a greater potential for making mistakes. Furthermore, the economic and financial demands of recent decades have led to the adoption of policies to contain health sector expenditure. This study will explore the causes of presenteeism—the fact that it entails costs far higher than absenteeism makes this investigation necessary—and aims to develop effective interventions to prevent or limit it [62]. We will collect frontline nurses' and nurse managers' perceptions of presenteeism and its impact on their work and the quality and safety of patient care from the point of view of their job function. This will provide us with information to formulate recommendations on reducing presenteeism to strengthen nursing and health care teams and to optimize the quality and safety of patient care. Researchers in both countries will supplement their analyses with contextual information (eg, policy, regulations, workplace management, employment conditions, geographic location) that reflects the results.

Ethical Considerations

The research protocol has been submitted for approval to the research ethics committees of both the institutions involved. A research information form and a consent form will be given to each participant, specifying the study's objectives, what participation will entail, and the measures taken to protect the participants' rights and data. All participants will be kept informed about the study and will be free to withdraw their signed consent. They will also be asked for their consent to participate in FGDs and be audio-recorded (for transcription purposes) and video-recorded (although these will not be kept). Volunteers will receive no compensation for their participation. All the data collected will be treated confidentially, coded, and kept under lock and key for 20 years. Results will be presented in a way that respects participant confidentiality, and none will be identifiable either in presentations or publications.

Methods of Disseminating Findings

Knowledge transfer will be appropriately considered and outlined in a dissemination plan focused on the needs of the audience that will use that knowledge. Researchers will also collaborate with knowledge users to craft messages and help disseminate research findings. Additionally, the researchers will prepare manuscripts and publish the study's results in relevant peer-reviewed journals and present their findings via poster and oral presentations at appropriate academic and nonscientific conferences.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guides.
[DOCX File , 24 KB - resprot_v10i5e27963_app1.docx]

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Abbreviations

FGD: focus group discussion

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Protocol

Comparing the Effectiveness of Education Versus Digital Cognitive Behavioral Therapy for Adults With Sickle Cell Disease: Protocol for the Cognitive Behavioral Therapy and Real-time Pain Management Intervention for Sickle Cell via Mobile Applications (CaRISMA) Study

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Abstract

Background: Patients with sickle cell disease (SCD) experience significant medical and psychological stressors that affect their mental health, well-being, and disease outcomes. Digital cognitive behavioral therapy (CBT) has been used in other patient populations and has demonstrated clinical benefits. Although evidence-based, nonpharmacological interventions for pain management are widely used in other populations, these treatments have not been well studied in SCD. Currently, there are no adequately powered large-scale clinical trials to evaluate the effectiveness and dissemination potential of behavioral pain management for adults with SCD. Furthermore, some important details regarding behavioral therapies in SCD remain unclear—in particular, what works best for whom and when.

Objective: Our primary goal is to compare the effectiveness of two smartphone–delivered programs for reducing SCD pain symptoms: digital CBT versus pain and SCD education (Education). Our secondary goal is to assess whether baseline depression

symptoms moderate the effect of interventions on pain outcomes. We hypothesize that digital CBT will confer greater benefits on pain outcomes and depressive symptoms at 6 months and a greater reduction in health care use (eg, opioid prescriptions or refills or acute care visits) over 12 months.

Methods: The CaRISMA (Cognitive Behavioral Therapy and Real-time Pain Management Intervention for Sickle Cell via Mobile Applications) study is a multisite comparative effectiveness trial funded by the Patient-Centered Outcomes Research Institute. CaRISMA is conducted at six clinical academic sites, in partnership with four community-based organizations. CaRISMA will evaluate the effectiveness of two 12-week health coach–supported digital health programs with a total of 350 participants in two groups: CBT (n=175) and Education (n=175). Participants will complete a series of questionnaires at baseline and at 3, 6, and 12 months. The primary outcome will be the change in pain interference between the study arms. We will also evaluate changes in pain intensity, depressive symptoms, other patient-reported outcomes, and health care use as secondary outcomes. We have 80% power to detect a difference of 0.37 SDs between study arms on 6-month changes in the outcomes with 15% expected attrition at 6 months. An exploratory analysis will examine whether baseline depression symptoms moderate the effect of the intervention on pain interference.

Results: This study will be conducted from March 2021 through February 2022, with results expected to be available in February 2023.

Conclusions: Patients with SCD experience significant disease burden, psychosocial stress, and impairment of their quality of life. CaRISMA proposes to leverage digital technology and overcome barriers to the routine use of behavioral treatments for pain and depressive symptoms in the treatment of adults with SCD. The study will provide data on the comparative effectiveness of digital CBT and Education approaches and evaluate the potential for implementing evidence-based behavioral interventions to manage SCD pain.

Trial Registration: ClinicalTrials.gov NCT04419168; https://clinicaltrials.gov/ct2/show/NCT04419168.

International Registered Report Identifier (IRRID):   PRR1-10.2196/29014

Introduction

Background

Sickle cell disease (SCD) is a genetic hemoglobinopathy disorder that predominantly affects those of African descent in the United States [1,2]. Adult patients living with SCD have acute and chronic complications, including daily chronic pain and recurrent, unpredictable, vaso-occlusive episodes of pain, which often require immediate medical attention [3]. These complications have a significant impact on patients' daily functioning, health-related quality of life (HRQoL), and mental health [1-5]. In addition, acute and chronic pain as well as depression have been associated with increased health care use and/or premature death [6-12].

Current standards for pain management in patients with SCD are inadequate [13,14]. There is a general overreliance on the use of opioids for pain management among providers and patients, despite the known physical and psychological consequences [15-18]. It is estimated that up to 87% of adults and 44% of children aged younger than 6 years with SCD are prescribed opioids [19], despite the lack of data to support their long-term efficacy. The chronic use of daily opioids is associated with side effects and hyperanalgesia, which in turn likely contribute to increased pain [20] and worse HRQoL [21]. There is a pressing need for effective, nonpharmacological interventions to optimize chronic pain management in patients with SCD [22].

Cognitive behavioral therapy (CBT) has been used in other patient populations, resulting in clinical benefits [23-27]. However, even with the broad use of CBT in other pain populations, its use has not been incorporated into pain management plans for individuals with SCD. Multiple barriers have prevented patients with SCD from receiving quality CBT pain services, including a lack of access, limited local availability, expected cost or copayments, and the stigma associated with seeing a mental health provider or specialist.

Advances in technology have had a major impact on the delivery of psychosocial treatments. Although limited access to the internet among minority populations has been problematic in the past, the emergence of mobile technology has helped bridge the *digital divide*. Many patients with SCD have reported wide access to or ownership of personal or mobile devices [28,29]. There has also been growing evidence to support the feasibility, acceptability, and effectiveness of mobile health interventions in patients with chronic medical conditions [30-32], including SCD [33]. For all these reasons, patients with SCD may greatly benefit from digital behavioral interventions that can be accessed on computers or mobile phones [34,35].

Despite the potential benefit of integrating digital CBT into routine SCD care, there are currently no large-scale trials demonstrating the benefits of this intervention approach in this population. In fact, no adequately powered clinical trials have demonstrated the effectiveness and dissemination potential of any behavioral pain management approach for adults with SCD [22,36-38]. There is also limited evidence to guide health care

providers on which nonpharmacological pain management strategies are feasible, acceptable, and effective for adult patients with SCD. Therefore, there is a need for an adequately powered pragmatic study to evaluate whether digital behavioral pain treatment strategies are effective and can be implemented at scale into routine SCD care in real-world settings.

Objectives

The primary objective of the CaRISMA (Cognitive Behavioral Therapy and Real-time Pain Management Intervention for Sickle Cell via Mobile Applications) trial is to compare the effectiveness of two mobile phone–delivered programs for reducing SCD pain symptoms at the 6-month follow-up: digital CBT versus pain and SCD education (Education). We will also evaluate the sustainability of the intervention effects at the 12-month follow-up. The secondary objective is to assess whether baseline depression symptoms moderate the effect of interventions on pain outcomes. We hypothesize that digital CBT will confer greater improvement in pain interference, pain intensity, and depressive symptoms at 6 months compared with Education. We also hypothesize that digital CBT will confer a greater reduction in health care use (eg, opioid prescriptions or refills or acute care visits) over 12 months compared with Education.

Methods

Study Design

CaRISMA is a multisite, randomized, pragmatic, comparative effectiveness trial that will be conducted at 6 comprehensive sickle cell centers and 4 community-based organizations (CBOs). A total of 350 adults with SCD who report chronic pain and/or use long-acting or daily opioids will be enrolled and randomized in a 1:1 ratio to receive either a digital CBT program tailored for adults with SCD (CBT) or pain and SCD education (Education) on their mobile phones for 12 weeks. Both programs will use identical mobile-based technology platforms, with the only difference being the content provided. The focus of the digital CBT program is to teach behavioral coping skills through participants' *seeing and doing*, whereas the pain education arm focuses on improving self-management through participants' *learning and knowing* more about pain and SCD.

Inclusion and Exclusion Criteria

English-speaking adults with any SCD genotype who are 18 years of age or older reporting chronic pain (ie, pain at least 4 days a week over the past 3 months or longer) and/or being prescribed long-acting or daily opioid medication for pain will be eligible to participate. As the intervention content and presentation were specifically designed for adults, age was restricted to individuals aged 18 years or older. Patients who do not meet the chronic pain criteria or simply do not want to participate in an intervention arm of the study have the option to complete the battery of questionnaires at baseline and each time they return to the clinic for a routine follow-up visit. This convenience sample of nonintervention patients will be used for exploratory comparisons and is not included in the target sample size of 350.

Individuals with cognitive dysfunction or low literacy may not benefit from all components of the intervention. During the electronic consent process, potential participants will be required to answer six consent comprehension questions correctly. These questions aim to ensure that all enrolled participants understand the study protocol and have the appropriate level of literacy and cognitive functioning to benefit from the intervention. Any participant who fails the consent comprehension assessment will be excluded from participation at the time of screening but may be rescreened in 3 months.

A smartphone is required for participation. Otherwise, eligible patients who do not own a smartphone will be provided one with cellular and data service for 12 months as part of the study.

Recruitment, Enrollment, and Randomization

The target sample size for this study is 350 participants. We will implement a hybrid strategy of in-person and web-based enrollment to ensure that we recruit a representative spectrum of the adult SCD population, regardless of their location. In-person recruitment will be from six clinical academic sites: University of Pittsburgh Medical Center, Duke University, Johns Hopkins University, Ohio State University, University of Illinois at Chicago, and East Carolina University. Remote, web-based recruitment will be done through the following CBO partners: Sickle Cell 101 (SC101), Sickle Cell Community Consortium (SCCC), Sickle Cell Warriors (SCWarriors), and Children's Sickle Cell Foundation.

In-Person Recruitment at Clinical Sites

At each of the enrollment sites, a tablet-administered screening tool and best practice alerts will be used to identify patients with SCD who have chronic pain, as indicated by self-reports. The tool will also flag patients with a chronic pain diagnosis or those who have been prescribed chronic opioid therapy for pain. Each clinical site will screen approximately 90-100 patients, and we expect to approach and screen 540-600 potential participants across all six sites.

Web-Based Recruitment Through Community Partners

Our partnering CBOs have created an active community that includes more than 10,000 patients with SCD. For this study, SC101, SCWarriors, Children's Sickle Cell Foundation, and SCCC and their partnering organizations will seek potential participants via message blasts on their CBO websites, social media groups, and email listservs and at patient or family meetings. Interested patients will access a short web-based screener on a mobile device to confirm their eligibility. Potential participants must be able to read the study consent and correctly answer comprehension questions to ensure their understanding of the study goals and procedures. Our group has published data on the use of this electronic consent process in a clinical study [39] and a large multisite trial of digital CBT [40], which is also used in other ongoing studies.

Participant Incentives

Participants who enroll in the intervention, but do not receive a study smartphone, will instead receive payment to cover the cost of smartphone data or use while on the study, for a total of US $250. This will be paid in increments throughout the

participants' 12-month participation in the study. At baseline, participants will receive US $75 after completing all baseline questionnaires, accessing and beginning the intervention program, and making one phone contact with their health coach. At each follow-up (ie, 3-month, 6-month, and 12-month time points), participants will receive US $50 after completing the questionnaires for the follow-up assessment. An additional US $25 will be given to those who complete all four follow-ups throughout the 12-month study period. Participants who are given a smartphone will not receive any monetary compensation. Participants in the nonintervention comparison group will not receive payment.

Randomization

Upon completion of eligibility, participants will be randomly assigned to either digital CBT or Education. Permuted block randomization will be stratified by study center (eg, one of the six clinical sites or from a community partner) in an effort to control for site-specific disease education and treatment approaches. The randomization schema was created by the lead statistician in the data coordinating center and integrated into the web-based data capture system.

Study Procedures

In the first 3 months of the study, intervention participants will be asked to complete the modules for their assigned study arm, that is, digital CBT or Education (Figure 1). The recommended progression is one module per week over 12 weeks, which will give participants time to practice the techniques they learn in each module.

Figure 1. CaRISMA (Cognitive Behavioral Therapy and Real-time Pain Management Intervention for Sickle Cell via Mobile Applications) study design with two intervention arms (digital cognitive behavioral therapy vs education) and 12 months of follow-up for all participants. CBT: cognitive behavioral therapy.
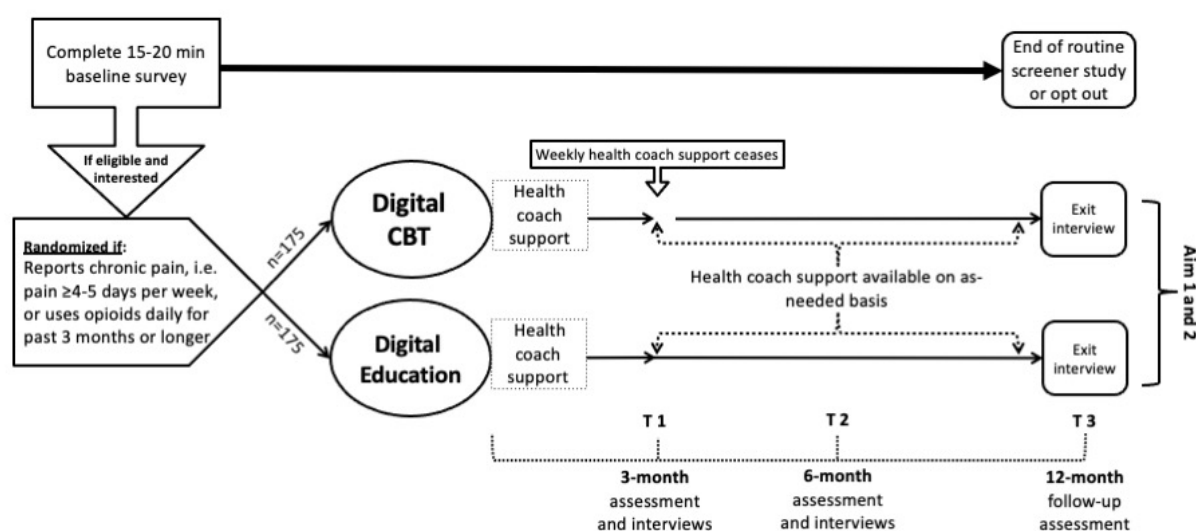
At 3-, 6-, and 12-month follow-up, participants will receive a link to a web-based survey tool to complete the study assessments, including Painimation, the Sickle Cell Self-Efficacy Scale (SCSES), Patient Reported Outcomes Measurement Information System measures, Adult Sickle Cell Quality of Life Measurement Information System measures, Patient Health Questionnaire-9 (PHQ-9), and General Anxiety Disorder Scale-7 (GAD-7). Between these follow-up assessments, participants will be expected to continue reporting their daily pain intensity diaries through a web-based survey tool that they can access on their smartphone app. A summary of the key study measures and outcomes is presented in Table 1.

Table 1. Schedule of study outcomes.

Outcome and measure	Month of study			
	0	3	6	12
Primary				
Patient Reported Outcomes Measurement Information System Pain Interference	✓	✓	✓	✓
Secondary				
Daily pain intensity (mobile web app) or Painimation[a]	✓	✓	✓	✓
ASCQ-ME[b] Emotional Functioning and Social Impact scales	✓	✓	✓	✓
Depressive symptoms (Patient Health Questionnaire-9)	✓	✓	✓	✓
Generalized Anxiety Disorder Scale-7	✓	✓	✓	✓
Medical				
Health care use (PCORnet): opioid prescriptions, emergency department visits, and hospitalizations				✓
Process evaluation				
Sickle Cell Self-Efficacy Scale	✓	✓	✓	✓
Program engagement and treatment dose	✓	✓	✓	✓

[a]Measured daily for 12 months.

[b]ASCQ-Me: Adult Sickle Cell Quality of Life Measurement Information System.

For intervention participants, in addition to the quantitative assessments, the University of Pittsburgh Qualitative, Evaluation, and Stakeholder Engagement (Qual EASE) Research Services will conduct a set of qualitative interviews at the end of the study. The goal of these interviews is to further understand the lived experience of patients in the trial and determine which intervention works best for whom and when. Qual EASE Research Services will select and interview 24 patients in each treatment group, stratified by high or low depression scores, for a total of 48 interviews (ie, 12 digital CBT patients with a PHQ-9 score ≤10, 12 digital CBT patients with a PHQ-9 score >10, 12 digital Education patients with a PHQ-9 score ≤10, and 12 digital Education patients with a PHQ-9 score >10). This distribution will allow us to qualitatively compare the experiences of patients with different depression levels and explore quantitative findings related to intervention efficacy in patients with various levels of depression severity. The patient

sample size has been selected to allow for a high likelihood of reaching thematic saturation regarding patient experience [41].

Description of Study Arms

There are three main components of the CaRISMA program (Figure 2): the chatbot app, a health coach, and an online support group. Both study arms will receive chatbot app interventions. Using a scripted chatbot and conversational interface, the chat component of the program provides 24/7 chat-style interactions to assess participants' needs and deliver personalized content to them. As users move through the chatbot, they can view their progress and gain access to all of the tools and lessons they have unlocked. They also have the ability to view their status and the badges they have received for specific accomplishments. The intervention encourages users to visit a publicly accessible social media group and virtual meet-up activities promoted by the CaRISMA program.

Figure 2. Screenshots of (A) the interactive chatbot that asks users questions and pushes appropriate content. (B) and (C) show examples of cognitive behavioral therapy content that teaches control of the negative thoughts and mood contributing to pain. (D) Example of educational content, curated by Sickle Cell 101, which teaches general facts about sickle cell disease and pain. (E) and (F) show videos of adults with sickle cell disease teaching content and talking about their experiences with stress.
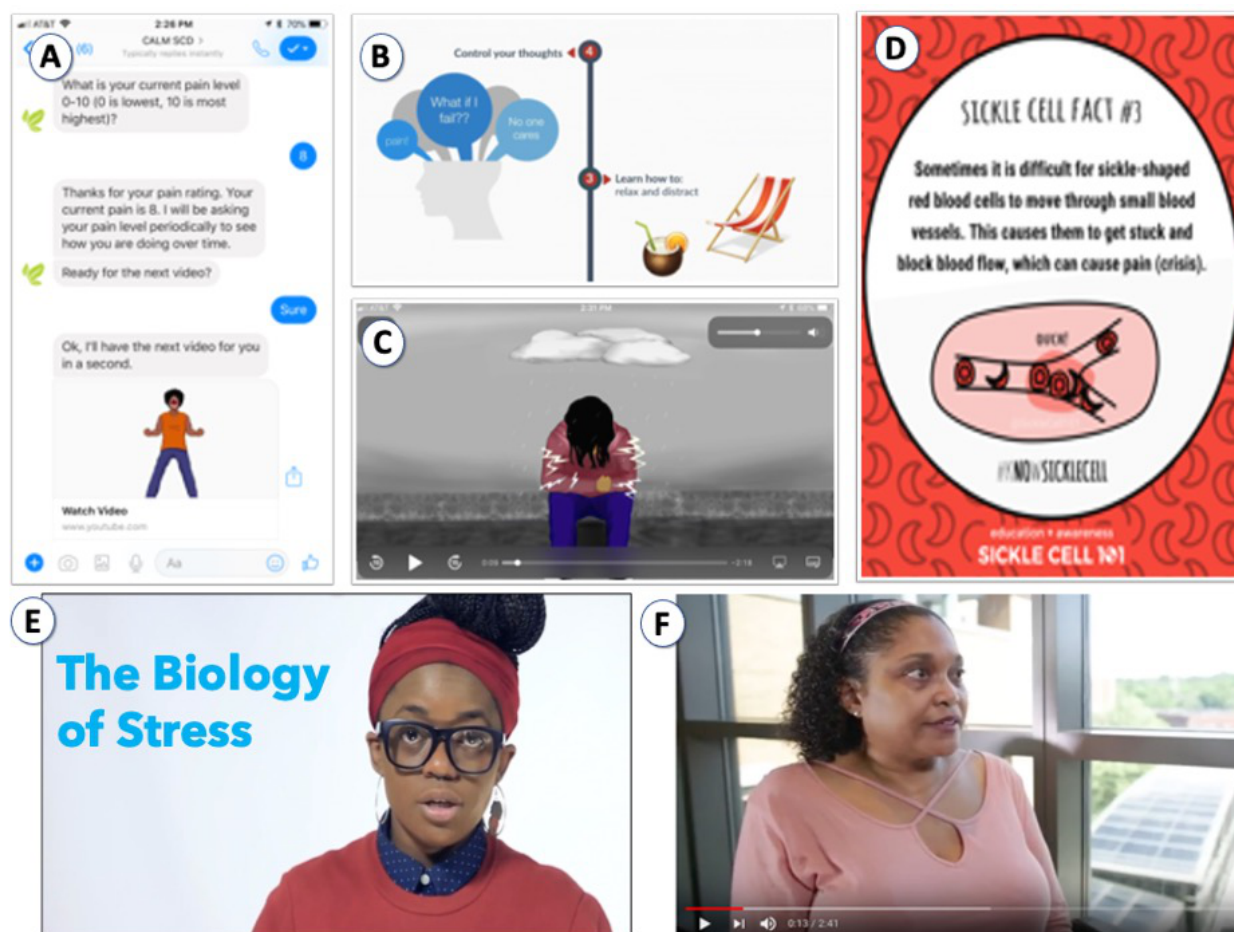
Digital CBT Arm

The digital CBT program for pain management will teach users how to recognize negative thoughts and emotions, use cognitive and problem-solving skills, and apply coping behaviors, such as distraction, activity scheduling, and relaxation. All of the video content on the CBT arm is co-designed with, delivered by, and features adults living with SCD. The digital CBT arm emphasizes skills acquisition and learning through practice; thus, the program involves homework assignments and challenges as well as continued check-ins with a health coach who helps reinforce CBT skills and encourages practice and program engagement. The digital CBT program also gives users access to a study-associated Facebook page where they can discuss with other patients the issues that they faced and what skills were or could be used to address them. This intervention is consistent with the tailored behavioral services that patients would receive individually or as a group when working with a psychologist or behavioral pain specialist.

Digital Education Arm

The digital Education intervention, also delivered via the CaRISMA chatbot, is focused on pain and SCD education. The Education program teaches users about chronic pain, healthy lifestyle tips (eg, nutrition and exercise), and facts about SCD.

The emphasis is on knowledge acquisition and gives users an opportunity to apply what they have learned through brief quizzes and discussions with the health coach and their social network. All of the education program content is developed and delivered by SC101 and features their community members, adults with SCD. This program is consistent with the education that patients and families would receive with a patient educator or what is currently provided via the web and social media through two of our community partners, SCWarriors and SC101. Users in the Education arm will also be asked to access publicly accessible social media groups and virtual meet-up activities.

Health Coaches

Both study arms will have access to a health coach. Health coaches all have minimum a college education with some background in community health, patient advocacy, or clinical psychology. Some health coaches are adults who live with SCD. The number of health coaches is expected to vary throughout the 3-year study, with 3-5 coaches active at any given time, some of whom will be adults with SCD. All health coaches undergo approximately 8 hours of training in CBT, motivational interviewing, acceptance and commitment therapy, problem-solving techniques, general counseling strategies, and advanced education on SCD. In addition to the initial training, over the course of the study, health coaches will attend a weekly

group supervision that includes role-playing and review of interactions (phone or text message) with participants and weekly one-on-one supervision sessions, with a clinical psychologist.

The primary function of the health coach is to provide emotional and informational support on a weekly basis. The health coach will reinforce the use of skills and interventions learned within the program. The health coach will touch base with participants once a week, ideally over the phone, but texting will also be acceptable. In addition, health coaches may send personalized texts in between weekly meetings to help participants stay motivated. After 12 weeks, participants will no longer be required to engage with their health coach; however, if they would like to remain in contact with their health coach, they will be able to reach out and make an appointment.

To maintain intervention continuity and fidelity, health coaches will participate in weekly supervision sessions led by a masters-level psychologist and the study principal investigator (PI) for review and discussion of participant interactions. Telephone calls will be periodically recorded, at random, for audits and reviews during supervision sessions. All text message communications will be sent from a common account, and the content of these messages is monitored and periodically audited.

Study Population: Recruitment and Retention

We will overrecruit by 15% to account for potential dropouts and loss to follow-up. However, every effort will be made to maintain participation in the study groups and obtain all posttreatment measures from all participants. Participants will receive a gift card for each outcome assessment completed. We will ask for multiple phone numbers, and we will use emails, text messages, and phone calls to remind participants of the various web-based assessments. Strategies to promote adherence include an appealing and engaging user-centered program,

gamification elements (eg, positive feedback loops and short-term goals), and social elements (eg, peer support). The characteristics of adherent versus nonadherent participants will be assessed for systematic differences, which if found will be examined with sensitivity analyses to determine their effect on outcomes.

Study Outcomes and Measures

Primary Pain Outcome: Pain Interference

Patient Reported Outcomes Measurement Information System Pain Interference [42] assesses the effect of patient-reported pain on relevant aspects of a person's life and may include the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. This measure will only be completed at baseline and 3, 6, and 12 months.

Secondary Pain Outcome: Daily Pain Intensity

Participants will be asked to enter their daily pain via a mobile website. They will receive reminder notifications via text messages for 2-week periods at baseline and 3, 6, and 12 months. However, between these automated-reminder periods, participants will be encouraged to continue entering their pain scores on the mobile pain web app.

Other Secondary Outcomes

Painimation

Painimation is an electronic pain assessment tool that allows users to better communicate pain symptoms [39]. Patients are provided with a selection of animations (*painimations*) that they use to describe the quality of their pain. The painimations can be adjusted to reflect pain intensity. Screenshots of the Painimation app illustrate the splash screen, paintable body image, and selection of painimations to indicate the quality and intensity of pain (Figure 3).

Figure 3. The Painimation screen allows users to select and adjust up to three animations to reflect pain quality and intensity.
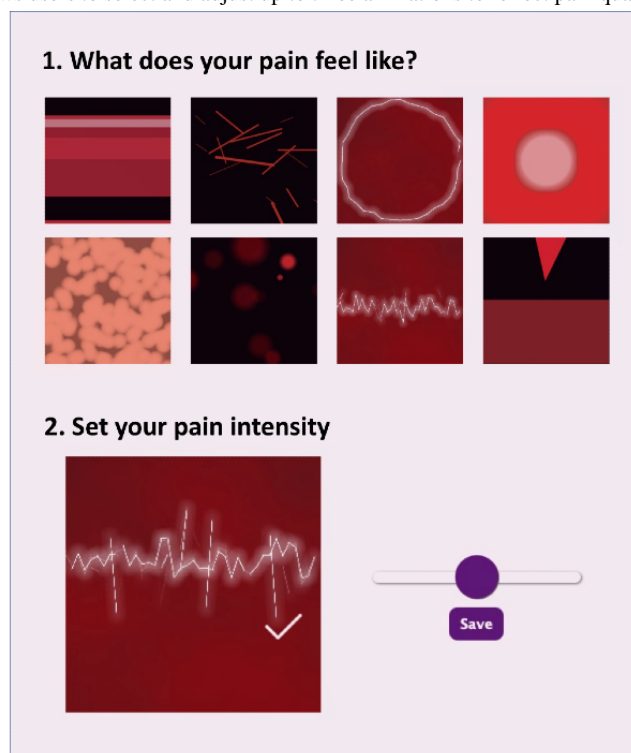
Medical Outcomes

For patients recruited at one of the six clinical sites, we will evaluate objectively measured opioid medication prescriptions and refills and emergency department visits or hospitalizations for pain episodes. We will work in collaboration with PCORnet to collect data retrospectively (12 months before enrollment) and prospectively (12 months after enrollment) from patients' electronic health records. These data will allow us to track opioid medication use, health care use, and laboratory values (eg, hemoglobin level), as well as other key clinical outcomes. For patients recruited from our CBO partners or on the web, we will only evaluate their medical records to confirm their SCD diagnosis if they do not receive their SCD care at one of the participating clinical sites.

Current Opioid Misuse Measure

Current Opioid Misuse Measure [43] is a self-report measure to monitor indicators of current aberrant drug-related behaviors in patients with chronic pain on opioid therapy. This measure will be completed only at baseline and 12 months.

Patient Health Questionnaire

PHQ-9 assesses the degree of depression severity [44]. The PHQ-9 total score is for nine items, all rated as *0* (not at all) to *3* (nearly every day), with total scores ranging from 0 to 27. Scores of 5, 10, 15, and 20 represent cut-off points for mild, moderate, moderately severe, and severe depression, respectively [45]. This measure will only be completed at baseline and 3, 6, and 12 months.

Generalized Anxiety Disorder Scale-7

GAD-7 evaluates the severity of anxiety [46]. The GAD-7 total score for the 7 items ranges from 0 to 21. Scores of 5, 10, and 15 represent the cut-off points for mild, moderate, and severe

anxiety, respectively [47]. This measure will only be completed at baseline and 3, 6, and 12 months.

Adult Sickle Cell Quality of Life Measurement Information System Emotional Functioning and Social Impact Scales

The ASCQ-ME emotional functioning and social impact quality-of-life measure was specifically designed for SCD and evaluates the health care experience of patients with SCD, emotional response to stress, and social relationships [48]. These measures will only be completed at baseline and 3, 6, and 12 months.

Sickle Cell Self-Efficacy Scale

SCSES is a self-report measure to assess the ability of patients with SCD to function on a day-to-day basis and manage their SCD symptoms [49]. This measure will only be completed at baseline and 3, 6, and 12 months.

Adverse Events

We adapted the following definition to address the negative effects of internet interventions [50] and face-to-face behavioral treatment [51]: adverse events consist of negative events that may emerge from treatment and are perceived as adverse by the patient, causing the deterioration of target symptoms and/or negative experiences that extend beyond the completion of treatment. Examples include increased anxiety during CBT training or being embarrassed by revealing negative thoughts and insecurities to the health coach. Adverse events could also reveal negative effects directly attributable to treatment, providing our team and other researchers with information on possible mechanisms underlying these negative effects. The health coaches will routinely assess for increasing negative affect, and the GAD-7 will be administered at 3, 6, and 12 months to assess for increasing anxiety. In addition, we

developed a suicide risk management protocol to illustrate risk triggers, assessments, and determinations (Figure 4).

Figure 4. Flow diagram for the Suicide Risk Management Protocol. CCC: Clinical coordinating center; HC: Health coach; PHQ-9: Patient Health Questionnaire-9; SRMP: Suicide Risk Management Protocol; SSI: Suicide Severity Index.
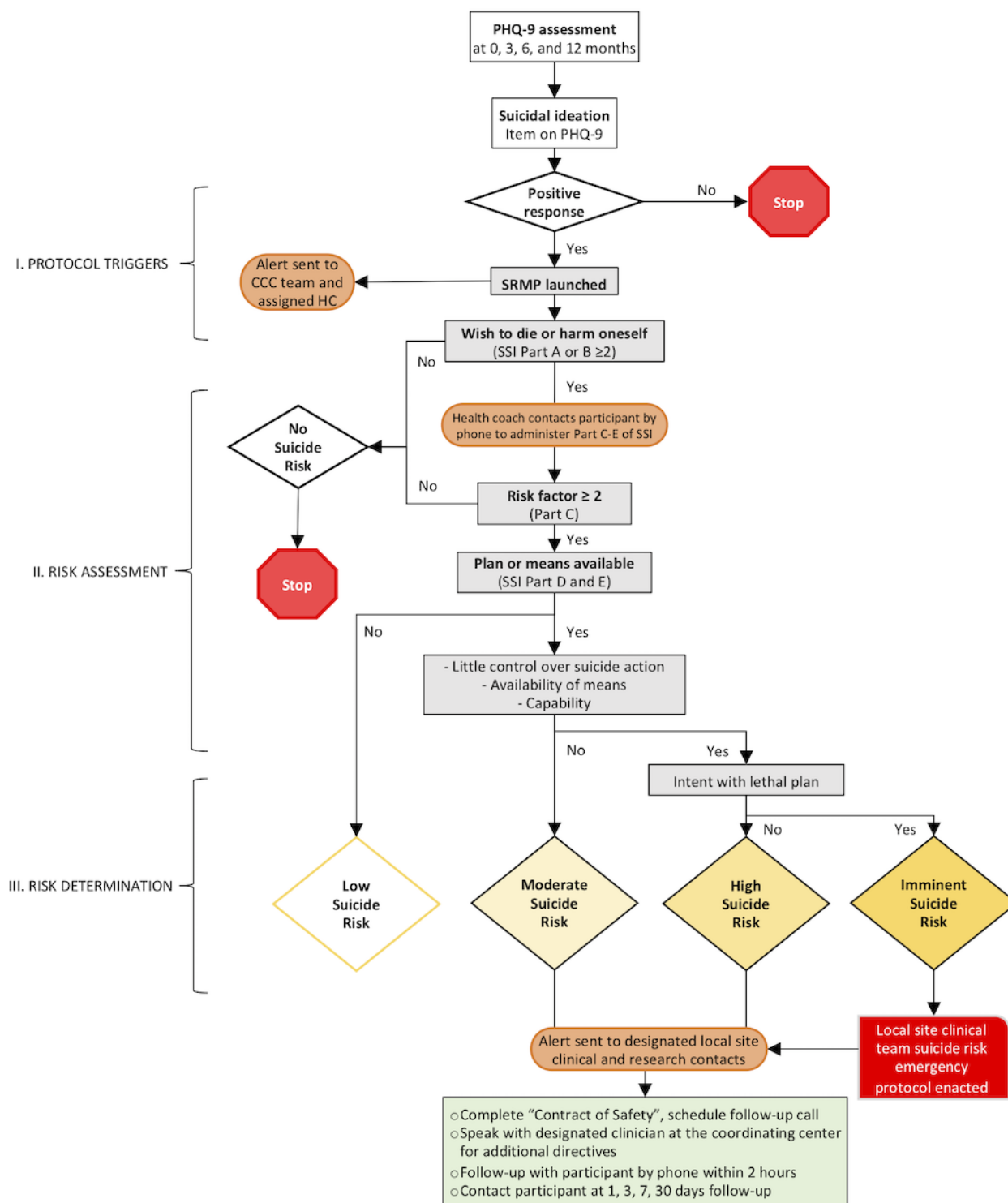
Sample Size Determination

For the primary test of comparative effectiveness of digital CBT versus mobile education (m-Education) for the trial (aim 1), the power calculation is based on the comparison of intervention groups for the main outcome of the 6-month change in pain interference. Specifically, our sample size of 350 participants enables 80% power to detect a difference of 0.37 SDs between study arms on 6-month changes. This detectable effect is also applicable to key secondary outcomes, such as pain intensity and depression, as measured by the PHQ-9. Our calculations account for 15% attrition at 6 months.

Statistical Analysis

All primary and secondary analyses will be preceded by descriptive analyses of the baseline and clinical characteristics. Summary statistics will include means and SDs for continuous variables and sample proportions for categorical variables. Median and IQR values will accompany nonnormal, continuous variables. The results will be presented both within and across study arms. All analyses will follow the intention-to-treat approach.

Analysis of Primary and Secondary Pain Outcomes

Linear mixed models will be employed for the primary outcome of pain interference as a function of time, study arm (digital CBT vs Education), time×study arm interaction, study site, and baseline depression level (PHQ-9≤10 vs PHQ-9>10). We will account for multiple observations for each participant by including a random effect for the subject. In addition, baseline variables with large, clinically meaningful between-arm differences will be included as covariates in the secondary analyses. Contrasts will be estimated to assess the impact of digital CBT and education intervention on 6-month improvements in pain intensity. As a secondary investigation, we will use the same linear mixed models to address whether the 6-month improvements are sustainable for 12 months. The analytic strategy for the key secondary outcome of pain intensity will be identical to that of the primary outcome.

As the confirmation of a sickle cell diagnosis may not be made immediately after randomization, we will conduct an a priori sensitivity analysis restricting eligible participants with the confirmation of SCD.

Analysis of Secondary Outcomes

Secondary outcomes such as PHQ-9, Current Opioid Misuse Measure, GAD-7, Adult Sickle Cell Quality of Life Measurement Information System, and SCSES will be analyzed using similar linear mixed models with time, study arm, time×study arm interaction, study site, and baseline depression level as fixed covariates and a random effect for each subject. Health care use will be compared between study arms using generalized linear models to account for count data (ie, Poisson regression) for each of the following: the number of opioid prescriptions, number of emergency department visits, and number of hospitalizations over 12 months after study entry. Predictors will include the study arm, study site, and baseline depression level. The corresponding health care use in the 12 months before study entry will be entered as a covariate in each model. We will offset each model by the participant's time in the study.

Subgroup Analysis

We will examine the heterogeneity of the treatment effect to determine whether the intervention works better for some than for others. Our prespecified analysis plan will examine differences in pain interference between patients with high (PHQ-9>10) and low (PHQ-9≤10) depression. We will augment the primary analysis models for pain interference with relevant main effects for the baseline depression level and 2- and 3-way interactions with the study arm and time. Of primary interest is the significance of the 3-way interaction (time×study

arm×baseline depression level). If significant, we will present the treatment effect estimates and 95% CIs within each subgroup.

Mediation Analysis

For coping skills, self-efficacy, and program engagement or dose measures, changes in scores from baseline to 3 months and from baseline to 6 months will be tested as potential mediating variables. We will use the framework of Kraemer et al [52] to calculate effect sizes, accounting for the impact of the potential mediator variable. In addition to modeling each mediator as a function of time, study arm, time×study arm interaction, study site, and baseline depression level (PHQ-9 ≤10 vs PHQ-9 >10), we will augment the original primary analytic models by including the potential mediator as a covariate.

Addressing Missing Data

We will minimize missing data by using an electronic data collection system and by contacting participants when data are not entered in a timely fashion. We will attempt to characterize the missingness mechanism (missing completely at random, missing at random, or not missing at random) by comparing rates of missingness or attrition between study arms. In addition, we will compare baseline characteristics between participants with and without missing outcome data. If we conclude that our missingness is random, then our likelihood-based approach for the primary analyses will address this. Otherwise, if the missingness can be characterized as nonignorable (not missing at random), we will use approaches such as joint modeling or shared parameter models to produce unbiased estimates of treatment effects. All reasons for dropout or other missing values will be entered by the research staff or community groups (if encountering the patient during community activities) and will be tabulated and summarized, and results will be reported using the CONSORT (Consolidated Standards of Reporting Trials) diagram. Patients who stop reporting data in the app will receive inquiry text messages or phone calls.

Qualitative Analysis

Interviews will be conducted and analyzed by Qual EASE Research Services in the data center of the Center for Research on Health Care at the University of Pittsburgh. An analysis of the interviews will combine thematic analysis and the constant comparison method [53]. Codes will be developed via open coding of the transcripts to determine topics and themes that emerged in the interview transcripts, but input on topics or themes that the study team anticipates being relevant will also be solicited, resulting in simultaneous inductive and deductive development of the codebook. Once the codebook is finalized, 2 data analysts from Qual EASE will be trained using the codebook, following which both coders will independently code 25% of the transcripts. Coding will then be compared to calculate Cohen κ intercoder reliability scores. Any coding discrepancies identified during this comparison will be adjudicated until full agreement is achieved. After satisfactory intercoder reliability (Cohen κ>0.6) is achieved, the primary coder will code the remaining transcripts. The completed coding will form the basis of a thematic analysis of the data and a

constant comparative analysis to compare the experience of patients with depression levels.

Supporting Documentation and Operational Considerations

Regulatory, Ethical, and Study Oversight Considerations

The procedures set out in this protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the investigator abides by Good Clinical Practice guidelines and the guiding principles detailed in the Declaration of Helsinki. The CaRISMA trial will rely primarily on the review of the Institutional Review Board, University of Pittsburgh Human Research Protection Office, while establishing an agreement that all site-specific institutional review boards (IRBs) will review their informed consent documents to ensure local concerns are adequately addressed. Modifications to the study protocol will not be implemented by the investigator without discussion and agreement by the data coordinating center and the study sponsor (ie, Patient-Centered Outcomes Research Institute [PCORI]). However, the investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to the trial patients without prior independent ethics committee or IRB approval or favorable opinion. Any deviations from the protocol must be explained and documented by the investigator. The PI at each institution or site will be responsible for ensuring that all the required data will be collected and properly documented.

Monthly meetings with the study co-PIs, clinical site PIs, community partners, and coinvestigators will help uncover and address study-related issues. These issues will be brought to quarterly data safety monitoring board meetings, which will be responsible for overseeing the trial's progress; making recommendations regarding the safety and benefit of continuing or stopping the trial; ensuring the trial is operating in accordance with similar trials, information from which will be gathered and reviewed; disseminating status and progress updates from the trial to sponsors, funders, and other groups; and making recommendations about how to present the results of the trial on a wider scale to a broader audience.

Informed Consent Process

Before performing any of the research study procedures or interventions, the participants must provide informed consent. Informed consent is a process that is initiated before the individual agrees to participate in the study and continues throughout the individual's study participation. The consent process will occur over the internet and is self-guided. Potential participants can access the consent website via their own electronic device or in a clinical setting via a tablet computer station (kiosk). A video presentation will explain the study to the potential participants in a language understandable to participants, providing all pertinent information (purpose, procedures, risks, benefits, alternatives to participation, etc). A comprehension test will be conducted to ensure participants' understanding of the study goals and procedures. In addition, the most pertinent consent language will be presented on separate webpages where the user must click a button indicating acknowledgment and understanding of the content to advance

to the next screen. Each segment of the consent is presented in concise, easy-to-understand language. Finally, the full consent document will be presented in the form of a PDF on the screen for the potential participant to read in its entirety.

Study Discontinuation and Closure

If this study is prematurely terminated or temporarily suspended, the PI will promptly inform ongoing study participants, the IRB, and the sponsor or funding agency. The PI will also provide the reason(s) for the termination or temporary suspension and describe the process of handling consented or enrolled participants in the event that the study is prematurely terminated.

Confidentiality and Privacy

All participant information, including contact information, questionnaires, and clinical information, will be monitored by the study staff and be available only to them in a Health Insurance Portability and Accountability Act–compliant database. Case report forms and other electronic data will be stored in password-protected files. Only authorized study staff will have access to the study data. Study reports will be deidentified and present findings in the aggregate (or by treatment group).

Results

All study investigators from academic clinic sites and all partners from CBOs convened in May and November 2020 to discuss study progress and finalize plans for study initiation. The IRB at the University of Pittsburgh Human Research Protection Office approved the protocol for the CaRISMA study in May 2020. Owing to COVID-19, enrollment was postponed for approximately 6 months. Study enrollment officially started in March 2021, and the study will be conducted through October 2022, with results expected to be available in February 2023. The study was registered at ClinicalTrials.gov (NCT04419168).

Discussion

Principal Findings

Patients living with SCD have several complications, including daily chronic pain and recurrent, unpredictable vaso-occlusive episodes that often require immediate medical attention [3]. These complications lead to significant impairment in patients' HRQoL across their lifespan, particularly mental and psychosocial well-being. Current standards for pain management in SCD are unsatisfactory and primarily focus on opioids, with little evidence for nonpharmacological interventions in this population [27,28]. The increasing use of opioids has led to several physical and psychological consequences, and the development of effective, nonpharmacological interventions is essential to optimize pain management in adults with SCD [22].

Behavioral interventions have been shown to be efficacious [54-56], but the lack of widespread availability of therapists and CBT-trained clinicians has made implementation into routine care challenging, especially in minority populations, such as patients with SCD. Despite strong evidence supporting the efficacy of digital CBT [23-27], its use remains limited in SCD. With the growing access to mobile and personal

technology [28,29], digital CBT has great potential to address patients' need for evidence-based, user-centered, and rigorous behavioral programs [34,35].

CaRISMA is a large-scale, multi-institution, adequately powered pragmatic study in partnership with CBOs aimed at comparing the effectiveness of two evidence-based behavioral approaches to pain management: CBT and Education. This study will ultimately determine how digital behavioral pain treatment strategies can be effectively implemented at scale in routine care for adults with SCD in real-world settings. CaRISMA has the potential to inform behavioral nonpharmacological pain management approaches with strategies that are feasible, acceptable, and effective, which medical providers can offer to their adult patients with SCD [22,36-38].

Conclusions

The CaRISMA trial will fill a knowledge gap in the SCD literature by evaluating the effectiveness of two remotely delivered pain management programs for adults with SCD: digital CBT and digital Education. In this trial, we will also evaluate the sustainability of intervention effects over time and other related key aspects of pain management, such as depression and emotional and psychosocial well-being. Addressing these questions will be essential to inform future research directions of digital behavioral interventions, not only for adults with SCD but also for children and adolescents with SCD as well as other chronic pain populations. If digital CBT demonstrates effectiveness in this trial, future dissemination and implementation efforts will be critical to ensure that this intervention is widely available and used by many adult patients with SCD in the United States and worldwide.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Comments from the grant proposal peer-review process with the Patient-Centered Outcomes Research Institute.
[DOCX File , 20 KB - resprot_v10i5e29014_app1.docx]

Multimedia Appendix 2
Responses to comments from the peer-review process using Patient-Centered Outcomes Research Institute.
[DOC File , 325 KB - resprot_v10i5e29014_app2.doc]

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Abbreviations

CaRISMA: Cognitive Behavioral Therapy and Real-time Pain Management Intervention for Sickle Cell via Mobile Applications
CBO: community-based organization
CBT: cognitive behavioral therapy
GAD-7: General Anxiety Disorder Scale-7
HRQoL: health-related quality of life
IRB: institutional review board
PCORI: Patient-Centered Outcomes Research Institute
PHQ-9: Patient Health Questionnaire-9
PI: principal investigator
SC101: Sickle Cell 101
SCCC: Sickle Cell Community Consortium
SCD: sickle cell disease
SCSES: Sickle Cell Self-Efficacy Scale
SCWarriors: Sickle Cell Warriors
Qual EASE: Qualitative, Evaluation, and Stakeholder Engagement

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Protocol

Cognitive Outcomes During COVID-19 Confinement Among Older People and Their Caregivers Using Technologies for Dementia: Protocol for an Observational Cohort Study

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Abstract

Background: The COVID-19 pandemic has led to worldwide implementation of unprecedented restrictions to control its rapid spread and mitigate its impact. The Spanish government has enforced social distancing, quarantine, and home confinement measures. Such restrictions on activities of daily life and separation from loved ones may lead to social isolation and loneliness with health-related consequences among community-dwelling older adults with mild cognitive impairment or mild dementia and their caregivers. Additionally, inadequate access to health care and social support services may aggravate chronic conditions. Home-based technological interventions have emerged for combating social isolation and loneliness, while simultaneously preventing the risk of virus exposure.

Objective: The aim of this cohort study is to explore, analyze, and determine the impact of social isolation on (1) cognition, quality of life, mood, technophilia, and perceived stress among community-dwelling older adults with mild cognitive impairment or mild dementia and on the caregiver burden; (2) access to and utilization of health and social care services; and (3) cognitive, social, and entertainment-related uses of information and communication technologies.

Methods: This study will be conducted in Málaga (Andalucía, Spain). In total 200 dyads, consisting of a person with mild cognitive impairment or mild dementia and his/her informal caregiver, will be contacted by telephone. Potential respondents will be participants of the following clinical trials: support, monitoring, and reminder technology for mild dementia (n=100) and television-based assistive integrated service to support European adults living with mild dementia or mild cognitive impairment (n=100).

Results: As of May 2021, a total of 153 participants have been enrolled and assessed during COVID-19 confinement, of whom 67 have been assessed at 6 months of enrollment. Changes in the mean values of the variables will be analyzed relative to baseline findings of previous studies with those during and after confinement, using repeated-measures analysis of variance or the nonparametric Friedman test, as appropriate. The performance of multivariate analysis of covariance (ANCOVA) to introduce potential covariates will also be considered. Values of 95% CI will be used.

Conclusions: If our hypothesis is accepted, these findings will demonstrate the negative impact of social isolation owing to COVID-19 confinement on cognition, quality of life, mood, and perceived stress among community-dwelling older adults with mild cognitive impairment and mild dementia, the impact on technophilia, caregiver burden, the access to and utilization of health

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and social care services, and the cognitive, social, and entertainment-related use of information and communication technologies during and after COVID-19 confinement.

Introduction

The COVID-19 pandemic has forced government authorities worldwide to implement unprecedented restrictions to control its rapid spread and mitigate its impact [1]. In response to the outbreak, Spain declared, by royal decree (463/2020), a national emergency, with the exceptional measure of a nationwide lockdown enforcing social distancing, quarantining of those exposed to the virus, and home confinement of those who remain healthy, while allowing only essential outings [2]. This home-confinement by restricting movement to carry out activities of daily life and social distancing from loved ones may be a challenging and unpleasant experience for those who undergo it, leading them to experience social isolation and loneliness and having health-related consequences. Vulnerable populations at a higher risk are fragile community-dwelling older adults whose chronic conditions may be aggravated by the consequences of the confinement and, in particular, people with mild cognitive impairment or mild dementia (PMCI/MD) [3].

Social isolation (the absence of social contacts, interactions, or relationships with other individuals including family, friends, or neighbors) and loneliness (perception of isolation or feeling of being lonely) have been well established as risk factors for health-related consequences and quality of life (QoL) [4] (an individual's perception of their position in life in a cultural context in relation to their goals, expectations, standards, and concerns [5], including physical and mental health, social relationships, and participation in activities).

Numerous observational studies have reported associations between social isolation and an increased risk of dementia and cognitive decline in older adults [6-8]. Reduction of social contacts and lower levels of participation in social activities are associated with declines in global cognition, processing speed, executive function, and visuospatial abilities [9].

Facing novel and unknown situations is a potential stressor, especially when cognition may be compromised [10], and loneliness may help predict changes in depressive symptomatology [11]. A systematic review on social relationships and depression in later life, which included 37 studies (25 cross-sectional and 12 longitudinal studies), reported that having a decreased social network was significantly associated with depression in older adults [12].

Social isolation is likewise associated with a higher prevalence of other comorbid conditions including cardiovascular diseases [13], stroke [13], and the risk of premature mortality [14]. Furthermore, studies on social isolation and health-related behaviors have reported that older people who are isolated are more likely to have less health-related behaviors such as poor diets, tobacco use, heavy alcohol use, and a lack of physical activity [6,15].

The burden of COVID-19 exerts pressure on health care and social support services [2] and caregivers. Spain's health care system is struggling to deliver emergency and intensive care. Routine interventions for service provision, such as primary and specialist care consultations, diagnostic testing, and nonemergency interventions, have been cancelled, postponed, or their delivery has shifted from an in-person to a technology-based format. Additionally, caregivers' burden may be worsened in an attempt to reduce the risk of virus exposure among their care recipients.

In the information age, with the increased use of information and communication technologies (ICTs), home-based technological interventions [16] including smartphones, tablets, computers, smart televisions, virtual assistants, and ambient assistive devices have emerged for combating social isolation and loneliness. A challenge associated with these interventions is that vulnerable populations at a higher risk of becoming severely socially isolated owing to the COVID-19 pandemic, such as older people, may have negative attitudes and lack of enthusiasm toward the use of ICTs, thus having low technophilia [17]. Technophilia is described as the "attraction, enthusiasm of the human individual determined by the activities which involve the use of advanced technologies. It is expressed by easy adaptation to the social changes brought by technological innovations" [18].

International recommendations stress the need to urgently identify the needs of people with dementia and their caregivers and establish technological strategies for their assistance and support [19]. In response to the COVID-19 pandemic, studies have shown increased interest in technology among people with dementia [20] and have emphasized the challenges associated with the adoption of technology-based interventions by people with dementia [21], but few studies have explored the impact of technologies on social isolation in this population.

The aims of this study are threefold: (1) to explore the impact of social isolation on cognition, QoL, mood, technophilia, and perceived stress of community-dwelling older PMCI/MD and on caregiver burden; (2) to investigate how social isolation affects the access to and utilization of health care and social support services; and (3) to determine the health-related,

cognitive, social, informative, and entertainment-related uses of ICTs during and after 6 months of COVID-19 confinement.

Methods

Study Design

This cohort study will be conducted in Málaga (Andalucía, Spain). The study will assess Cognitive Outcomes During COVID-19 confiNemeNt in Elderly and Their Caregivers Using Technologies for DEMentia (CONNECTDEM). Interviews will be conducted telephonically to guarantee the safest means to communicate during the COVID-19 pandemic. Researchers will contact participants by telephone, explain the study in detail, answer any questions which may arise, and ask those who are willing to participate in the study to provide consent. Interviews were conducted in May 2020. Follow-up assessments would be carried out after 6 months.

Setting

Participants will be identified from the support, monitoring, and reminder technology for mild dementia (SMART4MD; trial# NCT03325699) [22] and television-based assistive integrated service to support European adults living with mild dementia or mild cognitive impairment (TV-AssistDem; trial# NCT03653234) [23] clinical trials, both of which aim to assess the effects of ICTs to support dementia by using a tablet-based health app and a television-based assistive integrated service, respectively. Participants will include people with self-perceived cognitive impairment or their caregiver's perception of cognitive impairment that has been present for >6 months under primary and secondary care services, including those who are being followed-up at memory clinics, outpatient clinics, day hospitals, or other components of specialist mental health, geriatric medicine, and neurology services.

Participants

The participant dyads will comprise PMCI/MD and their informal caregivers, defined as the person who provides support or care, spends the most time with the patient, is unwaged for this role, and does not participate in a formal network of organized care [24]. In total 200 dyads, 100 from the SMART4MD trial 100 from the TV-AssistDem trial, from both the intervention and control groups will be potential respondents. A dyad will be eligible for inclusion in this study only if they have participated in the SMART4MD or TV-AssistDem clinical trials and they consent to participating in this study.

Outcome Measures

The primary outcome measure will be the change in cognition in PMCI/MDs. Additional assessments will be performed to assess secondary outcomes including the QoL, mood, technophilia, and perceived stress among PMCI/MDs; caregiver burden; access to and utilization of health and social care services; and cognitive, social, and entertainment-related use of ICTs.

Baseline assessments of cognition in PMCI/MDs prior to COVID-19 confinement (T0), their QoL, mood, and technophilia, and the QoL and burden of their caregivers will be compared with assessments carried out during COVID-19 confinement (T1) and at 6 months (T2). Additionally, perceived stress regarding the confinement situation, access to and utilization of health and social care services, and cognitive, social, and entertainment-related use of ICTs will be measured at T1 and T2. The assessments will be conducted under standardized conditions at the study center.

Primary Outcome: Cognition

The mini-mental state examination (MMSE) [25] will be performed to assess the cognitive function of the PMCI/MD. The most common cutoff scores for cognitive impairment and dementia range 23-27 out of 30. As telephonic interviews will be the safest means to communicate with the PMCI/MDs during and after the COVID-19 pandemic, a telephone-based cognitive assessment will be carried out using the 22-item telephonic version of the MMSE [26]. All items of the MMSE can be discussed through the telephone version, except for one question in the orientation section, regarding the floor on which the patient resides (as the researchers would not be able to ascertain that) and the last section assessing language and motor skills. In the telephonic version, we will ask the subject to repeat a phrase and name 1 item (for example: "Tell me, what is the name of the object you are using to talk to me?"). However, a second item will not be named, nor will the person be asked to follow a 3-stage command, read and carry out an instruction, write a sentence, or copy an intersecting pentagon as in the original version.

Secondary Outcomes

Patient QoL

The Quality of Life-Alzheimer's Disease (QoL-AD) scale [27,28] is an instrument specifically designed to measure QoL in PMCI/MDs from the perspective of both the patient and the informal caregiver. It is a 13-item scale, which includes assessments of the person´s relationships with friends and family, financial situation, physical condition, mood, memory, and an overall assessment of life quality. Response are 4-point multiple-choice options (1="poor," 2="fair," 3="good," and 4="excellent"). Scale scores range from 13 to 52, with higher scores indicating a greater QoL. As cognitive function may be compromised, informal caregivers will also complete the QoL-AD, in parallel with and on behalf of the PMCI/MD throughout the study.

The European QoL 5-dimension, 3-level instrument [29,30] is a standardized generic instrument consisting of a descriptive system and a visual analog scale. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has three levels: no problems, moderate problems, and extreme problems. A 1-digit number expresses the level selected for that dimension. The digits can be combined into a 5-digit number that describes the patient's health state. The visual analog scale records the patient's self-rated health on a vertical scale, where the endpoints are "the best health you can imagine" and "the worst health you can imagine." The European QoL 5-dimension, 3-level instrument has been shown to correlate well with the QoL-AD scale, indicating that using both measures in parallel is compatible [31].

Mood

The shortened form of the geriatric depression scale [32] will be used to assess mood. Of 15 items in this version, 10 indicate depression when answered positively, while the remaining 5 (items 1, 5, 7, 11, and 13) indicate depression when answered negatively. Scores of 0-4 are considered normal, 5-8 indicate mild depression, 9-11 indicate moderate depression, and 12-15 indicate severe depression.

Technophilia

The instrument for measuring older people's attitudes toward technology [33] measures older people's attitudes and enthusiasm toward health technology. This instrument refers to technophilia as a person's enthusiasm for and positive feelings toward their technology use and the absence of fears and doubts some older people could have about their ability to manage using new technology. The 6 items of this instrument measure 2 factors related to technophilia: 3 items concerning technological enthusiasm and 3 items concerning technological anxiety. Responses are based on a 5-point Likert scale ranging from 1="fully disagree" to 5="fully agree."

Perceived Stress

The perceived stress scale [34] measures the degree to which situations in one's life are appraised as stressful. The scale comprises 10 questions regarding feelings and thoughts during the past month, which are rated on the basis of frequency (0="never," 1="almost never," 2="sometimes," 3="fairly often," and 4="very often"). Scores are obtained by reversing the responses (eg, 0=4, 1=3, 2=2, 3=1, and 4=0) to the 4 positively stated items (items 4, 5, 7, and 8) and then summing the scores of all items.

Caregiver Burden

The 12-item Zarit burden interview [35,36] will be used to evaluate the informal caregivers' burden. This scale has responses scored on a 5-point Likert scale (4="nearly always," 3="quite frequently," 2="sometimes," 1="rarely," and 0="never"). It is a shortened version of the original scale and has been developed specifically for informal caregivers of PMCI/MDs and encompasses issues such as caregiver stress and the degree to which caregiving affects their health and social life. The total score ranges 0-48 (0-10="no to mild burden," 10-20="mild to moderate burden," and >20="high burden").

Service Utilization

The client service receipt inventory scale [37,38] will be used to evaluate the service utilization. This scale is an internationally used method for gathering data on service utilization and other domains relevant for economic analysis of mental health care. It has five sections: background client information, accommodation and living conditions, employment history, earnings and benefits, and a record of services usually used and information on informal caregiver support. The sections assessed will be consultations, admissions, and visits, grouped into subsections in accordance with hospital, specialist, primary, or home care. Treatment related to hospital admissions or illness exacerbation will also be assessed. The adaptability of this scale ensures that it is compatible with the study aims, context, participants' likely circumstances, and the quantity and precision of information required.

Use of ICTs

Use of ICTs, including smartphones, tablets, computers, smart televisions, or other devices, to contact health care and social support services, stimulate cognition, facilitate social connectedness (through telephone calls, video calls, and text messages), to access information on COVID-19 and to enable entertainment.

Covariables

Covariables will involve sociodemographic data including marital status, level of education, and living arrangements, medical history, health perception management, changes in living arrangements due to the lockdown, presence of COVID-19 symptoms in PMCI/MDs or their relatives, the frequency of access to COVID-19–related information, and understanding of the information, ability to manage illnesses, provision of support for purchasing medication and food, coping stress tolerance, mental health, well-being, and self-perceived mood, sleep and rest, alterations in usual sleep patterns and the use of additional medication, and leisure activities including preferred physical, intellectual, recreational, and social activities. The collected variables and data collection time are shown in Table 1.

Table 1. Data collection table.

Measure	Data collection timepoint			
	Outcome variable	Baseline	During COVID-19 confinement	At 6 months
Informed consent	N/A[a]	✓[b]	✓	N/A
Sociodemographic data	N/A	✓	✓	✓
Mini-mental state examination	Primary	✓	✓	✓
Quality of Life-Alzheimer's Disease scale	Secondary	✓	✓	✓
European quality of life 5-dimension, 3-level	Secondary	✓	✓	✓
Geriatric depression scale	Secondary	✓	✓	✓
Instrument for measuring older people's attitudes toward technology	Secondary	X[c]	✓	✓
Perceived stress scale	Secondary	X	✓	✓
Client service receipt inventory	Secondary	✓	✓	✓
Zarit burden interview	Secondary	✓	✓	✓

[a]N/A: not applicable.

[b]Data were collected.

[c]Data were not collected.

Statistical Analysis

The flow of participants will be shown schematically with counts and percentages in a CONSORT diagram. All variables collected will be summarized at baseline and at follow-up. Statistics considered for presentation for continuous measures in summary tables include the mean (SD), minima, and maxima, and if the criteria of normality are not met, the median and the first and third quartiles will be recorded. Categorical variables will be summarized as counts and percentages.

The change in means in the study variables will be analyzed in accordance with the results of previous trials (SMART4MD and TV-AssistDem) with those currently collected using repeated-measures analysis of variance or the nonparametric Friedman test as appropriate. The performance of multivariate analysis of covariance (ANCOVA) to introduce possible covariates will also be considered. A 95% CI will be used for all comparisons. R (version 3.6.1, The R Foundation) will be used for all statistical analysis [39].

Missing Data

Each researcher is responsible for ensuring that any missing data are reported as missing in the study database. Procedures can sometimes be considered when using statistical methods that fail in the presence of any missing values, or in the case of multiple-predictor statistical models, all the data for an individual would be omitted because of a missing value in one of the predictors.

Methods to Ensure the Validity and Quality of Data

Accurate and reliable data collection will be assured through verification and cross-checking of the electronic case report form (CRF). Discrepancies and queries will be generated accordingly in the CRF for web-based resolution by the researcher. In addition, the CRF data will be reviewed on an ongoing basis for scientific plausibility.

Results

This study (ClinicalTrials.org trial# NCT04385797 [40]) was approved by the North-East Malaga Ethics Committee (1078-N-20) on April 30, 2020. Participants will provide their written consent before participating in the study. Substantial amendments that require review by the ethics committee will not be implemented until they are granted favorable opinion for the study. As of May 2021, a total of 153 participants have been enrolled and assessed during COVID-19 confinement, of whom 67 have been assessed at 6 months.

Discussion

If our study hypothesis is accepted, these findings will demonstrate the negative impact of social isolation due to COVID-19 confinement on cognition, QoL, mood, and perceived stress, and technophilia in community-dwelling older PMCI/MDs, caregiver burden, and the access to and utilization of health and social care services, along with the cognitive, social, and entertainment-related use of ICTs during and after COVID-19 confinement.

Our findings will help assess the adoption of dementia technology by older people and their caregivers during the COVID-19 pandemic and may help alleviate the impact of present and future confinements in different aspects of their daily lives.

The preparedness and responses of governments to situations of the magnitude of COVID-19 will help determine related outcomes and consequences, which extend beyond the disease itself, with political, economic, cultural, health-related, and social impacts compromising the QoL of all. These responses,

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which include enforcing restrictive measures, lead to social isolation, which, in the context of an ecological framework, has an impact at the individual, relationship, community, and societal levels [4].

At an individual level, those with personal characteristics such as old age, life-course transitions, and health decline [10], particularly those with a diagnosis of dementia [3], are at higher risk. Abrupt and forced social isolation may be considered a disruptive event among older people and may predispose them to psychological distress [10]. Not being able to take part in daily activities, loss of usual routine, and nonattendance to memory workshops and day care services under closure may worsen cognition and functioning in this population. Daily activities such as going to grocery stores and pharmacies, may be carried out by caregivers to prevent risk of exposure, thus increasing caregiver burden.

At a relationship level, social distancing has compromised the reliability of social networks and the frequency of contact with others. Inadequate social support, when most needed, may aggravate depressive symptoms [12].

At a community level, interventions for the provision of health care and social support services are limited to prevent risk exposure, causing direct and indirect impacts on the prevention of ill health, promotion of health, and lifelong management and treatment of diseases.

At a societal level, social participation has been inhibited by policies that discourage social, economic, cultural, and physical activities. Regular participation in meaningful activities, including physical, intellectual, recreational, and social activities, serves beyond simple entertainment among PMCI/MDs, and discontinuing their participation in these activities may worsen cognition and regular functioning, thus increasing their dependence on instrumental activities of daily living [7].

Considering the extensive penetration of ICTs at home, home-based technological interventions have emerged for preventing health-related negative outcomes at all levels, including providing individual home-delivered cognitive stimulation, facilitating information sharing, and entertainment in daily life, fostering relations and social connectedness, enabling the delivery of routine health care and social support, preventing the risk of viral exposure, and offering home-based leisure activities. However, special attention must be paid to the use of ICTs among older people owing to the age-related digital divide and health-related conditions that compromise the use of ICTs (cognitive, visual, motor, etc). Fortunately, prior to this outbreak, Europe has, for several years, proactively invested in research and innovation programs in ICTs and their adaption among at-risk populations, promoting widespread, personalized, and accessible ICTs for all.

Limitations

Although telephonic interviews would be the safest means to communicate with the dyads during the COVID-19 pandemic, there will be several drawbacks. The amount of information gathered and provided on a single telephone call is limited and researchers will have to balance the time spent on each call. Moreover, the assessment of cognition will be partial as the language section of the MMSE requires the assessment of visual and motor skills, which cannot be accomplished through a telephone call. Although evidence for telephone-based cognitive assessment recommends using the telephone interview for cognitive status instrument and its modified version [41,42], the study population undertook the MMSE thrice over a period of 1 year prior to this study, thus providing relevant data to compare their decline before confinement (baseline data) and afterwards. Furthermore, overloading PMCI/MDs with a long interview is not advisable as it may feel tedious and time-consuming. Finally, older people may have hearing impairments, which may make telephone assessments difficult. Caregiver assistance will be requested to complete the interviews.

The assessments in this study involve minimal risk to the patients. To ensure the standardization of interventions, researchers have received web-based training on the standard operating procedure, which includes a working plan, different aspects of the study, the protocol scheme to identify the appropriate measures, and the details to assess each variable safely among older adults. This will guarantee that the procedure can be replicated elsewhere.

Conflicts of Interest

None declared.

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Abbreviations

CONNECTDEM: Cognitive Outcomes During COVID-19 confiNemeNt in Elderly and Their Caregivers Using Technologies for DEMentia

CRF: case report form

ICT: information and communications technology

MMSE: mini-mental state examination

PMCI/MD: people with mild cognitive impairment or mild dementia

QoL: quality of life

QoL-AD: Quality of Life-Alzheimer's Disease

SMART4MD: support, monitoring, and reminder technology for mild dementia

TV-AssistDem: television-based assistive integrated service to support European adults living with mild dementia or mild cognitive impairment

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Protocol

Using Computational Methods to Improve Integrated Disease Management for Asthma and Chronic Obstructive Pulmonary Disease: Protocol for a Secondary Analysis

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Abstract

Background: Asthma and chronic obstructive pulmonary disease (COPD) impose a heavy burden on health care. Approximately one-fourth of patients with asthma and patients with COPD are prone to exacerbations, which can be greatly reduced by preventive care via integrated disease management that has a limited service capacity. To do this well, a predictive model for proneness to exacerbation is required, but no such model exists. It would be suboptimal to build such models using the current model building approach for asthma and COPD, which has 2 gaps due to rarely factoring in temporal features showing early health changes and general directions. First, existing models for other asthma and COPD outcomes rarely use more advanced temporal features, such as the slope of the number of days to albuterol refill, and are inaccurate. Second, existing models seldom show the reason a patient is deemed high risk and the potential interventions to reduce the risk, making already occupied clinicians expend more time on chart review and overlook suitable interventions. Regular automatic explanation methods cannot deal with temporal data and address this issue well.

Objective: To enable more patients with asthma and patients with COPD to obtain suitable and timely care to avoid exacerbations, we aim to implement comprehensible computational methods to accurately predict proneness to exacerbation and recommend customized interventions.

Methods: We will use temporal features to accurately predict proneness to exacerbation, automatically find modifiable temporal risk factors for every high-risk patient, and assess the impact of actionable warnings on clinicians' decisions to use integrated disease management to prevent proneness to exacerbation.

Results: We have obtained most of the clinical and administrative data of patients with asthma from 3 prominent American health care systems. We are retrieving other clinical and administrative data, mostly of patients with COPD, needed for the study. We intend to complete the study in 6 years.

Conclusions: Our results will help make asthma and COPD care more proactive, effective, and efficient, improving outcomes and saving resources.

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Introduction

The Gap in Identifying Patients With Exacerbation-Prone Asthma and Patients With Exacerbation-Prone Chronic Obstructive Pulmonary Disease for Preventive Care

Management of Asthma and Chronic Obstructive Pulmonary Disease

In the United States, 9.6% of children and 8% of adults have asthma, leading to 1.8 million emergency department visits, 493,000 inpatient stays, US $56 billion in cost, and 3630 deaths every year [1-4]. Approximately 6.5% of adults have chronic obstructive pulmonary disease (COPD), the third leading cause of death, leading to 1.5 million emergency department visits, 0.7 million inpatient stays, and US $32 billion in cost every year [5]. One main goal in managing patients with asthma and patients with COPD is to reduce exacerbations, which expend approximately 40% to 75% of their total care cost [6-8] and accelerate their lung function decline [9]. Approximately one-fourth of patients with asthma and patients with COPD are prone to exacerbation [10-14], meaning that a patient has (1) ≥2 systemic corticosteroid orders in a year or (2) ≥1 emergency department visit or inpatient stay for asthma or COPD with systemic corticosteroid treatment in a year (Figure 1) [10,13,15]. These patients incur approximately two-thirds of all exacerbations [12,13,16] and experience a low quality of life; sleep disturbance; limitations of daily activities impacting independence, relationships, family life, socialization, and career; anxiety; distress; missed work with lost earnings; missed school; high care costs; high hospital use; intubation; and death [10,17-19]. Even a brief use of systemic corticosteroids to treat exacerbations can greatly increase the risk of venous thromboembolism, sepsis, and fracture [20,21].

Figure 1. Determining when a patient with asthma or chronic obstructive pulmonary disease becomes prone to exacerbation. COPD: chronic obstructive pulmonary disease.
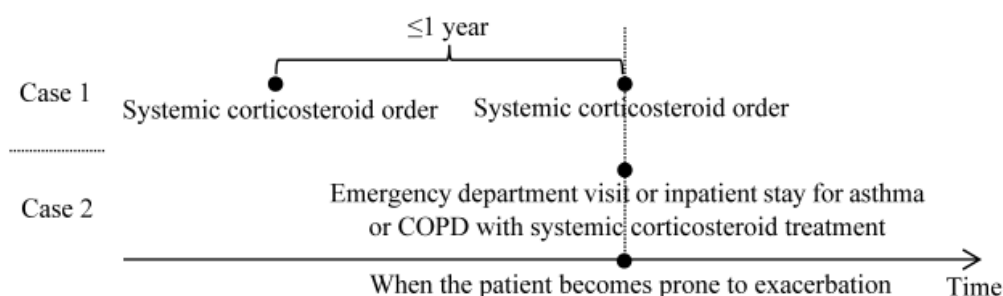
Many health care systems and health plans use predictive models as the best method [22] to identify high-risk patients for preventive care to improve outcomes and save resources [23-25]. For instance, this is the case with health plans in 9 of the 12 American metropolitan communities mentioned in the study by Mays et al [26]. However, no model exists to predict proneness to exacerbation, which only partly correlates with disease severity [16]. Exacerbation-prone patients are currently identified after exacerbations occur, making it too late to apply integrated disease management (IDM) for preventing exacerbations. IDM is defined as "a group of coherent interventions, designed to prevent or manage 1 or more chronic conditions using a community wide, systematic and structured multidisciplinary approach potentially employing multiple treatment modalities" [27]. IDM typically has several components, such as self-management education, skills training, care management, and structured follow-up [28,29]. Having a limited service capacity [29-33], IDM can lower hospital use by up to 40%; cut costs by up to 31%; greatly reduce symptoms; and enhance treatment adherence, patient satisfaction, and quality of life by 30%-60% [26,28-32,34-42]. Neither patient registries nor dashboards are able to identify exacerbation-prone patients before exacerbations occur and, thus, to apply IDM in a timely manner. A patient registry tracks a given patient cohort but cannot make predictions. Although many attributes are often needed to achieve high prediction accuracy [43-45], a dashboard tracks only a few attributes. To have prediction capability, a dashboard needs to be supported by a predictive model in the backend. Models for proneness to exacerbation are needed to guide the use of IDM and to prevent exacerbations. This cannot be done well with the current model building approach for other asthma and COPD outcomes, which has 2 major gaps due to the limited use of temporal features showing early health changes and general directions [46-94]. Each temporal feature is an independent variable computed on one or more longitudinal attributes, such as the slope of pulmonary function last year, the slope of BMI last year, the number of days in the previous week during which the sulfur dioxide level was ≥4 parts per million, and whether the patient's filling frequency of oral corticosteroid prescription increased over time. Although this study focuses on exacerbation-prone asthma and COPD as use cases, the proposed computing techniques and software can be harnessed to forecast outcomes of other diseases such as congestive heart failure and diabetes, with temporal features such as the slopes of cardiac function and blood glucose level over time.

Gap 1: Low Prediction Accuracy

Existing models for predicting an individual asthma or COPD patient's health outcomes typically have low accuracy [46-94]. The systematic review by Loymans et al [52] and our review [43] showed that for forecasting hospital use (emergency department visits and inpatient stays) for asthma in patients with asthma, each previous model, excluding the models of Zein et al [58], has an area under the receiver operating characteristic curve (AUC) within 0.61-0.81, a sensitivity within 25%-49%, and a positive predictive value within 4%-22% [46-57]. The models of Zein et al [58] and our recent new models [43-45] have similarly higher accuracy but are still not good enough for aligning preventive care with the patients needing it the most. The case with COPD is similar [59-94].

Existing models for predicting asthma and COPD outcomes typically have low accuracy for several reasons:

1. Existing models use elementary temporal features such as the count of inpatient stays and ever intubated last year, but they rarely use more advanced temporal features such as the slope of the number of days to albuterol refill showing general directions. Many highly predictive temporal features are yet to be identified or are unused. In 2018, Google used all of the attributes in the electronic medical record along with long short-term memory (LSTM) [95,96], one type of deep neural network, to discover temporal features automatically from longitudinal data [97]. This raised the AUC by approximately +10% for projecting each of long hospital stay, in-hospital mortality, and unanticipated readmissions in 30 days [97]. Several other studies [98-100] obtained similar results for various clinical prediction tasks. This matches recent progress in areas such as video classification, speech recognition, and natural language processing, where temporal features LSTM automatically discovered from data beat those that experts provided or other temporal and sequential pattern mining methods [101-104] mined from data. The LSTM model of Xiang et al for predicting asthma outcome [57] had a low AUC of 0.7 because it used only 3 types of attributes and mostly inpatient data without much outpatient data, not because LSTM is ineffective.

2. Although >100 potential risk factors for poor outcomes in asthma and COPD are known [50-52,105-112], a typical previous model uses only a few (eg, ≤17) [46-57,59-93]. None of the published models adopt all established risk factors contained in contemporary electronic medical records [113].

3. Weather and air quality variables impact asthma and COPD outcomes [114-117], but they are seldom used in existing models.

Gap 2: No Information Given on the Reason Why a Patient is Deemed High Risk and the Potential Interventions to Reduce the Risk

To provide preventive care well, clinicians need to know the reason a patient is deemed high risk and the potential interventions to reduce the risk. Sophisticated predictive models, including the bulk of machine learning models such as LSTM, are black boxes and provide no such information, although

explanation is critical for users' acceptance, satisfaction, trust, and decision correctness [118-121]. Often, a patient's clinical records include numerous variables on many pages recorded over multiple years [122]. As the model gives no explanation, already occupied clinicians need to expend extra time on chart review to identify the reasons. This is difficult and time consuming. In fact, the black-box issue has been a major reason for the slow adoption of machine learning in clinical practice, despite machine learning often producing the highest prediction accuracy among all predictive modeling methods [33,123-127].

A clinician can develop a care plan using subjective, variable clinical judgment. However, this care plan often misses some suitable interventions because of the following reasons:

1. Big practice variation, frequently by 1.6-5.6 times, shows up across facilities, clinicians, and regions [128-135].

2. A patient can become high risk for many reasons, each shown by a risk pattern given by a feature combination, for example, the sulfur dioxide level was ≥4 parts per million for ≥4 days in the previous week and the number of days to albuterol refill rose over 12 months. Many features and feature combinations exist. A clinician is a human, can typically process ≤9 information items at once [136], and can easily miss some key reasons for which the patient is high risk. Outcomes can degrade if suitable interventions are not used. Regular automatic explanation methods [137-140] cannot deal with longitudinal data and address this issue well.

Our Proposed Solutions

To enable more patients with asthma and patients with COPD to obtain suitable and timely care to prevent exacerbations, we will (1) use temporal features to develop the first set of models to accurately predict exacerbation-prone asthma and COPD, (2) automate finding modifiable temporal risk factors for every high-risk patient, and (3) assess the impact of actionable warnings on clinicians' decisions to use IDM to prevent proneness to exacerbation.

Innovation

We will develop new techniques to automate the extraction of temporal features from longitudinal data and explain machine learning predictions on longitudinal data. We will improve preventive care, notably for asthma and COPD, by steering it to the patients who need it more precisely and in a more timely manner than the current risk modeling methods:

1. To the best of our knowledge, this study will construct the first set of models to predict which patients with asthma and which patients with COPD will be prone to exacerbation. Currently, these patients are found after exacerbations occur, making it too late to apply IDM for preventing exacerbations. This is a major public health issue [29,31,32]. Our models can improve IDM and guide its use to avert exacerbations. Compared with the current model building method for other asthma and COPD outcomes that often produces low accuracy, our model building method will lead to more accurate predictions.

2. To the best of our knowledge, this will be the first study to extract comprehensible and predictive temporal features

semiautomatically from longitudinal data without needing any manually prespecified pattern template, which is required by many sequential and temporal pattern mining methods [102-104]. This helps raise the model accuracy and reduce the effort required to construct clinically usable models. At present, clinicians usually have to manually identify such features to construct such models. However, this is time consuming and difficult. Previous models for asthma and COPD rarely use more advanced temporal features, such as slope [46-94]. In addition, although current deep neural network methods can automatically discover temporal features, the discovered features are hidden in neurons and are often incomprehensible, making it difficult to explain the predictions [137,138].

3. To the best of our knowledge, this will be the first study to automate giving rule-formed explanations for machine learning predictions directly on longitudinal data. Clinicians need explanations to understand the predictions and decide IDM enrollment and interventions. Rule-formed explanations are easier to comprehend and can better hint at actionable interventions than other forms of automatic explanations. Most automatic explanation methods [137,138] for machine learning predictions cannot deal with longitudinal data. Our previous automatic explanation method [140-142] is no exception. It has 5 hyperparameters whose effective values vary by modeling problem and data set. A computing expert often requires several months to perform many trials to find these values laboriously for a data set. We will improve our previous method to deal with longitudinal data and automatically and efficiently select hyperparameter values; therefore, health care researchers with limited computing expertise can use our method with low overhead.

4. To the best of our knowledge, this will be the first study to automate finding modifiable temporal risk factors and recommending interventions on the basis of objective data, making IDM more efficient and effective. At present, clinicians rely on subjective, variable judgment to create care plans manually and overlook some suitable interventions for high-risk patients.

5. To the best of our knowledge, this will be the first study to assess the impact of actionable warnings on clinicians' decisions to use IDM to prevent proneness to exacerbation.

Methods

Computing Resources

We will conduct all experiments on a password-protected and encrypted computer cluster hosted at the University of Washington Medicine (UWM). With appropriate authorization and using their university computers, all research team members and test participants at UWM can remotely access this computer cluster.

Data Sets

All data that will be used in this study are structured. We will use clinical and administrative data stored in the enterprise data warehouses of 3 prominent American health care systems: UWM, Kaiser Permanente Southern California (KPSC), and

Intermountain Healthcare (IH). We will use >200 clinical and administrative variables listed in our papers' [43-45] appendices, with differing names of the same concept in distinct electronic medical record systems already manually matched by us. These variables cover a wide range of aspects, such as patient demographics, encounters, medications, laboratory tests, diagnoses, procedures, vital signs, and allergies. We can form the temporal features of most variables, which are longitudinal with timestamps.

In Utah, IH is the largest health care system, with 24 hospitals and 215 clinics. As in our previous work on asthma outcome prediction [43-45], an IH data analyst will run Oracle database queries to retrieve a deidentified IH data set (eg, shift dates, replace identifiers, and replace ages that are ≥90 years) and use Secure Shell (SSH) to encrypt it and transfer it to the password-protected and encrypted computer cluster, where we will perform analysis. The IH data set covers patient encounters from 2005 to 2020. For the previous 5 years, data for children cover >5000 pediatric patients with asthma (aged <18 years) per year. Data for adults cover >14,000 adult patients with asthma (aged ≥18 years) and >6000 adult patients with COPD per year. IH expends many resources on data integrity and accuracy. Owing to its large size and variable richness [143], the data set offers many advantages for exploring the proposed methods.

UWM and KPSC have similar strengths. In Washington, UWM is the largest academic health care system, with 4 hospitals and 12 clinics for adults. A UWM data analyst will execute SQL Server database queries to retrieve a deidentified UWM data set (eg, shift dates, replace identifiers, and replace ages that are ≥90 years) and use SSH to encrypt it and transfer it to the password-protected and encrypted computer cluster. The UWM data set covers adult patient encounters from 2011 to 2020. For the previous 5 years, data cover >12,000 adult patients with asthma and >5000 adult patients with COPD per year.

In Southern California, KPSC is the largest integrated health care system, with 15 hospitals and 231 clinics [144]. A KPSC data analyst will run database queries to retrieve a deidentified KPSC data set (eg, shift dates, replace identifiers, and replace ages that are ≥90 years) and use SSH to encrypt it and transfer it to the password-protected and encrypted computer cluster. The KPSC data set covers patient encounters from 2009 to 2020. For the previous 5 years, data for children cover >77,000 pediatric patients with asthma per year. Data for adults cover >172,000 adult patients with asthma and >78,000 adult patients with COPD per year.

In addition to the clinical and administrative data, we will adopt 11 weather and air quality variables that we have downloaded from public sources [145,146]: daily mean particulate matter ≤2.5 μm in diameter, daily maximum 8-hour carbon monoxide, daily mean particulate matter ≤10 μm in diameter, daily maximum 8-hour ozone, daily maximum 1-hour nitrogen dioxide, daily maximum 1-hour sulfur dioxide, hourly mean precipitation, hourly mean relative humidity, hourly mean wind speed, hourly mean temperature, and hourly mean dew point. These variables were recorded over 16 years (2005-2020) by

monitoring stations located in the areas covered by IH, UWM, and KPSC.

The following discussion focuses on asthma. Whenever we refer to asthma, the same applies to COPD.

Aim 1: Use Temporal Features to Accurately Predict Exacerbation-Prone Asthma and COPD

We will extract comprehensible and predictive temporal features semiautomatically from patient, weather, and air quality data and construct models to predict proneness to exacerbation. Each feature uses ≥1 raw variable. There is an almost infinite number of possible features. Traits of pediatric patients' parents and other factors could also impact patient outcomes. Our goal is not to test all possible useful features and obtain the theoretically maximum possible prediction accuracy. Instead, we intend to show that temporal features can be used to improve prediction accuracy and IDM. We will create a separate model for every disease and health care system pair. This study will focus on associations, as is sufficient for decision support for IDM and common with predictive modeling.

Data Preprocessing

All data sets will be converted into the Observational Medical Outcomes Partnership (OMOP) common data model format [147] and its linked standardized terminologies [148]. Much of the UWM data are already in this format. IH and KPSC have provided their data in an internal normalized format that is similar to this format. We will expand the data model to include patient, weather, and air quality variables that the original data model misses but exist in our data sets. We will use the method described in our paper [149] to choose the most pertinent laboratory tests. To reduce the number of features, we will use the Agency for Healthcare Research and Quality Clinical Classifications Software system [150,151] to merge diseases, use the Berenson-Eggers Type of Service system [152] to merge procedures, and use the Hierarchical Ingredient Code 3 system [153] to merge drugs. We will adopt the method used in our previous work [43-45] to identify, correct, or delete invalid values. To deal with missing values, we will test various imputation techniques [154,155], such as the last observation carried forward, replacement with mean values, and replacement with median values, and use the technique that works the best.

The patient, weather, and air quality variables will be used. The patient variables will cover standard variables studied in the clinical predictive modeling literature [128,129,154], such as diagnoses, and >100 known potential risk factors for poor asthma outcomes listed in our papers [43-45,156]. One such risk factor is the frequency of nighttime awakening recorded on the validated Asthma Control Test questionnaire [157] in the electronic medical record system. For weather and air quality variables, we will perform inverse distance weighting spatial interpolation [158] to compute their daily average values at the patient's residence zip code from their values at local monitoring stations, as we and others did before for asthma outcome prediction [159-161].

Asthma and COPD Cases and Outcomes

We will implement and test our method using (1) pediatric asthma, (2) adult asthma, and (3) COPD. We will use our previous method [44] adapted from the literature [47,162,163] to identify patients with asthma. We deem a patient to have asthma in a given year if the patient has ≥1 asthma diagnosis code (*International Classification of Diseases, Ninth Revision* [*ICD-9*] 493.x or *International Classification of Diseases, Tenth Revision* [*ICD-10*] J45 and J46.x) in the year. The outcome is whether the patient became prone to exacerbation (ie, had either ≥2 systemic corticosteroid orders or ≥1 emergency department visit or inpatient stay with a principal diagnosis of asthma and systemic corticosteroid treatment) in the following year [10,15].

We will use our previous method [164] adapted from the literature [165-168] to identify patients with COPD. As shown in Figure 2, we deem a patient to have COPD if the patient is aged ≥40 years and fulfills any of the following 4 conditions:

1. An outpatient visit diagnosis code of COPD (*ICD-9*: 491.22, 491.21, 491.9, 491.8, 493.2x, 492.8, and 496; *ICD-10*: J42, J41.8, J44.x, and J43.x), followed by ≥1 prescription of long-acting muscarinic antagonists (aclidinium, glycopyrrolate, tiotropium, and umeclidinium) within 6 months

2. ≥1 emergency department or ≥2 outpatient visit diagnosis codes of COPD (*ICD-9*: 491.22, 491.21, 491.9, 491.8, 493.2x, 492.8, and 496; *ICD-10*: J42, J41.8, J44.x, and J43.x)

3. ≥1 inpatient stay discharge with a principal diagnosis code of COPD (*ICD-9*: 491.22, 491.21, 491.9, 491.8, 493.2x, 492.8, and 496; *ICD-10*: J42, J41.8, J44.x, and J43.x)

4. ≥1 inpatient stay discharge with a principal diagnosis code of respiratory failure (*ICD-9*: 518.82, 518.81, 799.1, and 518.84; *ICD-10*: J96.0x, J80, J96.9x, J96.2x, and R09.2) and a secondary diagnosis code of acute COPD exacerbation (*ICD-9*: 491.22, 491.21, 493.22, and 493.21; *ICD-10*: J44.1 and J44.0) [164].

Figure 2. Determining when a patient starts to have chronic obstructive pulmonary disease. COPD: chronic obstructive pulmonary disease.
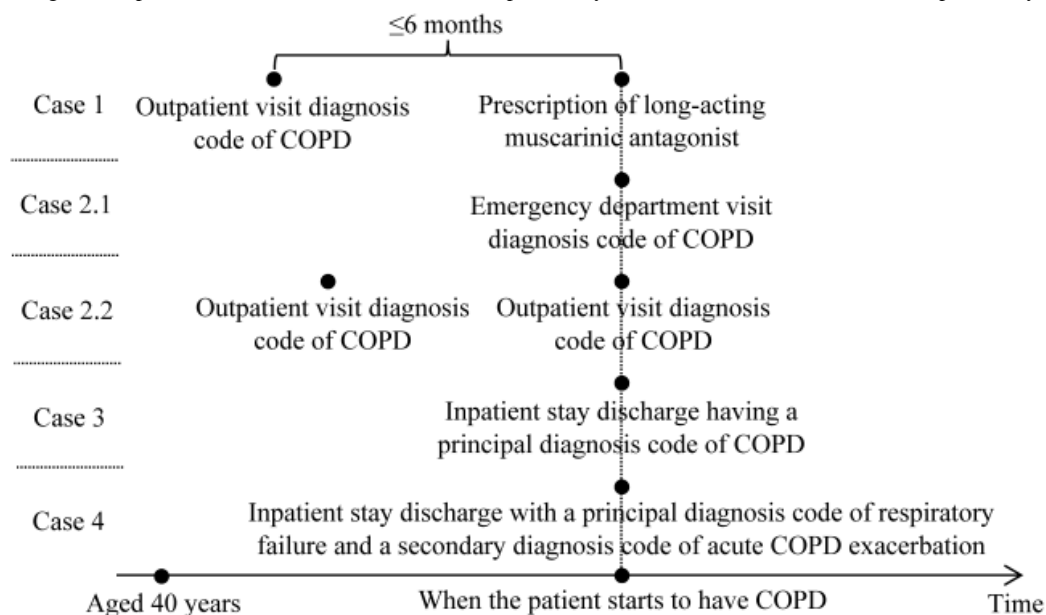
The outcome is whether the patient became prone to exacerbation (ie, had either ≥2 systemic corticosteroid orders or ≥1 emergency department visit or inpatient stay with a principal diagnosis of COPD and systemic corticosteroid treatment) in the following year [13].

Extracting Temporal Features

We will adopt the method described in our design paper [149] to extract comprehensible and predictive temporal features semiautomatically from longitudinal data. In aim 1, we will use the extracted features to construct the final predictive models. In aim 2, we will use the extracted features to automate finding modifiable temporal risk factors for every high-risk patient. The main idea of our temporal feature extraction method is to build a so-called multi-component LSTM deep neural network model on longitudinal data, use a so-called exclusive group Lasso (least absolute shrinkage and selection operator) regularization method to restrict the number of attributes used in each component LSTM network, and then perform visualization to identify comprehensible temporal features from certain cell vector elements in each component LSTM network. The final step of using visualization to identify temporal features and providing their definitions involves humans and is semiautomatic. All other steps are automatic. Our temporal feature extraction method is general and can be used for many clinical applications. Our method has never been implemented in computer code. In addition, some of its technical details are not provided in our design paper [149]. In this study, we will fill in all of the missing technical details and code and test this method.

The Final Predictive Models in Aim 1

We will use the extracted temporal features, such as the slope of the number of days to albuterol refill, to transform longitudinal data into tabular data, producing 1 column per temporal feature, and add static features. We will place no artificial upper or lower bound and use as many features as needed (likely several dozen to several hundred features based

on our previous experience [43-45]). Our data are relatively balanced [10-14]. We will harness Weka [169], a major open-source machine learning toolkit, to create the final models in aim 1. As aim 2 shows, these models are suitable for automatic explanations. Weka implements many classic machine learning algorithms and feature selection techniques. We will adopt supervised algorithms and our previous method [170] to automate selection of the machine learning algorithm, feature selection technique, and hyperparameter values out of all applicable ones. When needed, we will manually perform fine-tuning.

We will use past data up to the prediction time point to construct 5 sets of models, 1 set for each of 5 combinations: pediatric asthma at IH and KPSC and adult asthma at IH, UWM, and KPSC. UWM has rather incomplete data on many of its patients, partly because most of its patients are referred from elsewhere. To reduce the impact of incomplete data on model performance, we will harness our previous constraint-based method [164,171] to identify the patients apt to get most of their care from UWM, and we will construct models for them. As mentioned earlier, we will also implement and test our method on COPD.

Evaluating Model Performance and Power Analysis

The discussion below focuses on IH data. The cases with UWM and KPSC data are analogous. As we need to calculate outcomes in the following year, we effectively have 15 years of IH data over the previous 16 years. We will train and test the models in a standard way. On the data of the first 14 years, we will perform stratified 10-fold cross validation [169] to train models and gauge their performance. On the data of the 15th year, we will appraise the performance of the best models, reflecting future use in practice. We will use the standard performance metric AUC [169] to choose the best model and record its AUC. We will show the model's accuracy, sensitivity, specificity, and positive and negative predictive values when the cutoff threshold of binary classification varies from the top 1% to the top 50% of patients with asthma with the highest predicted risk. To find the variables essential for achieving high model performance,

backward elimination [154] will be adopted to remove features as long as AUC drops by ≤0.002. We will compare the variables essential for achieving high model performance on IH data with those on UWM and KPSC data. The gender's predictive power will be checked explicitly. We will use the variables appearing in both the UWM and IH data sets to construct a best model on IH data and compare its performance on UWM data with that on IH data. We will use the variables appearing in both the KPSC and IH data sets to construct a best model on IH data and compare its performance on KPSC data with that on IH data.

We will test the hypothesis that adopting our techniques could enhance model performance twice, once for adults and once for children. To do this, we will compare the AUCs of 2 predictive models built using the attributes in our data set and the best machine learning algorithm. The first model will harness all the features essential for achieving high model performance. The second model will be performed in the same way as our recent model for predicting hospital use for asthma [44] related to proneness to exacerbation. We anticipate that the second model will have an AUC around our recent model's AUC of 0.86. Our hypothesis is as follows:

1. Null hypothesis: the second model has the same AUC as the first model.
2. Alternative hypothesis: the second model has a smaller AUC than the first model.

The categorical outcome variable of proneness to exacerbation has 2 values (classes). According to the standard method developed by Obuchowski and McClish [172] for AUC-related sample size computation, using a 2-sided Z test at a significance level of 0.05 and assuming for both classes a Pearson correlation coefficient of 0.6 between the 2 models' predictions, a sample size of 464 instances per class provides 90% power to identify an AUC difference of 0.05 between the 2 models. The 15th year's IH data cover >5000 children with asthma and >14,000 adults with asthma, offering sufficient power to test our hypothesis. If the real correlation coefficient is different from the assumed one by no more than a moderate degree, the conclusion would remain valid.

Sensitivity Analysis

IH, UWM, and KPSC each recorded many variables. Another health care system could record fewer variables. We will test miscellaneous variable combinations and assess the performance of the corresponding modified models. This will help us ensure generalizability and identify critical variables. If a health care system does not record a particular critical variable, the assessed performance numbers can suggest alternative variables with minimal degradation of model performance. On the basis of our clinical experts' judgment, we will merge variables apt to co-occur, such as the variables appearing in a lab test panel, into groups. We will form and publish a table listing possible combinations of variables by groups, accompanied by the performance numbers and the trained parameters of the corresponding predictive models. A health care system interested in deploying the model can use the table to assess the expected model performance for their data environment and determine the variables to be recorded. The table contains a distinct column for each of IH, UWM, and KPSC. Many variables recorded by

IH, UWM, and KPSC and used in this study are common and recorded by many other health care systems. Hence, these health care systems already have all the variables appearing in each of many rows in the table.

Aim 2: Automate Finding Modifiable Temporal Risk Factors for Every High-Risk Patient

Overview of Aim 2

For patients with predicted risk over a fixed bar, such as the 75th percentile, we will automate explaining warnings, finding modifiable temporal risk factors, and recommending customized interventions. This will help clinicians make decisions regarding IDM enrollment and develop customized care plans. To create the new function, we will enhance our previous method [140] of automatically explaining machine learning predictions with no loss of model performance. Our previous method cannot deal with longitudinal data, has hard-to-tune hyperparameters, and has not been previously used for COPD or IDM.

Explanation Method

As aim 1 shows, we will use temporal features to transform longitudinal data into tabular data, producing one column per temporal feature. Our previous automatic explanation method [140] can then be used. Each patient is labeled as either high risk or not high risk. Our method mines from past data association rules tied to high risk. One example rule is as follows: the sulfur dioxide level was ≥4 parts per million for ≥4 days in the previous week AND the number of days to albuterol refill rose over the previous 12 months → the patient is high risk. The second item on the left-hand side of the rule is a modifiable temporal risk factor. Three interventions for it are to (1) assess the patient on asthma triggers and ensure that the patient avoids them; (2) evaluate compliance with asthma controller medications and prescribe, modify, or increase the doses of the medications if necessary; and (3) create a new asthma action plan to use more aggressive interventions when the patient is in the yellow zone [173]. Our paper [149] presented multiple interventions for several other temporal risk factors. Through discussion and consensus, our clinical team will examine the mined rules and remove those that make little or no clinical sense. For each rule left, our clinical team will identify the modifiable temporal risk factors in the rule and provide zero or more evidence-based interventions from the literature addressing the reason that the rule provides. The rules are used to provide explanations instead of predictions.

At prediction time, for each patient our most accurate model (initially resulting from aim 1) marks high risk, we will identify and present all association rules tied to high risk and whose left-hand side conditions are fulfilled by the patient, as well as show the rules' linked interventions as our recommendations. Every rule presents a reason why the patient is predicted to be at high risk. Users of the automatic explanation function could provide input to facilitate the identification and removal of unreasonable rules [174].

Automatically and Efficiently Selecting Hyperparameter Values

Our previous automatic explanation method [140-142] uses 5 hyperparameters. Their effective values differ according to the modeling problem and data set. In our previous work [140-142], for each data set, a computing expert took several months to perform many trials to laboriously find these values. To reduce this overhead and to allow health care researchers with no extensive computing background to use our method, we will extend the progressive sampling-based approach, which we previously developed for expediting automatic machine learning model selection [170], to automatically and efficiently select the values of the 5 hyperparameters. On average, our progressive sampling-based approach performs the search process 2 orders of magnitude faster than the modern Auto-Weka automatic selection approach [170,175]. Our approach generalizes to many clinical applications.

We will also develop our techniques on COPD.

Aim 3: Assess the Impact of Actionable Warnings on Clinicians' Decisions to Use IDM to Prevent Proneness to Exacerbation

Goal of Aim 3

To prepare for future clinical use, in a UWM test setting, we will assess the impact of actionable warnings on clinicians' decisions to use IDM in patients with asthma to prevent proneness to exacerbation. We will also access UWM physicians' (primary care doctors, pulmonologists, and allergists) and nurses' subjective opinions of automatic explanations.

Recruiting Subjects

As an UWM operational project, we are building asthma outcome prediction models and have access to approximately 700 physicians and approximately 1700 nurses managing adult patients with asthma. Through personal contact and advertising in their email lists, we will recruit 20 test participants (10 physicians and 10 nurses) with purposeful sampling to guarantee sufficient variability in their work experience [176]. Every test participant will offer consent before participation and be current on UWM's policy training on information security and privacy. To protect privacy, every test participant will receive a pseudonym linking their responses. Upon task completion, each physician will receive US $2300 as compensation for participation and for approximately 20 hours of work. Each nurse will receive US $1200 as compensation for participation and for approximately 20 hours of work.

Procedures

Using the 15th year's (2019) IH data, we will randomly select 800 IH adult patients with asthma and automatically explain the predictions of the best performing IH model formed in aim 1. Using patients outside the UWM can help ensure that no test participant knows the outcome of any of these patients in the following year. We will present a distinct subset of 40 patients to each test participant and proceed in the following 4 steps:

1. Step 1: For each patient, we will display to the test participant the 2005-2019 deidentified patient data in reverse chronological order, as in the electronic medical records, and ask the test participant to write down the IDM enrollment decision (yes or no) and any interventions that the test participant plans to adopt on the patient.

2. Step 2: For each patient, we will display to the test participant the 2005-2019 deidentified patient data, the prediction, the automatic explanations, and the interventions connected to them. We will ask the test participant to write down their IDM enrollment decision (yes or no) on the patient after seeing the prediction and the explanations, the linked interventions they agree with, those they disagree with, and the interventions that they come up with in step 1 but whose concepts are missed by the linked interventions.

3. Step 3: Perceived usefulness is closely linked to future use intentions and actual function use [177,178]. Using the classic Technology Acceptance Model satisfaction questionnaire [179], we will survey the test participant to know their perceived ease of use and usefulness of automatic explanations.

4. Step 4: We will conduct a focus group with 10 randomly chosen test participants to assess what helps them use or prevents them from using the automatic explanations in clinical practice and why they agree or disagree with the automatically recommended interventions.

Quantitative and Qualitative Analyses

Quantitative Analyses

We will provide descriptive statistics for each quantitative outcome measure, including the mean and SD of each of the following: (1) the number of times that a test participant changes their IDM enrollment decision on a patient after seeing the prediction and the explanations, (2) the number of linked interventions for a patient a test participant agrees with, (3) the number of linked interventions for a patient a test participant disagrees with, (4) the number of interventions that a test participant comes up with for a patient in step 1 but whose concepts are missed by the linked interventions, and (5) the rating of every item in the Technology Acceptance Model satisfaction questionnaire. We will test the hypothesis that giving actionable warnings will improve clinicians' decision to use IDM to prevent proneness to exacerbation, that is, the degree of IDM enrollment decision matching whether the patient will become prone to exacerbation in the following year. Our hypothesis is as follows:

1. Null hypothesis: The degree of IDM enrollment decision matching whether the patient will become prone to exacerbation in the following year in step 2 is the same as that in step 1.

2. Alternative hypothesis: The degree of IDM enrollment decision matching whether the patient will become prone to exacerbation in the following year in step 2 is larger than that in step 1.

We will fit a random effect logistic model that accounts for the correlation among the outcomes related to the same test participant.

Power Analysis for the Quantitative Analyses

Assuming a modest intraclass correlation of 0.1 within the same test participant on the outcome, a sample size of 40 patients per test participant for the 20 test participants is equivalent to a total of 82 independent patients after factoring in the clustering effect. We will have, at a 2-sided significance level of .05, 80% power to detect a 9.7% increase in the chances of improving clinicians' decisions to use IDM with actionable warnings. If the real correlation is different from the assumed one by no more than a moderate degree, a similar conclusion would hold.

Qualitative Analyses

Using the inductive method described in Patton et al [176,180], test participants' comments recorded in text during the focus group will be loaded into ATLAS.ti qualitative analysis software (ATLAS.ti Scientific Software Development GmbH) [181]. Three people from our research team will highlight the quotations independently. Through discussion and negotiated consensus in multiple iterations, these people will review quotations, categorize quotations into precodes, merge codes into categories, and synthesize categories to identify general themes.

Exploring for Other Diseases

Preventive care is also widely adopted for patients with heart diseases and diabetes. To explore what will be needed to generalize our techniques to predict outcomes of these diseases in the future, we will conduct 2 phases of focus groups, each phase with a distinct set of 6 UWM clinical experts on these diseases, and add more phases if these 2 phases do not reach saturation.

As stated immediately before aim 1, the discussion above concentrates on asthma. Whenever we refer to asthma, the same applies to COPD and will be implemented and tested on COPD in aims 1 and 2 but not in aim 3.

Ethics Approval

We have received approval from the UWM institutional review board for this study and are applying for approval from IH and KPSC.

Results

We have downloaded 2005-2020 weather and air quality data from public sources [145,146]. For the clinical and administrative data, GL at UWM has obtained the 2005-2018 data of patients with asthma from IH [44], the 2009-2018 data of patients with asthma from KPSC [45], and the 2011-2018 data of patients with asthma from UWM [43]. We are retrieving the other clinical and administrative data, mostly of patients with COPD, from IH, UWM, and KPSC. We intend to complete the study in 6 years.

Discussion

Using Our Results in Clinical Practice

IH, UWM, KPSC, and many other health care systems use IDM and use inaccurate predictive models with AUC<0.8 and sensitivity ≤49% for preventive care via care management

[22,24-26,46-57,59-93]. Similar to our recent work of using IH, UWM, and KPSC data to greatly increase prediction accuracy for hospital use for asthma [43-45] related to exacerbation proneness, we expect our models predicting exacerbation proneness to be more accurate than those inaccurate models, benefit many patients, and have practical value. We will automate explaining warnings and recommending interventions to aid clinicians to review structured data in patient clinical records faster and create customized care plans based on objective data. After our methods find patients with the greatest predicted risks and offer explanations, clinicians will review patient clinical records, look at factors such as social dimensions [182], and make IDM enrollment and intervention decisions. As feature patterns linked to high risk and patient status keep changing, our techniques can be used continuously to move patients out of and into IDM and to discover new feature patterns.

In addition to making the predictive model more accurate, using temporal features showing early health changes and general directions could also boost warning timeliness. If a patient will be admitted to the hospital for COPD or asthma and the model would not predict this until 1 week before the hospital admission, intervening at that time could be too late to avoid the admission. If the model uses suitable temporal features and runs continuously, this patient could be found several weeks earlier, when health decline just begins and preventing hospital admission is likely.

Generalizability

Predictive models vary by diseases and other factors and could be dissimilar to each other. However, our proposed methods and software for extracting temporal features and automatically explaining machine learning predictions are general and do not rely on any special property of a specific health care system, disease, or patient cohort. Given a new data set with a different disease, set of variables, patient cohort, or prediction target, one can plug in our software to extract temporal features and to automatically explain machine learning predictions. Besides being used for patients with asthma and patients with COPD, preventive care is also widely adopted for patients with heart disease and patients with diabetes [128], where our techniques could be harnessed, for example, to predict hospital use. Our sensitivity analysis results in aim 1 can be used to identify critical variables and determine how to generalize a predictive model to a health care system recording a different set of variables from IH, UWM, and KPSC.

We will use data retrieved from 3 health care systems, UWM, IH, and KPSC, to demonstrate our techniques on patients with asthma and patients with COPD. These systems include an academic system that has most of its patients referred from elsewhere (UWM), 2 integrated systems (IH and KPSC), and 42 hospitals and 458 clinics. Spreading across 3 large geographic areas, these heterogeneous facilities range from tertiary care hospitals in large cities served by subspecialists to community rural and urban clinics served by general practitioners and family physicians with limited resources. These health care systems use 4 distinct electronic medical record systems: KPSC uses Epic; UWM uses Epic and Cerner; and IH uses Health Evolution

through Logical Processing, Health Evolution through Logical Processing 2, and Cerner. Variations in health care system type, patient population, geographic location, cultural background, staff composition, electronic medical record system, and scope of services enable us to identify factors that generalize to other facilities nationwide. The OMOP common data model [147] and its linked standardized terminologies [148] standardize administrative and clinical variables from ≥10 major American health care systems [183,184]. Our models will be based on OMOP and apply to these health care systems using OMOP.

With appropriate extension, our techniques can be adopted for miscellaneous diseases and decision support applications and can improve clinical machine learning. For example, our techniques can enhance the prediction accuracy of other outcomes such as no-shows [185], hospital use [186], and treatment adherence [187]. This will enable us to target resources, such as telephone reminders to reduce no-shows [185], home visits by nurses and care management to reduce hospital use [186], and interventions to boost treatment adherence [187].

We can use the features extracted by our temporal feature extraction method to create a feature library to ease feature reuse [188]. This will help reduce the effort required to create predictive models for other modeling projects.

Significance Thresholds

In both the *Evaluating Model Performance and Power Analysis* and *Quantitative and Qualitative Analyses* sections, we use the widely adopted significance level of .05 to perform power analysis. The statistics community has debated a lot about the *P* value and its dichotomization [189-191]. Setting a threshold for the *P* value is essential for power analysis and sample size estimation [189]. In addition, to the best of our knowledge, no consensus has been reached on what the best alternative is if *P* values and statistical significance are not used [189]. Following the advice given by Amrhein et al [191], after obtaining the results of this study, we will report the actual *P* values, treat them as continuous measures of evidence against the null hypotheses rather than as parts of binary decision rules, and acknowledge that multiple independent studies are needed to provide stronger support for or against our hypotheses.

Conclusions

Our results will help make IDM for asthma and COPD more proactive, effective, and efficient, improving outcomes and saving resources. Future studies will evaluate our methods for heart diseases, diabetes, and other diseases; deploy our methods at UWM, KPSC, and IH for IDM for asthma and COPD; and test the performance against the current IDM practice.

Authors' Contributions

GL was mainly responsible for this study. He conceptualized and designed the study, performed the literature review, and wrote the paper. FN offered feedback on study design and medical issues, participated in performing the literature review, and revised the paper. BS offered feedback on study design and medical issues and revised the paper. XS took part in conceptualizing and writing the statistical analysis sections. CK took part in retrieving the KPSC data set of patients with asthma and interpreting its detected peculiarities. SH took part in retrieving the IH data set and interpreting its detected peculiarities. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AUC: area under the receiver operating characteristic curve
COPD: chronic obstructive pulmonary disease
ICD-9: International Classification of Diseases, Ninth Revision
ICD-10: International Classification of Diseases, Tenth Revision
IDM: integrated disease management
IH: Intermountain Healthcare
KPSC: Kaiser Permanente Southern California
LSTM: long short-term memory
OMOP: Observational Medical Outcomes Partnership
SSH: Secure Shell
UWM: University of Washington Medicine

Protocol

Usability Testing of a Digital Assessment Routing Tool: Protocol for an Iterative Convergent Mixed Methods Study

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Abstract

Background: Musculoskeletal conditions account for 16% of global disability, resulting in a negative effect on millions of patients and an increasing burden on health care utilization. Digital technologies that improve health care outcomes and efficiency are considered a priority; however, innovations are often inadequately developed and poorly adopted. Further, they are rarely tested with sufficient rigor in clinical trials—the gold standard for clinical proof of efficacy. We have developed a new musculoskeletal Digital Assessment Routing Tool (DART) that allows users to self-assess and be directed to the right care. DART requires usability testing in preparation for clinical trials.

Objective: This study will use the iterative convergent mixed methods design to assess and mitigate all serious usability issues to optimize user experience and adoption. Using this methodology, we will provide justifiable confidence to progress to full-scale randomized controlled trials when DART is integrated into clinical management pathways. This study protocol will provide a blueprint for future usability studies of mobile health solutions.

Methods: We will collect qualitative and quantitative data from 20-30 participants aged 18 years and older for 4 months. The exact number of participants recruited will be dependent on the number of iterative cycles required to reach the study end points. Building on previous internal testing and stakeholder involvement, quantitative data collection is defined by the constructs within the ISO 9241-210-2019 standard and the system usability scale, providing a usability score for DART. Guided by the participant responses to quantitative questioning, the researcher will focus the qualitative data collection on specific usability problems. These will then be graded to provide the rationale for further DART system improvements throughout the iterative cycles.

Results: This study received approval from the Queen Mary University of London Ethics of Research Committee (QMREC2018/48/048) on June 4, 2020. At manuscript submission, study recruitment was on-going, with data collection to be completed and results published in 2021.

Conclusions: This study will provide evidence concerning mobile health DART system usability and acceptance determining system improvements required to support user adoption and minimize suboptimal system usability as a potential confounder within subsequent noninferiority clinical trials. Success should produce a safe effective system with excellent usability, facilitating quicker and easier patient access to appropriate care while reducing the burden on primary and secondary care musculoskeletal services. This deliberately rigorous approach to mobile health innovation could be used as a guide for other developers of similar apps.

International Registered Report Identifier (IRRID): DERR1-10.2196/27205

Introduction

Background

Musculoskeletal conditions are recognized as a global issue, with between 20%-33% of people living with a painful musculoskeletal condition. These conditions are the highest contributor to global disability at 16%, resulting in a negative effect on millions of patients and an increasing burden on health care utilization [1]. Musculoskeletal conditions are prevalent throughout the lifespan and are associated with early work retirement and reduced ability to participate socially [2]. In developed countries, they present the most significant proportion of lost productivity in the workplace, leading to a significant impact on the gross domestic product and health care costs [3-6]. Musculoskeletal conditions can affect as many as 1 in 4 adults and are set to continue rising, being associated with increased life expectancy and reduced activity [4,5]. Access to the "right person, right place, first time" is considered a key factor in improving musculoskeletal condition outcomes and in reducing unwarranted variations in clinical pathways, such as unnecessary secondary care consultations and investigations [7]. Musculoskeletal triage as a single point of access is effective across various outcome measures, including user satisfaction, diagnostic agreement, appropriateness of referral, and reduction in patient waiting times [8]. Importantly, triage has also shown a reduction in cost across the musculoskeletal pathway, which is particularly crucial in overburdened health care systems, where triage can be performed effectively via several methods and by a range of clinicians [9-11]. For example, the National Health Service England is introducing physiotherapists as musculoskeletal first-contact practitioners; however, this is dependent on the recruitment of a significant number of clinicians with the associated challenges [7]. Mobile health (mHealth) technology is proposed as a cost-effective solution for improving health care delivery [12,13]. Although many mHealth tools have not demonstrated cost-effectiveness or have shown merely to shift spending to another part of the health system [14], it would seem logical that a digital alternative to physio-led triage, able to replicate the same stratification of care and reduction in costs, is a desirable objective. Thus, Optima Health has developed the Digital Assessment Routing Tool (DART) mHealth system to assess the patient's musculoskeletal presentation through a series of questions and responses accessed via their mobile devices. The patient is taken through a subjective assessment, which is driven by 9 sets of clinical algorithms that cover all body regions, similar to a clinician performing a virtual triage by telephone or videocall. At the end of the assessment, the patient is given a signposting recommendation to one of the clinical services available to them within the musculoskeletal pathway. The objective is to provide patients with easily accessible, safe, and effective access to musculoskeletal services, while releasing valuable clinical resources to consistently work at the top of their skill set, where

they add the greatest value to the patient journey. The development of more remote health care delivery options has been greatly accelerated by the COVID-19 pandemic and the benefits offered by a virtual approach are likely to support further uptake of systems such as DART. Patients are already making their own decisions about accessing health care for a range of conditions or increasingly turning to unvalidated self-help apps for advice that can be unhelpful or even potentially harmful [15,16]. Guidance for safe and effective development of mHealth apps has been published by several national and international organizations [17-20]. While these recommendations provide advice for developers, it is recognized that there remains no single regulatory framework to which all mHealth developments must conform [21] and that work remains to develop a suitable legal framework [22].

Up to 2017, there was an exponential increase in the rate of mHealth app releases, resulting in over 259,000 apps available in just the major app stores alone [23,24]. However, many mHealth apps have subsequently fallen, with many unsuccessful attempts to scale up from a prototype to successful implementation. Inattention to usability during the design and testing phases has been cited as the potential cause [25-27], contributing to the high abandonment rate [28]. Usability is crucial in the development of mHealth systems and is reflected within guidance documents relating to standards for design, development, testing, and implementation of these devices [17-19]. Usability has been defined as the extent to which a system can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use [19]. These constructs will all be assessed during the study (Figure 1). However, there is little agreement about the most effective methodology for usability testing, with researchers using a combination of different design components to assess mHealth apps [29]. The iterative convergent mixed methods design used for this research will provide a more holistic assessment of DART compared with other mHealth studies. Although quantitative questionnaires are the most frequently used method for assessing mHealth system usability [29], they are unlikely to identify the specific problems that need to be addressed. Questionnaire scores only give a general overview of usability, without providing the level of understanding of usability problems required for system iteration. Qualitative studies alone are not able to provide a definitive level of acceptability of a system. Iteration is recognized as a key enabler of successful products but is not included by most developers, where the usability testing of a final version is often immediately prior to deployment [29]. The inclusion of patient and public involvement during mHealth testing allows users to bring their own personal perspectives into the process, giving researchers the understanding of usability issues that would not have otherwise been recognized [30]. This study will combine all these elements into a methodology specifically developed to assess an mHealth triage

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or symptom checker. The iterative approach of cyclical evaluation and improvement plus mixed methods allows richness while quantifying use, thus maximizing usability and system adoption.

Figure 1. ISO 9241-210:2019 constructs and definitions and examples of digital assessment routing tool context of use. DART: Digital Assessment Routing Tool; mHealth: mobile health.

ISO Construct	Definition	Examples of DART context of use
Effectiveness	Accuracy and completeness with which users achieve specified goals	Did the participant arrive at a clinical recommendation? Was the recommendation correct?
Efficiency	The resources expended in relation to the accuracy and completeness with which users achieve goals	How long did the assessment take? Was the participant able to answer the questions without ambiguity?
Satisfaction	Freedom from discomfort and positive attitudes toward the use of the system	Satisfaction measured using System Usability Scale (SUS)
Accessibility	Use of the system by people with the widest range of capabilities	Participant sampling includes groups where mHealth may differ, for example older people, English for Speakers of Other Languages

DART Overview

DART is a first-contact mHealth system utilizing 9 musculoskeletal clinical algorithms, configured to provide the patient with a recommendation to the correct intervention level (Figure 2). Designed specifically for managing musculoskeletal conditions, it delivers a narrower but deeper assessment than that found with more generic symptom checkers. The patient can self-assess using a computer, tablet, or smartphone. Alternatively, the content can be delivered by a remotely situated clinician or a nonclinical administrator by telephone or videocall. The patient selects the body region related to his/her primary problem and is then presented with a varying number of questions, depending on the nature of his/her symptoms and previous responses. Serious pathology is identified and signposted at the start of the assessment, with less urgent

medical referrals being identified as the patient passes down the questioning. Algorithms are configured to match the provider's clinical services based on evidence-based practice and sector-specific referral criteria. DART can be applied across any number of health care systems, including public and private services. DART typically signposts to emergency or routine medical assessment, specific condition specialists, physiotherapy, self-management programs, or psychological support services. Referral thresholds can be configured to match service requirements, such as increasing the volume of patients directed to self-management or physiotherapy. Situated next to the questions are information boxes, which assist the patient in answering the question, thereby improving the accuracy of the responses. DART has an integral reporting function, thereby allowing the analysis of individual and amalgamated patient data to assess the system and clinical pathway performance.

Figure 2. Digital Assessment Routing Tool mobile health system.
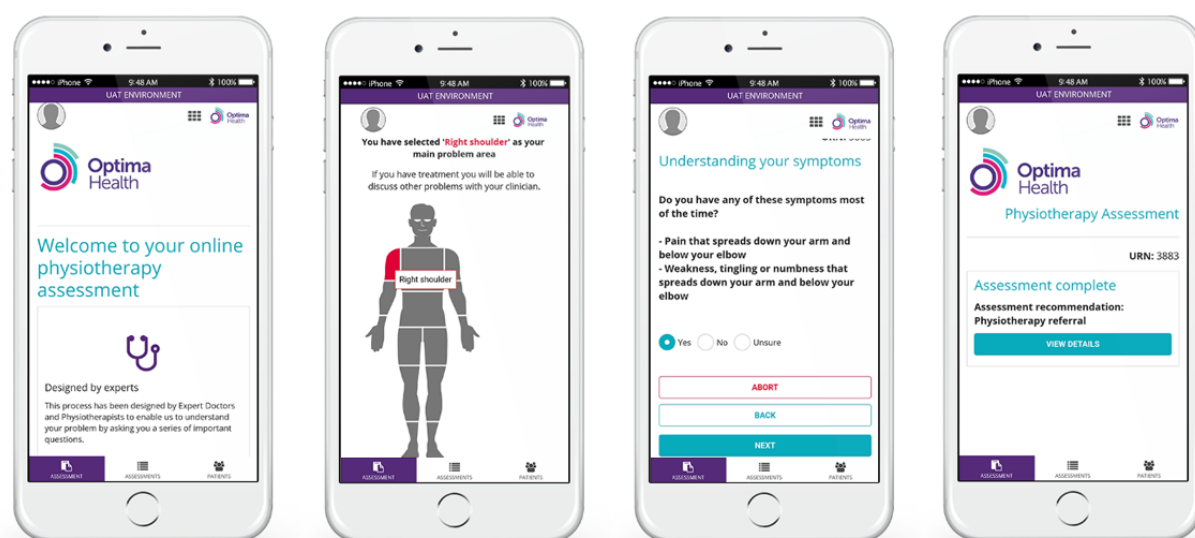
Previous Work

This usability study is part of a larger project, bringing DART from concept to implementation through a series of clinical and academic research work packages. To assess algorithm clinical validity, 2 reports were commissioned by Optima Health and undertaken by a panel of 5 consultant clinicians prominent in the musculoskeletal field. The first round of desktop evaluation consisted of experts inputting symptoms from 98 clinical scenarios (including red flags and complex presentations) into DART. The DART recommendation was assessed by the expert as being correct, arguably correct, or disagree. Feedback from the experts was incorporated into a new iteration, leading to improved DART accuracy during the second panel review. Based on their opinions, the panel recommended that the clinical validity was sufficient to allow DART to proceed to further research studies. The initial usability study protocol went through a series of iterations within an internal review process, comprising the research project team and DART system developers to arrive at the final version presented in this paper. Using a new usability testing methodology, this study will provide a rich understanding of how users interact with DART and guide further iterations. The impact of this will be to optimize usability before evaluating the safety and effectiveness of DART in a randomized controlled trial.

Research Aim, Objectives, and End Points

The aim of this study is to assess and optimize DART usability, which could result in maximizing user adoption. The objectives are as follows: (1) to understand what users consider to be strengths and weakness of using DART, (2) to identify usability issues and map to a usability problem grade to inform the next DART iteration development, and (3) to complete a cycle of iterations until usability reaches a predefined acceptable level. The end points are as follows: (1) all Grade 1 and 2 usability problems have been mitigated following a minimum of 3 user group sessions and (2) system usability scale score is 80 or greater after a minimum of 3 user group sessions plus 1 additional session, representing a "good" or better system.

Methods

Study Design

This study will use an iterative convergent mixed methods design, as described by Alwashmi et al [31]. The collection and integration of quantitative and qualitative data of direct relevance to the DART mHealth app will be used to inform subsequent DART usability improvements (Figure 3). The first phase of data collection will consist of 5 interviews with individual participants who have used the tool to identify key usability issues and gain a baseline system usability scale score. It has been suggested that 5 participants are likely to expose about 80% of the usability issues [32]. Although it is recognized that the DART target population will be heterogenous, the first round of interviews is expected to expose key issues from the sample. This will be followed by group sessions to capture a greater diversity of potential DART user population to improve validity of the data. Owing to logistic requirements, interview sessions will be conducted remotely using Microsoft Teams videoconferencing software and web-based questionnaires.

Figure 3. Digital Assessment Routing Tool usability study iterative convergent mixed methods design. DART: Digital Assessment Routing Tool; SUS: system usability scale.
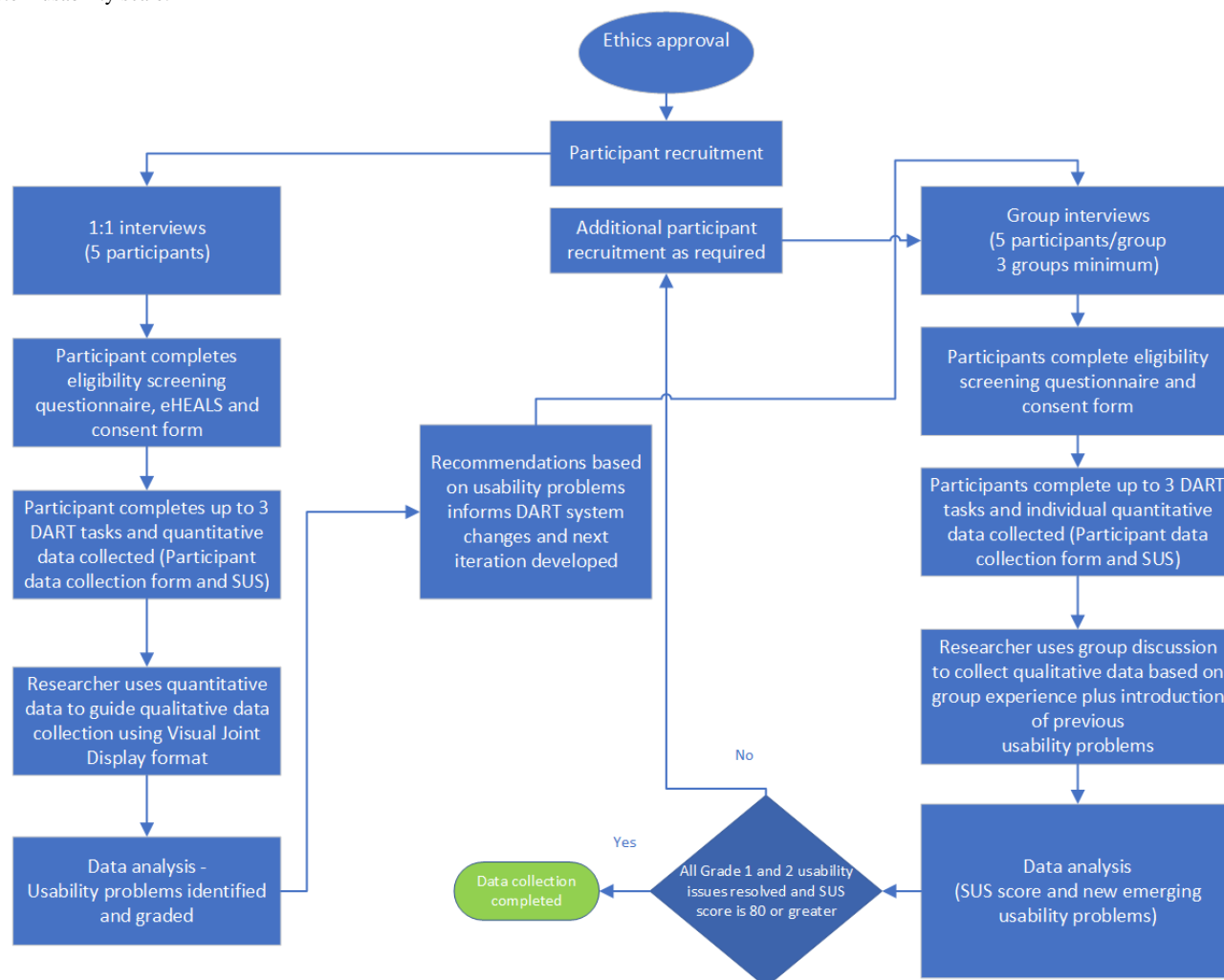
Participant Recruitment

A stratified purposive sampling method will be used to gather information from participants able to access the internet as well as to explore the scope of potential DART accessibility [33]. We will use a criterion-based selection, categorizing participant characteristics of age, internet use, sex, English for Speakers of Other Languages groups—all of which are subgroups that have shown to contribute small differences in internet use [34]. To ensure that participants are included from groups potentially less likely or able to use mHealth systems, a sampling matrix will be used, which provides quotas specifying the number of people required for each characteristic [33]. Recruitment of 20-30 participants will be via convenience sampling and snowballing; study recruitment will continue until there is a representative sample from each category defined by the sample matrix and the study end points being reached. Recruitment material will be distributed to local community groups, Optima Health's existing client base of employers and their staff, plus Queen Mary University of London (QMUL) students. Potential participants expressing an interest will be sent a patient information sheet and consent form (Multimedia Appendix 1). They will have an opportunity to review this material and if they wish to proceed, they will be registered for the study.

Inclusion Criteria

The study participant inclusion criteria are as follows: (1) adults older than 18 years; (2) able to speak and read English; (3) live in the United Kingdom; (4) access the internet at least once every 3 months; (5) has access to a smartphone, tablet, or laptop; and (6) current or previous experience of a musculoskeletal condition.

Exclusion Criteria

The study participant exclusion criteria are as follows: (1) significant visual or memory impairment sufficient to affect the ability to answer questions and recall information in an individual or group discussion setting; (2) medically trained, musculoskeletal health care professional, for example, doctor, physiotherapist; (3) relatives or friends of the researchers; and (4) Optima Health employees.

Study Duration

It is anticipated that this study will last for up to 3 months after receiving the ethical approval. However, this will be dependent on the number of DART iterations required to achieve the end points. Participants who have raised high-grade usability problems will be invited to participate in a subsequent study session to assess the impact of DART system changes.

Theoretical Framework

The iterative convergent mixed methods design, as described by Alwashmi [31], involves simultaneous qualitative and quantitative data collection and analysis that continues cyclically through rounds of mixed methods data collection and analysis until the mHealth technology under evaluation is found to work to the agreed criteria. This design will be used to enhance the usability of the DART system by using strategies of matching, diffracting, and expanding. The *matching* process involves aligning qualitative questions with quantitative variables which, in this study, are defined by the constructs within the ISO 9241-210-2019 standard [19] and the system usability scale [35-37]. These are presented as a visual joint display [38], which allows the researcher to explore usability themes as they emerge during the data collection. As the participant responds to the quantitative questioning, the researcher highlights in real time areas on the visual joint display that they wish to explore in more detail during the qualitative element of data capture (Figure 4). *Diffraction* allows the addition of qualitative questions that explore different aspects of the quantitative data that are not addressed through the scales or items being collected. Examples for this study include trust and intention to act, as well as the importance of clinical escalation. *Expanding* further supports the ability of the researcher to examine findings from the divergence of the qualitative and quantitative data, exploring different aspects of a single phenomenon. This could include an instance where the DART task completion time may be longer for some participants, to whom spending longer understanding and answering the questions accurately is more important than being able to finish the assessment quickly.

Figure 4. An extract from a joint visual display showing how a researcher uses responses to quantitative data to guide qualitative data collection in real time.

Data Collection

Following consent being given, participants will complete a short questionnaire providing demographic data. Five one-to-one sessions scheduled to last up to 60 minutes will be conducted using Microsoft Teams (videoconferencing facility developed by Microsoft) video calls. After completing the eHEALS health literacy questionnaire [39], the participant will be asked to log in to DART. Using an existing or previous musculoskeletal condition to complete the assessment, they will be encouraged to give feedback using the concurrent think-aloud method [40]. This can be repeated for up to 3 different conditions. They will then complete 2 quantitative data questionnaires concerning ISO effectiveness, efficiency, satisfaction, and accessibility constructs. Satisfaction will be measured using the system usability scale. This data will inform and direct subsequent qualitative data collection. The researcher will identify variables with low scores, for example, "I found the product unnecessarily complex" and focus their qualitative questions to target these areas, interactively considering both types of data in the context of each other. The interviews will be recorded and transcribed verbatim using Otter (automated video and audio transcription software developed by otter.ai), with a final review for accuracy by the researcher using the original recording for comparison.

As the study progresses and usability issues are addressed during each iteration, the emphasis for data collection moves from being largely qualitative to become more focused on the quantitative data driving the study end points. Up to 5 participants will attend a web-based session where they will be asked to explore DART. They will complete the quantitative data questionnaires and be invited to discuss any comments they may have. Qualitative questioning at this stage will be broader in nature, with postuse debrief questions as follows: (1) were you asked about what was important to you? (2) how did you find the questions? and (3) could we improve the system?

The researcher will use this opportunity to raise any previous usability problems to assess the impact of changes made to the previous iteration. The group sessions will be recorded and transcribed.

Data Analysis

Qualitative data will be transcribed and analyzed using thematic analysis by 2 researchers working independently using NVivo (qualitative data analysis software developed by QSR International) to create an initial thematic framework (Figure 5). Data will be indexed into usability problems of key

importance to the study and presented in a data summary display. The researchers working initially independently and then together will achieve a consensus and agree on allocating a problem severity grade to each data theme. This is obtained by considering the impact of the problem on the user and the frequency with which it occurs, which leads to a decision on the risk of not addressing the problem versus the reward of correcting it. Once the problems have been allocated a severity grade, matched recommendations are given for each to guide system development of the next DART iteration. Actions to address all Grade 1 and 2 usability problems are completed for the next iteration, with Grade 3 and 4 problems remaining on record and reassessed and, if necessary, regraded after each round of testing. After each round of testing, participant system

usability scale raw scores will be converted and reported, together with a cumulated score across rounds of testing. The final mean score will also be converted into a percentile score to allow benchmarking against other web-based systems [41]. Participant responses to the following questions were also analyzed and reported: (1) did you get a recommendation? (2) would you trust the recommendation you were given? and (3) would you act on the given recommendation? If the participant is willing to discuss the details of their musculoskeletal conditions, the researcher (a physiotherapist) will provide an opinion regarding whether they thought the DART signposting was arguably correct. Usability will also be considered in the context of participant eHealth literacy.

Figure 5. Qualitative data translates into system improvement in the iterative convergent mixed methods design. DART: Digital Assessment Routing Tool.
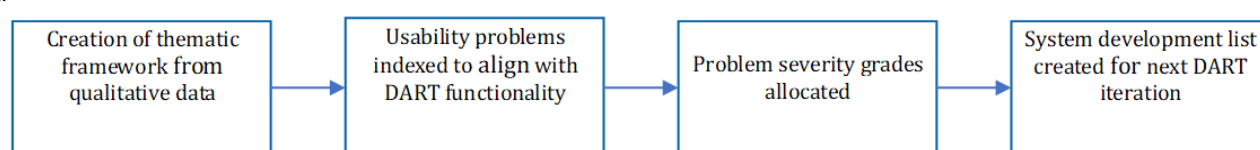
Bias

This study is funded by the developers of DART, Optima Health and therefore is at risk of bias. The lead researcher is an employee of Optima Health and enrolled in a PhD program at QMUL. The second researcher, with no connections to Optima Health, will participate in data collection and analysis. To mitigate bias, participants are excluded if they are employees of Optima Health or QMUL or if they are relatives or friends of the lead researcher. Participants will not have seen or used DART previously. To address unconscious bias during the recruitment process, the use of a purposive sampling framework will ensure that people fulfilling the criteria of central importance to the research objectives are included in the study. The 2 study researchers will work independently for the data collection and initial analysis before combining their results and coming to a consensus for usability problem grading. Quantitative data will be collected by the researcher who has no connection to Optima Health or DART system development.

Risks and Benefits

There is no form of physical intervention during this study and participants are interviewed remotely, with no travel being required. A possible benefit, albeit unlikely, is that a previously undiagnosed serious pathology could be revealed during the testing process and the researcher (a physiotherapist) could immediately advise the participant on the most appropriate action to ensure their safety. Following completion of the DART assessment by the participant, the researcher will discuss the DART disposition with the participant in the context of his/her symptom presentation. If indicated during this discussion, the researcher will also provide appropriate clinical advice and reassurance about the condition management to the participant.

Informed Consent

Each participant will receive the participant information sheet and consent form (Multimedia Appendix 1), which outlines the purpose of the study and the nature of the participation. This

includes information about the format of the interaction (one-to-one or group), potential risks, confidentiality and protection of personal data, the anonymity of study findings, and the right to withdraw at any time without prejudice. After reading the participant information sheet, the participant is given the opportunity to email or request a call with the lead researcher to discuss any questions. The participant will be required to provide written, signed consent prior to any data collection, which will then be posted or emailed to the lead researcher.

Data Management

Participants have the right to withdraw from the study at any time. If they do, data collected up to the point they withdraw will be retained, but not then added to. Research data will be stored separately to personal data and linked by a unique reference number only accessible to the researchers. Electronic and paper data will be managed and stored securely in accordance with general data protection regulations.

Results

Ethics approval was received from QMUL Ethics of Research Committee (QMREC2018/48/048) on June 4, 2020. At manuscript submission, the first round of individual interviews has been completed and recruitment commenced for the group sessions. Results will be reported in a follow-up paper later in 2021.

Discussion

Overview of This Study

A systematic evaluation of the DART mHealth system in line with the international and national guidelines [17-20] will provide a more precise assessment of its usability and potential adoption. It will also address areas of poor usability that could otherwise become confounding factors within the subsequent noninferiority trial, where DART will be compared with current

practice virtual physiotherapy triage. To date, there are no published studies evaluating similar musculoskeletal mHealth systems or indeed the knowledge of clinician error rates in usual care against which to benchmark DART. For this reason, we have set the target usability standard of 80 to be achieved, which will place DART in the top 10% of products tested using the system usability scale [41]. Usability testing will rely on an iterative convergent mixed methods design, which allows data collection specific to the functionality of the DART system, while incorporating validated and widely published usability quality measures. The iterative approach ensures that system changes made in response to identified usability problems are retested by study participants to validate the success of the updates. Based on the data collected, this section will benchmark DART usability as an app, discuss the limitations of the evaluation, and consider essential implications for future DART testing and deployment. The study methodology has been designed to rigorously test the DART mHealth app and could be adopted by other researchers to improve usability and adoption of other similar systems.

Methodological Limitations

The purpose of this study is to assess usability problems that could influence DART signposting, routing, and user acceptance. This study will not determine the safety and effectiveness of DART, as this will be the subject of a subsequent study. Some limitations have already been identified, such as the challenge of recruiting a representative section of a potentially large and diverse DART user population. The study design is proportionate to the resources available to deliver the study, and it is acknowledged that a more significant number of participants could yield a richer data set. Owing to the limitation of the study resources and the current iteration of DART only being available in the English language, participants unable to read English are excluded. Moreover, because of logistic constraints, all interviews and group sessions will be conducted remotely by video call. It is not known how this may impact the richness or quality of data collection, although this has been considered and attempts will be made to mitigate possible negative effects, which includes ensuring all participants are briefed in advance on how to use the key features of Microsoft Teams and are supported with this during data collection. It is recognized that within virtual group sessions, the researcher will be required to take a more proactive approach to running the session, putting people at ease, and inviting everyone in turn to share their views.

Methodological Strengths

It is rare that this level of evaluation of an mHealth system is completed [29], with none published in the musculoskeletal field [42]. This protocol provides a template for other researchers and developers to use across triage and referral mHealth systems. The protocol was research in and of itself and has the unique benefit of combining widely accepted methods of assessing system usability together with important factors specific to clinical practice, making it generalizable across systems and adaptable for specific clinical pathways. The incorporation of stakeholder engagement during the study design ensures links between the protocol and the published mHealth system design standards, including requirements for transparency of the research. This protocol is suitable for remote delivery, supporting efficient cost-effective research within the constraints of the social distancing required by the current pandemic restrictions.

Authors' Contributions

CL conceived the study topic and adapted the study design from that originally published by Dr Meshari Alwashmi in 2019. The protocol was written by CL, with input from Professor Dylan Morrissey. CL and MB will collect data and perform data analysis. CL drafted the manuscript, which was reviewed by DM, WM, MA, and HHS prior to submission.

Conflicts of Interest

Optima Health has developed the DART system and is the owner of the associated intellectual property. The principal investigator (CL) is an employee of Optima Health and a PhD Research Student at QMUL. HHS is a research assistant employed by Optima Health and holds an Honorarium at QMUL.

Multimedia Appendix 1
Patient information and consent form.
[DOC File , 104 KB - resprot_v10i5e27205_app1.doc]

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Abbreviations

DART: Digital Assessment Routing Tool
mHealth: mobile health
QMUL: Queen Mary University of London

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Health Care Professional Association Agency in Preparing for Artificial Intelligence: Protocol for a Multi-Case Study

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Abstract

Background: The emergence of artificial intelligence (AI) in health care has impacted health care systems, including employment, training, education, and professional regulation. It is incumbent on health professional associations to assist their membership in defining and preparing for AI-related change. Health professional associations, or the national groups convened to represent the interests of the members of a profession, play a unique role in establishing the sociocultural, normative, and regulative elements of health care professions.

Objective: The aim of this paper is to present a protocol for a proposed study of how, when faced with AI as a disruptive technology, health professional associations engage in sensemaking and legitimization of change to support their membership in preparing for future practice.

Methods: An exploratory multi-case study approach will be used. This study will be informed by the normalization process theory (NPT), which suggests behavioral constructs required for complex change, providing a novel lens through which to consider the agency of macrolevel actors in practice change. A total of 4 health professional associations will be studied, each representing an instrumental case and related fields selected for their early consideration of AI technologies. Data collection will consist of key informant interviews, observation of relevant meetings, and document review. Individual and collective sensemaking activities and action toward change will be identified using stakeholder network mapping. A hybrid inductive and deductive model will be used for a concurrent thematic analysis, mapping emergent themes against the NPT framework to assess fit and identify areas of discordance.

Results: As of January 2021, we have conducted 17 interviews, with representation across the 4 health professional associations. Of these 17 interviews, 15 (88%) have been transcribed. Document review is underway and complete for one health professional association and nearly complete for another. Observation opportunities have been challenged by competing priorities during COVID-19 and may require revisiting. A linear cross-case analytic approach will be taken to present the data, highlighting both guidance for the implementation of AI and implications for the application of NPT at the macro level. The ability to inform consideration of AI will depend on the degree to which the engaged health professional associations have considered this topic at the time of the study and, hence, what priority it has been assigned within the health professional association and what actions have been taken to consider or prepare for it. The fact that this may differ between health professional associations and practice environments will require consideration throughout the analysis.

Conclusions: Ultimately, this protocol outlines a case study approach to understand how, when faced with AI as a disruptive technology, health professional associations engage in sensemaking and legitimization of change to support their membership in preparing for future practice.

Introduction

Background

Many health care professionals are on the cusp of welcoming a new partner into their collaborative practice model, artificial intelligence (AI). Recently, there has been significant discussion in lay media about the impact of AI's integration on the workforce. Advancements in AI in health care in the coming years will require significant attention to employment, training, education, and regulation [1]. As AI strategies are increasingly being developed in health care, it is important to assess how health care professions and their representative associations will be affected by changes to traditional roles and tasks, some of which will be modified or replaced by technological solutions.

AI in Health Care

Russell and Norvig [2] define AI as "the study of agents that receive percepts from the environment and perform actions." In its broadest sense, this can be conceived of as a computer system performing some manipulation of an input (ie, informational or sensory data) to create a novel output without active human intervention [3].

AI encompasses a diverse array of technologies, including automation, aspects of robotics, machine learning, and other approaches for interpreting big data. In health care, such innovations are increasingly mastering menial and rule-based tasks or acting as powerful decision-making tools or monitoring systems to support clinicians. Big data, including both structured data, such as demographics and laboratory medicine results, and unstructured data, such as those extracted from electronic clinical notes using natural language processing, have also been used to develop automated clinical decision-making tools and outcome prediction via predictive analytics [4].

Among other uses, AI has been applied in dermatology, radiology, drug reconciliation, and adverse event management, often outperforming internists in extracting relevant information from unstructured free-text or imaging data [4-6], and in optimizing aspects of pharmacy in drug discovery, tracking, and dispensing [7].

AI constitutes a disruptive technology for health care systems, given the spectrum of applications of related technologies and the associated implications for those who interact with it, from practical clinical workflows to the higher-level considerations related to regulation, scopes of practice, and education.

Potential Professional Impact

From the perspective of human actors in AI-related health care disruption, there are numerous stakeholder groups, from clinical organizations to academic institutions and from professional and regulatory bodies to related industries. AI is a broad phenomenon, not one that is borne and leveraged within a given professional or academic setting, and the expertise in predicting and planning for its impact may not reside in an easily identified individual role or institution. It is not a single strategy whose impact can be quantified, itemized, and considered. Different stakeholders in the *AI in health care* arena may hold different perspectives on the nature, scope, and role of AI in clinical practice. However, although it is important to consider the role of all stakeholders and the interplay and tensions between these roles and interests in future practice, the health professional association has a unique role in representing affected health professions and takes on frontline responsibility for helping health professions navigate changes due to AI. This will be the focus of this study.

Role of Health Professional Associations

Although there is some important variation in the structure and mandate of the health professional association, its core business is the protection of a defined scope of practice, with the intention of maintaining the exclusivity of practice and protecting its members from encroachment of other groups. health professional associations, thus, serve to bring members of a certain profession into a formal membership structure to self-manage the definition and maintenance of these attributes. To this end, many assume the role of a certifying body, establishing the entry-to-practice standards of the profession, accrediting those academic programs tasked with training to those standards, and serving as a gatekeeper to the profession by granting membership based on meeting those standards. To further maintain exclusivity, health professional associations assume advocacy roles, furthering the image of the profession and often lobbying for protective practice rights through related health legislation.

Health professional associations are well situated to guide and inform service delivery–level change from a system vantage point. It is incumbent on professional bodies to assist their membership in preparing for change and informing the scope of that change. By design, health professional associations have a unique role in establishing and maintaining the sociocultural, normative, and regulative elements of professional scope and practice [8]. These tasks can serve to protect the exclusivity of their membership, restricting access to an established knowledge base to define their role in society [9]. In times of change, they can be pivotal in legitimizing novel practice both to their membership and to other professions and related stakeholders [10]. They often serve to direct other related entities, such as accrediting bodies and academic programs, in defining the evolution of professional scopes of practice and knowledge bases, within the bounds of any existing regulation.

AI heralds a change in health care that will impact many professions. Contrary to much of the lay media hype, most

academic reflections on AI as a disruptive technology have posited that professions are not fundamentally at risk of obsolescence with AI, but then suggest that this position is balanced precariously on the condition of health care professionals' engagement in informing practice evolution [11-14]. As health professional associations begin to consider implications for their practice, some are convening task groups and putting out calls to action to highlight the role that should be taken by the professions to define their own future within an AI-enabled practice environment [15,16]. Recognizing that many manual, repetitive, and primarily rule-based tasks are expected to be outsourced to AI, professions are seeing the need to reposition themselves within the system on multiple levels. Depending on the magnitude of potential change anticipated by an individual health professional association, these might include advocacy for responsible integration of AI, consideration of changing roles within an evolving health care team, and preparedness for interacting directly with novel technologies and data.

Objectives

In the context of the traditional role of health professional associations as gatekeepers to a protected knowledge base, there is value in exploring how health professional associations engage in sensemaking and relational work to guide and support their membership when faced with disruptive technology. Although AI implementation may be at its nascent stages in most areas of health care, there is also value in beginning to look at the enactment and monitoring of change as well—the form the change is expected to take and how groups go about implementation. This considers the scope and impact of AI as conceived by the health professional association, regardless of formal conventions.

This proposed work will seek to investigate the following research question: When faced with AI as a disruptive technology, how do health professional associations engage in sensemaking and legitimization of change to support their membership in preparing for future practice?

Within the scope of this project, we also hope to consider from whom, and in what ways, health professional associations seek insight to make sense of AI strategies as they relate to their members' practice; how that contributes to conceptualizing a relational model for interprofessional collaboration in practice; and, finally, to what extent health professional associations engage in reflexive monitoring and feedback to support their memberships through AI-related change.

Methods

Overview

The proposed study will take an exploratory multi-case study approach to address these objectives, using the normalization process theory (NPT) as a theoretical context. Approval for this study has been obtained from the University of Toronto Research Ethics Boards (protocol #00038733).

Theoretical Approach: NPT

Negotiation of new knowledge, roles, and workflows, in light of a technology that will infiltrate significantly into traditional practice boundaries, often requires a process of validating change against a profession's established (and socially constructed) value and belief systems [9]. An understanding of where national health professional associations envision and position themselves as stakeholders in AI innovation and how they support a membership faced with AI integration can help to inform active strategies for engaging it in preparing for relevant complex interventions and the future of practice.

Complex interventions in health care, such as the integration of a disruptive technology, are those changes to delivery of care that involve several interacting elements that must all be coordinated for the intervention to be successfully and sustainably implemented [17]. The NPT provides a valuable framework to distill the behavioral elements of a complex intervention from other elements, focusing on the action necessary to effect change [18]. It defines 4 social mechanisms that come together to enact the processes necessary for complex intervention: coherence, cognitive participation, collective action, and reflexive monitoring. Those integrating change must first make sense of the expectations and goals of the new practice (coherence) and then actively engage with it to appreciate its role and scope (cognitive participation). Where there is a decision to engage in change, critical to the ultimate success of its integration into standard practice, users must interact meaningfully with each other and relevant stakeholders to enable its use (collective action), followed by an evaluative phase that feeds back to iteratively inform practice (reflexive monitoring) [19].

A recent systematic literature review conducted by May et al [20] highlighted that although NPT had been used on occasion to investigate formal changes in professional roles, few have explored NPT constructs from a macro perspective. They suggested that this might be a valid future area of consideration. Although each of the domains of NPT may be necessary for ultimate success, health professional associations have a distinct role, from a macro perspective, in both coherence and cognitive participation, essentially the sensemaking and relational work required to enact change. Considering NPT at this level may strengthen the theory and suggest unique factors to be considered when looking beyond individuals within a team.

Case Study Approach

Case study research values a comprehensive and multifaceted exploration of an uncontrolled and yet formally defined area, rather than a constrained and variable-driven correlational investigation [21]. Thus, it tends to value depth over breadth in the substance and applicability of its results. In consideration of how health professional associations address disruptive technology, the use of a case study approach was indicated based on the following factors: (1) a bounded case and relevant context are readily defined, (2) context is essential to the understanding of the phenomenon, (3) relevant insight cannot likely be gleaned from one source, and (4) a theory exists to provide a worthwhile foundation on which to build. A well-selected case or set of cases can provide nuanced

context-dependent insight that might not be readily available when focusing on the generalizability of a more statistical approach, when "the boundaries between phenomenon and context may not be clearly evident" [21-23].

Defining the Cases

Case Selection

A collective of 4 instrumental cases within 2 related areas of health care practice was sought. The intention was to identify fields that are traditionally heavily reliant on technology and where AI is currently being explored. Engaging multiple health professional associations with a stake in interdependent practice

environments also highlights the interprofessional dynamic that could inform change integration.

The related fields of medical imaging and radiation medicine were chosen as the overlapping case contexts, with 4 involved health professional associations selected as cases: the Canadian Association of Radiation Oncology (CARO), the Canadian Association of Radiologists (CAR), the Canadian Organization of Medical Physicists (COMP), and the Canadian Association of Medical Radiation Technologists (CAMRT). The contextual relationship of these health professional associations and their members within their respective frontline practice environments are represented graphically in Figure 1.

Figure 1. Relational case and context. CAMRT: Canadian Association of Medical Radiation Technologists; CAR: Canadian Association of Radiologists; CARO: Canadian Association of Radiation Oncology; COMP: Canadian Organization of Medical Physicists.
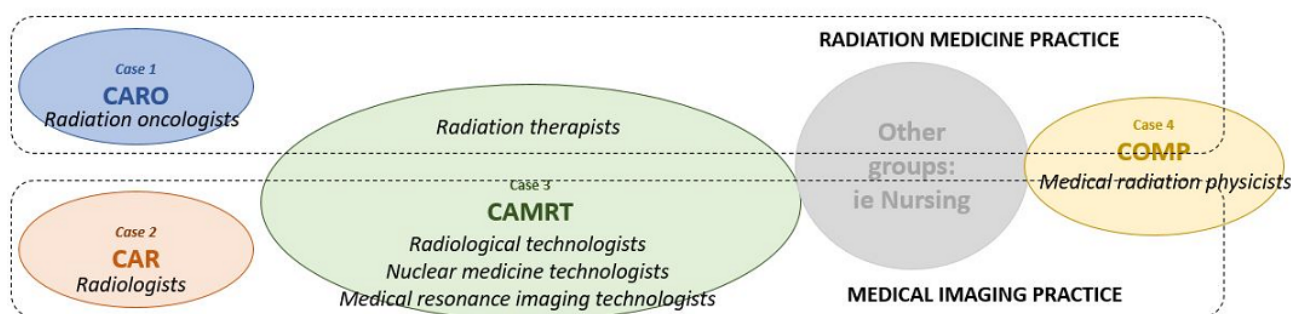
Radiation Medicine

Radiation therapy is one of the main pillars of cancer care, in addition to surgery and chemotherapy. It involves focused delivery of ionizing radiation, which is carefully targeted to a defined anatomical area, capitalizing on the ability of radiation to selectively kill actively reproducing cells, namely, those that are cancerous, while attempting to minimize side effects to normal healthy tissues. Oncologists diagnose the cancer and prescribe the radiation treatment, whereas therapists map the plan for treatment and deliver it, commonly over the course of several weeks. Physicists focus on how radiation behaves in the body and ensure calibrated functioning of related machines and treatment planning software.

There are 47 radiation treatment facilities in Canada, which are operated by provincial governments in the country's publicly funded health care system [24]. Facilities range from large academically affiliated departments in dedicated multidisciplinary cancer centers to smaller hubs within community hospitals and some individual satellite treatment bunkers. In 2014, approximately 118,350 courses of radiation therapy treatment were administered in Canada, and it is estimated that 50% of all cases of cancer could likely benefit from radiation therapy at some point in the treatment trajectory [25].

Medical Imaging

Medical imaging is the process of creating visual representations of the inside of the human body (primarily using radiation but also involving other modalities such as ultrasound and magnetic resonance) to identify and characterize a disease or injury (diagnostic radiology). The related area of interventional

radiology can also involve minimally invasive imaging techniques to assist in therapeutic care. Technologists position patients and acquire the imaging studies, whereas radiologists interpret the images, often for the purposes of diagnosis, and consult with referring physicians [26]. Similar to radiation medicine, physicists commission and maintain image acquisition and visualization infrastructure.

In 2012, over 6 million medical resonance and computed tomography examinations were performed in Canada, almost twice the number as the previous decade [26]. Although many imaging examinations are performed in large medical imaging departments in publicly funded hospitals and community clinics, approximately 10% of imaging facilities are small, private, stand-alone businesses [27].

Technology has always been, and remains, at the heart of contemporary radiation medicine and medical imaging practice [28,29]. The professions at the heart of these fields are adept at adapting to novel technologies, being heavily reliant on both computer software systems and large and complex medical machines to provide care. Examples of automation and machine learning in radiation medicine and medical imaging have emerged in recent years, and providers are becoming familiar with the ways in which AI could augment care and necessitate a shift in professional roles [15,16,28-33].

Although there has been significant research and development work regarding the potential for AI strategies [5,34-37] to facilitate more efficient and higher quality care, little attention has been paid to the impact on the professionals who engage in care delivery.

Cases and Replication Logic

Table 1 provides a case logic table that summarizes the relevant comparative characteristics between the 4 health professional associations, highlighting similarities and differences that can inform the use of data to make theoretical and practical inferences [21].

The characteristics of the 4 cases suggest that CARO and CAR reflect similarly positioned and sized physician bodies, suggesting similar professional autonomy and influence. The fact that CAR employs a robust administrative structure, however, suggests that there may exist different bandwidths between CAR and CARO to formally support coordinated professional initiatives. CAMRT and COMP differ from CAR and CARO and from each other in the size of their relevant membership and associated professional backgrounds but align in the intrahealth professional association heterogeneity of their membership, with representation in both medical imaging and radiation medicine. For CAMRT, as a significantly larger allied health group than the other groups, although with traditionally less autonomy in defining practice in a hierarchical health care environment, it may perceive itself as having less agency in defining its own future practice, looking to the other organizations for guidance in how to position themselves within the AI landscape. COMP differs in its current lack of regulation but is similar to the CAMRT in the different subspecialties under its purview, with members practicing in both medical imaging and radiation medicine. COMP also represents a professional group that tends to hold a large stake in the commercialization efforts around novel technologies. This may suggest a more robust baseline understanding of the nature of AI and its impact across the organization, reinforcing a theoretical replication in terms of the maturity of a perspective on AI manifested across COMP initiatives and membership.

Table 1. Case logic table.

Elements of organization	CAMRT[a]	CARO[b]	CAR[c]	COMP[d]
Year founded	1942	1988	1937	1989
Membership				
Professions	Radiation therapy (also diagnostic imaging professions)	Radiation oncology physicians (also associate membership offered to other related professions—radiation therapy, medical physics)	Physicists or engineers in medicine	__[e]
Number of members	~12,000 (~15% radiation therapist)	~500	~300	~300 (~50% radiation physics)
Mandatory?	No	No	No	No
Regulation of practice?	No; provincially, where required	No; provincially, required	No; provincially, required	No, not regulated (in progress in most provinces)
Entry-to-practice oversight?	Yes, sets competency profiles and certification examinations	No (managed by RCPSC[f]); oversees liaison specialty committee to inform entry-to-practice	No (managed by RCPSC); oversees liaison specialty committee to inform entry-to-practice	No (managed by CCPM[g]—common management and MOU[h])
Entry-to-practice requirements	Primarily undergraduate	MD[i]; medical residency	MD; medical residency	Primarily PhD; primarily residency
Organizational structure				
By-laws	Yes	Yes	Yes	Yes
Board of directors	Yes, elected volunteers; practicing professional members	Yes, elected volunteers; practicing professional members	Yes, elected volunteers; practicing professional members	Yes, elected volunteers; practicing professional members
Administration	CEO[j], directors, staff of 20	Secretariat central (association management firm)	—	Executive director, staff of 3 (joint with CCPM)
Provincial-level counterparts?	Yes, provincial member associations (sometimes joint body with provincial regulatory arm)	No	Yes, in some provinces	No
Professional guidance				
Code of ethics	Yes	Yes	No	Yes
Practice guidelines	Yes	Yes	Yes	Yes
Education committee	Yes	Yes	Yes	Yes
Formal continuing education portfolio	Yes	No	Yes	No
Professional practice or affairs committee	Yes	Yes	Yes	Yes
Affiliated academic journal	Yes; *Journal of Medical Imaging & Radiation Sciences*	No (collaborates with European Society in *Radiation Oncology)*	—	No

[a]CAMRT: Canadian Association of Medical Radiation Technologists.

[b]CARO: Canadian Association of Radiation Oncology.

[c]CAR: Canadian Association of Radiologists.

[d]COMP: Canadian Organization of Medical Physicists.

[e]Not available.

[f]RCPSC: Royal College of Physicians and Surgeons of Canada.

[g]CCPM: Canadian College of Physicists in Medicine.

[h]MOU: Memorandum of understanding.

[i]MD: Doctor of Medicine.

[j]CEO: Chief executive officer.

Bounds to the Cases

To bound the cases spatially and temporally, the following parameters will be defined. Temporally, the timeline of this work will be bounded by the individual health professional association's current, immediately previous, and pending strategic plans. Although this may differ slightly for each health professional association, the timeline will run from approximately 2012 to the present time for each health professional association (including documentation prepared for future strategic plans that has been prepared by the time of data collection). With respect to bounds placed on scope, or spatial bounds, consideration will be primarily on the health professional associations' consideration of AI-enabled practice. Other stakeholders, such as those depicted in the preliminary network map in Figure 2, will be captured through insights into how the health professional association engages them and the nature of that engagement.

Figure 2. Artificial intelligence strategy integration in Canadian radiation therapy and medical imaging fields.
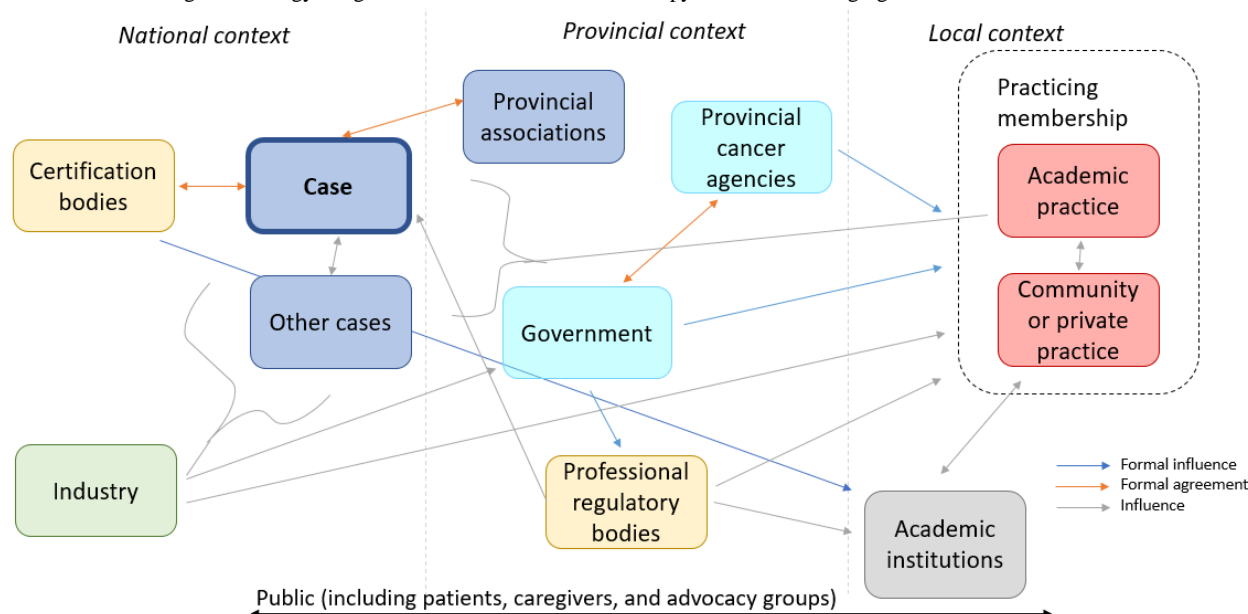
Data Collection

For each case, 3 phases of data collection will be pursued: document review (phase 1), interviews (phase 2), and observation (phase 3), with a cross-cutting reflexivity phase that will span study design, data collection, and analysis.

Phase 1: Document Review

Phase 1 will consist of a review of formal health professional association documentation, that which is available publicly through health professional association websites and that which will be sought through the chief executive officer or other administrative contact identified as the representative of the organization at the time of agreeing to participate in the study and able to facilitate documentation identification and access. A preliminary list of documentation sought is provided in Textbox 1. Additional documents may be identified by key informants at each health professional association, namely, those engaged in phase 2 (interviews). The final compiled list will be reviewed with the administrative lead (ie, chief executive officer) before concluding data collection to ensure that all relevant documents have been captured.

Documents will be uploaded to a case study database managed using Excel. The database will be organized by data type, medium, and year and potentially subcategorized in other ways depending on the nature and volume of collected documentation [21].

Textbox 1. Preliminary list of documentation and content sought in document analysis.

Documentation

- Strategic plans (previous, current, and upcoming)

- Terms of reference for relevant task forces and working groups

- Meeting minutes from strategic and artificial intelligence (AI)–related meetings (board meetings, task group meetings)

- Professional competency profiles maintained or administered by PA (including Royal College of Physicians and Surgeons in Canada documentation maintained by Canadian Association of Radiologists and Canadian Association of Radiation Oncology)

- Annual reports (starting at the implementation of previous Strategic Plan [2012])

- Programmatic review (continuing professional development offerings, summits, scientific meeting themes etc)

- Position statements, white papers, and other formal communications regarding AI published or released by PA

- Original posts by health professional associations Twitter accounts since 2012

Content Sought in Document Review

- Level, nature, or timing of attention given to AI within the PA

- Degree to which AI is considered in entry-to-practice training or other educational offerings

- Formal collaborations with (or even reference to or consideration of) other PAs or stakeholders

- Volume, nature, or scope of formal opportunities presented to membership or to external stakeholders, by the PA, to communicate a position on AI

Phase 2: Interviews

Between 3 and 5 purposively selected, semistructured interviews will be conducted for each case [21]. An interview guide will be used, with potential probes included to help direct the conversation, as necessary (refer to Multimedia Appendix 1 for the interview question script). Interviews, scheduled for 60 minutes, will be conducted by telephone or in-person by the lead investigator (CG) and audio-recorded for subsequent transcription. Written consent will be sought and reconfirmed verbally at the time of the interview. Notes will be taken as needed. The interview guide will be piloted with at least one leader in another health professional association not participating in this study.

The full interview guide, minus probes, will be provided via email to each participant at least 48 hours before the interview. The board president of each health professional association will be the first to be invited to participate in an interview for each case, followed by the administrative lead. Both of these interviews will involve discussion of other relevant interviews that might follow (ie, snowball sampling), including the head of any relevant technology-focused task force or committee and any identified key subject matter consultants within the health professional association structure or formally engaged on behalf of the health professional association.

Interview audio-recordings, transcripts, and notes will be maintained and indexed in the case study database.

Phase 3: Observation

A third phase of data collection will involve the observation of strategically identified health professional association meetings that relate to its strategic stance on AI and approach to addressing it with members and stakeholders. The spectrum of the health professional association board, board subcommittee, health professional association committee, and task force meetings will be reviewed, and the following will be identified within a 12-month period:

1. Organizational strategic meetings (board meetings and strategic planning retreats)
2. Focused technology or AI-related strategic or operational meetings (task force meetings and AI-themed conference planning meeting).

A 12-month window will represent a normal cycle of standing meetings for a health professional association, even those held only annually. Committee chairs and/or administrative assistants will be approached to facilitate access to relevant meetings.

Observation will consist of the lead investigator (CG) attending the scheduled meeting by teleconference as a nonparticipant observer, with the written consent and permission of the meeting chair and the awareness of all participating members. Field notes will be taken to maintain a record of any discussions, debates, and/or action items relating to AI and will be maintained in the case study database.

Reflexivity

Throughout the process of study design, data collection, and analysis, the lead investigator (CG) will engage in reflective exercises, including journaling, to consider how her position within the case contexts might impact the data and how the data are interpreted. As a professional member and past board member of one of the health professional associations (CAMRT), any increased identification with this group or acknowledgment of traditional professional hierarchies, culture, or knowledge base in any study interviews might warrant consideration with the broader study investigators and in reporting on the study.

Data Analysis

A hybrid inductive and deductive model that uses NPT as an analytical framework will be used to analyze the data. This avoids the need to force data that do not naturally fit with theory and will be of value in informing the macro applications of the NPT model. The inductive element will be managed using NVivo software (QSR International) and will involve an inductively coded and concept-driven thematic analysis [38-40], first within cases and subsequently between cases using a constant comparison method. Concurrent to the thematic analysis, a network map will be prepared that reflects how information and knowledge flows between identified stakeholders, using arrows and notes to suggest linkages and the nature of interactions (preliminary network map included as Figure 2) [41]. Document data can then be integrated within those themes to further inform the themes and demonstrate where action aligns with perception or intent. Documentation that provides overarching perspectives or positions on AI, such as position papers or strategic plans, will be prioritized to provide initial scaffolding to guide analysis. Observation data will primarily serve to highlight the nature of any internal information sharing, consensus building, debate, or other collaborative work that might have contributed to the actions or direction taken by the health professional association as it relates to AI.

Using the framework of the domains and individual constructs of the NPT, fit will be assessed between the theoretical framework and the data as interpreted through pattern matching [21]. Emergent themes will be mapped deductively against the domains of NPT to assess fit and identify areas of discordance. The network map will be annotated according to knowledge acquisition or sharing efforts relating to different constructs. Areas where coherence or cognitive participation efforts align or differ between cases will be considered, and the fit and tensions between study themes and NPT will also be considered.

The study will be reported using the guidelines suggested for organizational case studies, as defined by Rodgers et al [42] and accessible via the EQUATOR (Enhancing the Quality and Transparency of Health Research) Network (Multimedia Appendix 2).

Results

As of January 2021, we have conducted the majority of the interviews expected to be required for this study (n=17), with representation across the 4 health professional associations. Of these 17 interviews, 15 (88%) have been transcribed. The document review is underway, with 2 of the 4 health professional association websites fully reviewed for related documents, and 2 health professional associations have contributed additional documents. Twitter feeds for all health professional associations have also been reviewed, dating back to the inception of each health professional association's account, but will require updating for future content within the data collection period. Observation opportunities have been challenged by competing priorities during the COVID-19 pandemic and may require revisiting.

Discussion

The research will be reported as a linear analytic process, prioritizing the cross-case analysis to highlight both the contributions to theory and strategies and their rationale for those health professional associations approaching change themselves [21]. The research findings will be presented according to the NPT constructs in the coherence and cognitive participation domains, considering the internal and collaborative efforts of a health professional association to define its perspective and role. The collective action and reflexive monitoring domains of NPT will be the primary lens for considerations of future practice models, competencies, and potential changes to the scopes of practice and education for which health professional associations are responsible.

Following this presentation of data, implications for NPT will be presented, suggesting where this study might reinforce its constructs more strongly at the often-neglected macro level of the health professional association or introduce tensions that might require further attention. Implications for practice, limitations of the case study approach, and potential for future work will be highlighted.

It is anticipated that health professional associations will be at varying stages of considering AI and its impact on the profession and its practice, which may challenge direct comparison of approach or alignment with NPT. Factors impacting this may include the perceived impact on the profession; the perceived contribution of professional expertise to informing AI in the relevant practice environment; and other organizational and professional characteristics such as size, administrative structure, and competing professional priorities. The use of mechanisms such as task forces, position papers, and continuing education forums (webinars and conference panels) will likely vary depending on the expertise within the health professional association and the priority assigned to AI. Although academic work done within the professions might be of value in building a sense of the future impact of AI, and engagement with industry may also contribute to perspectives, it is anticipated that formal collaborative consideration between health professional associations of how the practice environment might change will be minimal and superficial. Thus, the collaborative constructs within NPT may be impacted by a passive lack of engagement between professions, as opposed to an active resistance to considering the scopes of practice. Given the nebulous nature of AI strategies (in terms of their origin and application) and the current state of implementation in practice, it is likely that insight into later stages of NPT, related to action and monitoring, will be based primarily on anticipated future action rather than reflection on past or ongoing events.

The fields of radiation medicine and medical imaging are 2 areas—related in many ways but unique in others—that rely heavily on technology and are already exploring the potential of AI. A picture of how such professions envision themselves as stakeholders in approaching disruptive technology can help to direct future initiatives to prepare for evolution and can potentially inform relevant policy and practice change as AI strategies are introduced. How different stakeholders, including

other health professional associations whose professions interact in the same practice environment, are engaged in informing sensemaking and preparation for change can also suggest what influences contribute to professional perspectives at the front lines of health care practice and, ultimately, to the nature of AI-enabled practice.

As AI is increasingly positioned to significantly disrupt many aspects of the society, it is incumbent on those whose roles may be replaced, displaced, augmented, or otherwise impacted by AI to be proactive in preparing for associated change. Using NPT as a framework to consider the behavioral aspects of change at the level of the profession, rather than the individual, is important in establishing professional readiness and adaptation for AI.

Authors' Contributions

CG conceived the study with conceptual, methodological, and theoretical inputs from BH, DW, and MD. CG drafted the manuscript. All authors have read, edited, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview script.
[DOCX File , 26 KB - resprot_v10i5e27340_app1.docx]

Multimedia Appendix 2
Consensus standards for the reporting of organizational case studies.
[DOCX File , 292 KB - resprot_v10i5e27340_app2.docx]

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Abbreviations

AI: artificial intelligence
CAMRT: Canadian Association of Medical Radiation Technologists
CAR: Canadian Association of Radiologists
CARO: Canadian Association of Radiation Oncology
COMP: Canadian Organization of Medical Physicists
EQUATOR: Enhancing the Quality and Transparency of Health Research
NPT: normalization process theory

Protocol

Psychometric Evaluation and Workflow Integration Study of a Tablet-Based Tool to Detect Mild Cognitive Impairment in Older Adults: Protocol for a Mixed Methods Study

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Abstract

Background: With the rapid aging of the global population, experts anticipate a surge in the prevalence of mild cognitive impairment (MCI) and dementia worldwide. It is argued that developing more sensitive, easy to administer, and valid MCI screening tools for use in primary care settings may initiate timely clinical and personal care planning and treatment, enabling early access to programs and services. Including functional competence measures in screening tests makes them more ecologically valid and may help to identify cognitive deficits at an earlier stage.

Objective: We aim to conduct a preliminary evaluative study comparing the sensitivity, specificity, and reliability of the BrainFx Screen (referred to as SCREEN hereafter), a novel digital tool designed to assess functional competence and detect early signs of cognitive impairment, with the Quick Mild Cognitive Impairment, a validated and highly sensitive tool that detects MCI in the older adult population. We will also investigate the perceived usefulness and integration of the SCREEN into primary care practice to identify demonstrable impacts on clinical workflow and health care providers' (HCP) perceptions of its success as a screening tool. Patients' perceptions of completing the SCREEN and its impact on their quality of life will also be explored.

Methods: This study has a concurrent, mixed methods, prospective, and quasi-experimental design. Participants will be recruited from 5 primary care family health teams (FHTs; defined by multidisciplinary practice and capitated funding) across southwestern Ontario, Canada. Participants will include HCPs, patients, care partners, and FHT administrative executives. Patients 55 years and older with no history of diagnoses for MCI, dementia, or Alzheimer disease rostered in one of the FHTs participating in the study will be eligible to participate. Their care partners will help triangulate the qualitative data collected from patients. Participating FHTs will identify an occupational therapist from their site to participate in the study; this HCP will both administer the research protocol and participate in semistructured in-depth interviews and questionnaires. Principal component analysis will be conducted on the SCREEN data to understand the test components better. Tests comparing sensitivity, specificity, and test-retest reliability will assess the validity of SCREEN as a screening tool for MCI.

Results: This paper describes the study protocol and its activities to date. Data collection was halted early because of COVID-19 restrictions on research activity, and data analysis is currently in progress.

Conclusions: At the end of the project, we anticipate having an initial comparative evaluation of the SCREEN as a tool for early detection of MCI in primary care older adult patient populations. Resource constraints on this research study limit our ability to conduct a randomized controlled trial; however, the results will assist developers of the SCREEN in determining whether rigorous controlled testing is warranted.

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Introduction

Background

More than cancer and cardiovascular disease, declining cognition threatens an individual's ability to age in place by living independently at home alone or with family caregivers [1]. According to the Centers for Disease Control and Prevention, 1 in 8 adults (more than 12%) 60 years and older reported experiencing memory loss and confusion, and 35% of that group reported functional difficulties with tasks related to mobility and self-care that reflect basic activities of daily living (ADL) [2]. With the rapid aging of the global population [3], experts anticipate a worldwide surge in the prevalence of mild cognitive impairment (MCI) and dementia, and with it challenges to health care systems, the labor force, and the lives of those assuming caregiver roles [4,5]. Studies have reported a gap between expected and observed prevalence of MCI, partly because of concerns that screening might lead to loss of independence, such as the right to drive [6-8], and reliance on case finding as the primary method of evaluation [9]. However, earlier identification of individuals with MCI, where true dementia is not present but the reduced cognitive function is detectable, may provide health care professionals with an important window for intervention [10]. It is argued that developing more sensitive, easy to administer, and valid screening tools for MCI may initiate more timely clinical and personal planning and treatment, enabling early access to programs and services supporting aging in place rather than institutionalization [11].

MCI Disorder

MCI is a neurocognitive disorder that describes a state between normal cognition and dementia is characterized by a slight but noticeable deterioration of cognitive abilities that predominantly impairs memory and thinking skills [12,13]. MCI is clinically distinct from dementia, which is marked by progressive and irreversible neurodegenerative changes leading to loss of functional competence and independence (ie, loss of both simple ADL and instrumental activities of daily living [IADL]—everyday activities that require intact higher-order complex cognitive skills to complete, including managing finances, preparing meals, driving, or administering medications) [14-17]. In general, individuals diagnosed with MCI retain both basic ADL and complex IADL; however, a subset of individuals present with observable and measurable impairments in some IADL related to cognitive decline that impacts their day-to-day function [18,19]. The notion of functional impairment in MCI remains controversial because it does not present consistently among those diagnosed with MCI [10,14,18], and there are no standard measurement tools or a clear operational definition of what functional impairment is within clinical and research communities [14,19,20]. To account for this ambiguity, contemporary diagnostic criteria acknowledge that individuals may present with minor impairments in functional IADL, whereas ADL are spared [14]. Depending on how cases are

classified, the tests used, and the characteristics of the population, up to 42% of the world's population older than 60 years have MCI, with an increasing prevalence among people older than 65 years [21]. In a general practice study, approximately 23% of MCI patients developed dementia within 3 years and three-quarters were stable or improved within the same period [22]. Although interactions between prescribed medications, alcohol or drug abuse, metabolic disorders, infections, and/or traumas may cause dementia-like symptoms not directly caused by dementia [23], only 0.6% of real dementias are reversible (0.29% partially and 0.31% fully [24]).

Early detection and diagnosis of declining cognition may not only allow health care providers (HCPs) to intervene in cases where the condition is reversible but also provide early and optimal management, tailored treatment planning, and timely access to education and psychosocial support to those at high risk for dementia [25-27]. However, screening for MCI in asymptomatic people 65 years and older is not recommended in Canada [9,28,29] or the United States [30,31]; case finding is the favored approach [32]. This is partly because of the limited availability of randomized controlled trials and clinical heterogeneity, which impedes our ability to generalize what may be small-to-moderate short-term improvements in cognitive function through early interventions such as exercise and cognitive training or pharmacotherapies [33-39]. Furthermore, dementia is a syndrome, not a disease [6,40,41], where the indicators are continuous and affected by a wide variety of factors such as education and genetics, and thus require expert clinical judgment for a definitive diagnosis [40,42]. Diagnosis is difficult because HCPs rely in part on patients to self-identify or informants to report symptoms of cognitive dysfunction [25]. In Canada, it is estimated that up to 10% of community populations aged 65 years and older have some form of undetected cognitive impairment [35], and in the United States, up to 76% of those who have experienced confusion or memory loss do not consult a health care professional [43]. Consequently, only 20%-50% of people with dementia are recognized and documented in primary care [44]. Asymptomatic screening is not recommended [45], and some believe that MCI screening may generally cause anxiety (although there is no supporting evidence [46]) and possible overtreatment of patients who are unlikely to develop dementia [22].

Not screening for cognitive changes may be a lost opportunity to identify individuals before they are biomarker-positive [47] and to improve the quality of their lives and those of their caregivers through timely planning. Patients report favoring access to information about their cognitive health as it provides a sense of personal agency on treatment planning and opportunities for shared decision making [48]. Other studies indicate that early diagnosis of cognitive impairment may lead to early interventions that improve patients' and caregivers' ability to cope [23]. Furthermore, a diagnosis of MCI or dementia is typically required to access support that may improve the lives of older adults with MCI and their caregivers. Hence, the ability to reliably diagnose early cognitive decline,

including measures of functional impairment, may be an important gateway to receiving timely state-funded interventions. To this end, an attending clinician must not only confirm the presence of symptomatic changes in cognition but also that cognitive impairment is not caused by factors other than neurological decline, and then recommend appropriate interventions [10,37].

Screening for MCI in Primary Care Settings

Typically, screening for MCI is triggered when someone raises concerns about their memory and thinking abilities with their general practitioner [49]. At present, no single screening or diagnostic tool has been identified as the gold standard for confirming the presence of MCI, largely because of its clinical heterogeneity [37,49-51]. Instead, MCI is clinically inferred based on a combination of the patients' clinical history, subjective memory complaints, and objective measures of cognitive impairment on any number of validated cognitive tests along with complementary functional assessments, neuroimaging, and serology [13]. If MCI is suspected, additional neuropsychological assessments are necessary to rule out alternative explanations, including but not limited to dementia or delirium, and to aid in the process of determining the specific subtype of MCI present [10,25]. In Canada, patients receive a diagnosis of MCI, on average, 5 months after their initial memory complaint [49]. Confirming a diagnosis can also be a lengthy process, as general practitioners refer patients to geriatricians and neurologists for additional performance tests and often a combination of neuroimaging (computed tomography and magnetic resonance imaging) and bloodwork (thyroid and B12) [49].

The *current usual practice* screening tools for MCI used by clinicians in Canada are the Mini-Mental State Exam (MMSE) [52] and the Montreal Cognitive Assessment 8.1 (MoCA 8.1) [53]. Both are paper and pencil screens, administered in 10-15 minutes, scored out of 30, and validated as MCI screening tools across diverse clinical samples [53,54]. Universally, the MMSE is most often used, consisting of 20 items that measure orientation, immediate and delayed recall, attention and calculation, visual-spatial skills, verbal fluency, and writing. The MoCA 8.1, which was developed to improve the MMSE's ability to detect early signs of MCI, places greater emphasis on evaluating executive function and language, memory, visual-spatial skills, abstraction, attention, concentration, and orientation across 30 items [53,55]. However, it was primarily designed to detect moderate-to-severe cognitive impairments and not the milder dysfunction characteristic of MCI, and it does not allow HCPs to determine the specific subtype of MCI [25,53,56,57]. The MMSE also lacks the high sensitivity needed to reliably detect subtle cognitive changes associated with MCI [57-61]. Moreover, the clinical efficacy of both screens for tracking changes in cognition over time is limited, as they are sensitive to practice effects with repeated administration [62].

Although not commonly used in Canada, the *Quick Mild Cognitive Impairment (Qmci)* screen is a more sensitive, specific, and validated screening tool for detecting MCI in older adults than other tests (including both the MMSE and MoCA

8.1) [59,63-67], and it is freely available for clinical or research use; instructional booklets and tear-off sheets are purchased separately. The Qmci evaluates 6 cognitive domains: orientation (10 points), registration (5 points), clock drawing (15 points), delayed recall (20 points), verbal fluency (20 points), and logical memory (30 points) [68]. The relative contribution of points from each subtest to the overall score complement findings that delayed recall, verbal fluency, and logical memory are the most accurate subtests for differentiating MCI from normal cognition [69]. It is not known whether Qmci is subject to practice effects. However, there is evidence to suggest that tests of logical memory are sensitive to practice effects among participants with both normal cognition and MCI [70]. Therefore, as the logical memory subtest on the Qmci makes the largest relative contribution to the overall screen score, it is possible that the Qmci may be subject to some degree of practice effects.

Designing cognitive screens with greater ecological validity (ie, designing questions that are reflective of relevant life activities [71]) to detect early changes in executive function may also improve early MCI detection [72], suggesting that including measures of functional competence on cognitive screens may be beneficial. Although measures of functional competence have been used to supplement cognitive or other neurological evaluations in the hope of improving diagnosis and outcomes, its value is not fully understood [71], particularly concerning how to assess functional competence in early-stage MCI [20]. Finally, aside from the need for MCI screening tools in the primary care setting to be psychometrically tested, they should also be easy to administer, accessible, efficient, and affordable [64,73].

BrainFx is a for-profit firm that creates proprietary neurological assessment software designed to identify signs of brain function impairment. The BrainFx Screen (SCREEN) is an unvalidated, digitally administered, 15-minute, 7-question screen designed to identify early signs of MCI by assessing functional deficits that may not be readily identified by existing screens (refer to Table 1 for a summary of SCREEN activities), such as the MoCA 8.1, MMSE, and Qmci. The SCREEN is a short version of the BrainFx 360 Performance Assessment, which is designed to assess cognitive, physical, and psychosocial areas of neurofunction [74]. This is a 90-minute test administered digitally to test 26 cognitive domains across 49 tasks that are timed, scored, and subsequently compared with the Living Brain Bank (LBB), a database of all BrainFx 360 and SCREEN tests collected to date. The 7 activities used on the SCREEN were taken directly from the BrainFx 360 on the basis of clustering and regression analyses of LBB records in 2016 (N=188) [75]. The reliability of the BrainFx 360 has been validated in healthy adults (mean 22.9 years of age, SD 2.4 years), and results suggest that the overall test-retest reliability of the tool is high (intraclass correlation coefficient=0.85 [74]); however, only 2 of the 7 cognitive domains selected for the SCREEN have reliability coefficients above 0.70 (visual-spatial and problem-solving abilities). To date, BrainFx 360 has been used in clinical settings to assess neurofunction among youth and in a variety of other rehabilitation settings.

Table 1. Summary of SCREEN activities.

Activity	Description	Time to complete (s)
Abstract reasoning	Twenty everyday items are displayed, and the patient touches the item on the screen and slides each item, one at a time, into 1 of the 5 categories into which they best belong, while being timed.	90
Constructive ability	Two rounds of a photo being displayed and breaking into 9 pieces. The patient touches the pieces and slides each piece into a grid to reassemble, while being timed.	90
Prioritizing	Five everyday activities or tasks are presented, and the patient is told what time of day it is (eg, 7 PM), and the patient touches the screen and slides each item to prioritize the order in which the activities or tasks should be completed.	60
Numerical problem solving	Ten math questions requiring 1- or 2-digit answers are presented for a patient response using a numerical pad (+, −, ×, and /) while being timed.	90
Visual-spatial ability	Two rounds of patient selecting (by touch) into which shape a word fits best, while being timed.	30
Divided attention	The patient watches a pot on the stove about to boil over (denoted by boiling water and red signal) and must touch the pot and move it to the sink to dump out the water, while also touching the screen to match as many objects as they can within the kitchen scene.	90
Route finding	A map is presented with roads and multiple locations. In the first round, the patient traces the most efficient route between 2 locations, while being timed. In the second round, the patient traces the most efficient route between 2 locations but is instructed to make 2 stops on the way, while being timed.	90

The objectives of this research study are as follows:

1. To evaluate the psychometric properties of the SCREEN to assess functional competence and detect early signs of cognitive impairment when administered in a primary care setting to adults 55 years and older
2. To investigate the integration and use of the SCREEN in primary care practice and any demonstrable impact on clinical workflow and planning
3. To explore HCPs', patients', and care partners' perspectives on adopting and using the SCREEN.

Methods

Study Design and Setting

The study has a concurrent, mixed method, prospective, and quasi-experimental design. Participants will be recruited from 5 primary care family health teams (FHTs; defined by multidisciplinary practice and capitated funding) across southwestern Ontario, Canada. FHTs that employ a registered occupational therapist as staff will be eligible to participate in the study, and participating FHTs will receive a nominal compensatory payment for their time spent collecting data for the study by administering the SCREEN, Qmci, and Geriatric Anxiety Scale (GAS) [76] screening tools; training; and communicating with the research team. A multipronged recruitment approach will be used in this study. All participants (HCPs, patients, care partners, and FHT administrative executives) will be assigned a study identification number that allows for category but not individual classification.

Study Participants and Recruitment

Patients

Patients 55 years and older with no history of diagnoses for MCI, dementia, or Alzheimer disease rostered in one of the FHTs participating in the study will be eligible to participate. The age of eligibility includes those 55 years and older to capture an at-risk population with no current diagnosis of MCI who might be healthy or experiencing early symptoms of MCI that may or may not be apparent to the participant. Prospective participants may also be excluded based on a diagnosis with any of the following conditions that are associated with MCI or dementia-like symptoms (Textbox 1): major depression requiring hospitalization, psychiatric disorders (ie, schizophrenia and bipolar disorder), psychopathologies, epilepsy, substance use disorders, and sleep apnea (without the use of a continuous positive airway pressure machine [77]). These criteria have been used in similar MCI screen validation studies to exclude participants that may confound the interpretation of the screen results because they are experiencing symptoms of MCI or dementia, not because of the true presence of MCI but rather unrelated conditions. The use of tablets to complete the SCREEN requires that participants are able to read and think in English, discern color, and read 12-point font on the tablet and that they have adequate hearing and vision to interact with the administering HCP and adequate hand and arm function to manipulate and hold the tablet. Exclusion criteria, therefore, include colorblindness or any disability that impairs a person's ability to hold and interact digitally with the tablet. Finally, patients must be available to participate in a minimum of 2 screenings, performed 3 months apart, and an entry and exit interview to participate in the study. Prospective participants will be required to be rostered with 1 of the 5 participating FHTs to ensure that HCPs can access their electronic medical record (EMR) and that there was a physician responsible for follow-up referral. Before study enrollment, HCPs will be required to screen their EMR to verify participant eligibility and, on an ongoing basis, update their EMR with the results of the MCI screens.

Textbox 1. Eligibility criteria for patient participants.

Inclusion criteria

- Aged 55 years and older

- Able to read and think in English

- Rostered with a participating family health team

- Depression:

- Symptom-free for the last 6 months

- No history of hospitalization

- Use of low-dose antidepressants

- Brain injury

- Stroke

- Taking prescription neuroleptics, hypnotics, or antiepileptics medications:

- Whether taken for pain and not epilepsy

- Low dose

- Stable (no dose or medication change for the last 6 months)

Exclusion criteria

- Less than grade 6 education

- Diagnosis of mild cognitive impairment, dementia, or Alzheimer disease

- Color blindness

- Paralysis (in hands)

- Physical handicap that may influence test results

- Epilepsy

- Severe vision or hearing impairments (hearing aids are acceptable)

- Psychopathology

- Major depression (that has required hospitalization)

- Diagnosed psychiatric disorders

- Diagnosis of condition with susceptibility to causing dementia or cognitive deficits

- Alcohol or drug dependence

- Sleep apnea (with no use of continuous positive airway pressure machine)

Recruitment of patients will include diverse media strategies in both clinical and community settings. At the FHT, recruitment posters and 1-page summaries of the study will be posted in waiting rooms; exam rooms; and the FHT's website and social media platforms, including Facebook and Twitter, where available. Recruitment posters will also be posted at public establishments local to the FHT (eg, YMCAs, libraries, pharmacies, and recreational sites). Interested participants may self-identify to the FHT HCP via telephone or to the research team via a dedicated study email or phone number. The research team will host information sessions at each participating FHT to provide clinical and nonclinical health team staff with information about the study to support seamless recruitment and onboarding of new patient participants.

Care Partners

Once enrolled in the study, the HCP will ask patients to identify a care partner (defined as someone who might be concerned about and or interested in the patient's well-being), if there is one, who might be interested in participating in qualitative interviews and questionnaires as part of the study. This is not a requirement of the study; qualitative data collected from care partners will help triangulate the data collected from the patient participants. There are no eligibility requirements for care partners other than having a self-identified relationship with the patient and being able to read and write in English.

Health Care Providers

Participating FHTs will identify 1 occupational therapist from their site to participate in the study. This HCP will both administer the research protocol and participate in semistructured, in-depth interviews and questionnaires. To be eligible to participate, the HCP must have the approval to participate from the appropriate corporate agent (the Executive Director of the FHT). Before starting data collection, the HCP must complete a web-based training program—consisting of 3

self-directed training modules—and learn how to administer the Qmci to become a certified BrainFx administrator. The research team will conduct in-person training to cover the research protocol and administrative processes.

FHT Administrative Executives

Where available, the managing director or equivalent at the FHT will be interviewed to better understand contextual factors such as workload, funding, and patient population characteristics that may impact the results.

Ethics and Consent

The study protocol has been reviewed and has received ethics clearance from the Wilfrid Laurier University Research Ethics Committee (ORE# 5820) and has been reviewed and approved through each FHT's research approval process. All participants (HCPs, patients, care partners, and administrative executives) will read and sign an information and informed consent package before participating in the study. We will conform to recommendations for acquiring informed consent and conducting qualitative interviews with persons with dementia when recruiting patients who may be affected by a neurocognitive disease [78-80]. During oral informed consent, we will use plain language, repeat information that is not understood, and ask the participant to explain their understanding of what the study entails. During the interview, we will use plain language; be prepared to repeat questions as needed and ask questions in a different way, possibly using the participant's own words to rephrase; allow participants ample time to respond to each question; and provide cues to what they were saying if they lose train of thought. If they dwell overly long on a particular question, we will validate the meaningfulness of their response, gently redirect them to the next question, monitor for fatigue, and allow them to continue the interview at another time. Participants will be informed that they can choose not to answer the questions asked to them. All participants will be assigned a study participation number, and when reporting, identifying information will be removed from verbatim quotes if approval has been provided for use.

Measures

The 10-Item GAS

The GAS-10 is a 10-item self-report screen for anxiety in older adults [81] developed for rapid screening of anxiety in clinical settings (GAS-10 is the short form of the full 30-item GAS [82]). The screen includes 10 questions taken directly from the GAS that measure somatic (ie, *I felt tired*), cognitive (ie, *I could not control my worry*), and affective (ie, *I was irritable*) symptoms of anxiety that reflect those used to diagnose anxiety disorder in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision. Participants will be asked to use a 4-point Likert scale (0=not at all, 1=sometimes, 2=most of the time, and 3=all of the time) to rate how often they have experienced each symptom during the past week, including the day of the visit [82]. The GAS-10 has a maximum score of 30, with higher scores indicating higher levels of anxiety [81-83]. Although 3 subscales have been identified, the GAS-10 is reported to be a unidimensional scale of general anxiety [84,85]. Validation of the GAS-10 suggests that it is

optimal for assessing average to moderate levels of anxiety in older adults, its total and subscale scores are highly and positively correlated with the GAS, and it possesses high internal consistency [81]. This tool will assess the patients' anxiety level as it relates to screening for cognitive impairment at the time of the assessment and any change in subjective ratings after completion of the MCI screen and between visits. Although the association between neuropsychological assessment anxiety and test performance is unclear [86,87], the inclusion of a pre-post anxiety measure will allow researchers to control this issue and to explore any variation in performance or anxiety related to tablet technology. Given the exclusion criteria for this study (Table 1), we do not anticipate high levels of nontest anxiety.

The SCREEN

The SCREEN (version 0.5, beta) will be administered on a tablet (ASUS ZENPAD 10.1" WXGA IPS Display, 1920×1200), powered by a quad-core 1.5 GHz, 64-bit MediaTek MTK 8163A processor with 2 GB RAM and 16 GB storage. The tablet comes with a tablet stand for optional use and a dedicated stylus that is recommended for completion of a subset of activities. At the start of the study, HCPs will be provided with identical tablets, preloaded with the BrainFx app software for use for the duration of the study.

Using a standardized administration protocol developed by BrainFx, the HCP will instruct the patient to use either their finger or the provided stylus to complete the SCREEN. Following acclimation to the tablet, the patient will be required to complete a short survey to collect demographic information (eg, age, the highest level of education attained) and any history of pre-existing conditions and questions about the patients' state of well-being at the time of testing (eg, self-reported concerns about their thinking, mood, hours slept, and pain). The questionnaire will be immediately followed by 7 activities that are modeled after everyday real-world actions purported to evaluate functional competence related to a variety of cognitive domains, including abstract reasoning, divided attention, or visual-spatial abilities (refer to Table 1 for a detailed description of the activities). Tasks will be timed and digitally scored, and an activity score for each activity will be generated based on a combination of the patients' accuracy (ie, number of correct responses) and processing speed (ie, speed of completion). The relative weight that accuracy and processing speed contribute to the activity score is proprietary to BrainFx and is the same for each of the 7 activities.

At the end of each SCREEN, the patient will be prompted by the app to consent to contribute their scores to a database of results maintained by BrainFx, known as the LBB. The mean and SD of the LBB database will be updated in response to the addition of every new SCREEN. The patient's performance on the SCREEN will be evaluated by comparing their results with the global reference population (ie, all available SCREEN results in the LBB at the time of testing). Filters are available that allow the HCP to compare the patients' results with subcohorts using factors such as gender, education, age, or primary diagnosis. Individual SCREEN results reports display the individual's activity score, the LBB mean (for the global reference

population unless the operator selects subcohorts based on selected filters), and whether the activity score falls within 1 SD of the LBB mean. If the patient's activity score falls 1 or more SD below the global mean, it is classified as an *area of challenge*. The HCP is instructed to use their clinical judgment to interpret the results by applying any number and combination of filters relevant to the patient. For the purpose of this study, the patient's performance will be compared against all results in the LBB completed by people aged 55 years and older at the time of testing.

The Qmci Screen

The Qmci is a sensitive and specific screen that differentiates normal cognition from MCI [63,65]. The HCP will administer the screen by asking the patient questions and recording their response on a dedicated Qmci assessment form provided by the screen developers. The patient will be required to answer 1 question via paper and pencil. The Qmci takes approximately 5 minutes to complete, is scored by hand out of 100 points, and evaluates 6 cognitive domains: orientation (10 points), registration (5 points), clock drawing (15 points), delayed recall (20 points), verbal fluency (20 points), and logical memory (30 points) [68]. The overall cut-off score to distinguish normal cognition from MCI on the Qmci is ≤67, from cognitive impairment (MCI or dementia) ≤62, and dementia alone ≤54 [88]. Although not as broadly adopted as the MoCA 8.1 in Canada, its psychometric properties, administration time, and availability for use suggest that Qmci is the optimal market assessment tool for MCI screening in FHT settings.

The Task Technology Fit Questionnaire

In the Task Technology Fit (TTF) model, technologies refer to any tool(s) used to complete a task, and the task itself is any number of actions performed to complete the task. Operationally, *fit* is defined as the extent to which the technology assists in completing these necessary actions [89,90]. Building on the TTF, Goodhue and Thompson [89] introduced the technology-to-performance chain model to acknowledge, first, that measuring perceived net benefit to use requires that the technology be used to complete the task for which it is designed and, second, to factor in the impact of related social norms or personal attributes on the evaluation of the technology and its utilization. Evidence suggests that the better the fit between the characteristics of the technology and task, the better the impact technology has on performance, which positively influences its utilization [89,90]. TTF models have been used to evaluate technologies across diverse sectors, including health care [91] and education [92], via questionnaires that tap constructs related to the technology, such as perceived satisfaction, reliability, the

accuracy of the task, task completion time, ease of use or training, risk, and trust [90]. Across studies, individuals are asked to rate their perspective on the technology using a 7-point Likert scale ranging from entirely disagree (1) to entirely agree (7), and questions are tailored to address the technology and research questions at hand [89].

In this study, the questions on the TTF questionnaire are designed to measure how the SCREEN system (ie, assessment, handouts, hardware, and technical support) influences the HCP's ability to screen for MCI. Tasks include, but are not limited to, collecting data from the patient that are relevant to MCI and using those data to make necessary decisions (eg, the decision to refer patients for further neuropsychiatric evaluation or provide particular intervention recommendations for MCI [37,51]). HCPs will be asked to rate the SCREEN system according to how the technology impacts the characteristics of their tasks and their ability to perform them, user satisfaction, utilization, and their perceived net benefits to using the tool [89,92].

Zarit Burden Interview

Care partners will complete the 12-item Zarit Burden Interview (ZBI) [93] as part of their entry or exit interviews scheduled within 1 month of their partner's first and last screening appointments. The ZBI is the most common self-report screen used to measure subjective burden reported by people caring for those with chronic health conditions who require, over time, increasing support for managing their day-to-day ADL and IADL (ie, cognitive impairment) [94,95]. The 12-item ZBI [94] is one of several validated short-form screens used for brevity in place of the full 22-item ZBI [96]. The 12-item ZBI is reported to measure 2 dimensions of burden (personal and role strain) [94], is highly and positively correlated with scores on the full 22-item ZBI, presents with high internal consistency, and is a reliable tool for measuring changes in caregiver burden over time [93,94,97,98]. Participants are asked to use a 5-point Likert scale (0=never, 1=rarely, 2=sometimes, 3=quite frequently, and 4=nearly always) to rate how they feel in response to items such as, "Do you feel strained when you are around your relative?" and "Do you feel that your health has suffered because of your involvement with your relative?" [94]. Participants can score a maximum of 48 points, and scores equal to or higher than 17 are classified as a high or severe burden [94,99]. Data from this questionnaire will be used to triangulate the test results, impact, and patient self-reported anxiety.

Data Collection and Procedures

The summary of the study protocol for the data collection process is included for reference in Figure 1.

Figure 1. Study protocol data collection process. AOC: area of concern; ED: executive director; EMR: electronic medical record; ET: evaluation team; FHT: family health team; GAS: Geriatric Anxiety Scale; HCP: health care provider; IC: informed consent; MCI: mild cognitive impairment; PEF: patient encounter form; Qmci: Quick Mild Cognitive Impairment Screen.
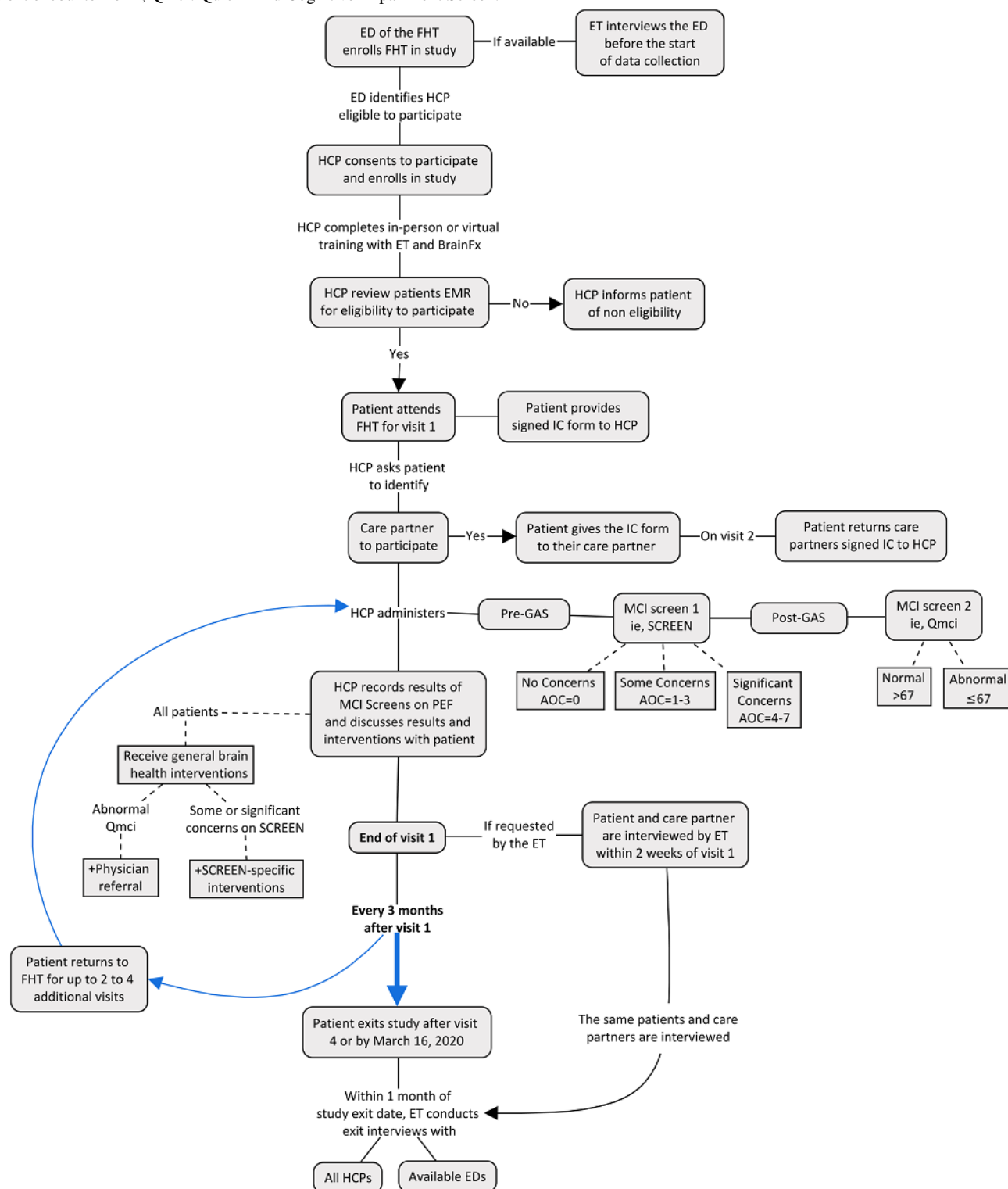
Psychometric Evaluation

Data collection for the psychometric evaluation study will take place in person at the patients' respective FHT. Standard operating procedures have been developed for the research study, which will be followed by the research team and HCP staff trained in the study protocol and administration of all data collection tools. A member of the research team will observe at least one in-clinic HCP data collection visit to confirm adherence to the protocol and training procedures.

To assess the reliability and perceived usefulness of the SCREEN, depending upon when a patient enters the study, they may repeat the screening protocol up to 4 times. Each visit is structured around the administration of 2 MCI screens; the GAS-10 [81,82]; and a series of questions that measure the patient's use of technology, change in their general health and

well-being, or any interactions with the health care system related to MCI that occur in the 3 months since their last appointment. The HCP will be required to complete a patient encounter form at each appointment, which includes a summary of the patient's MCI screen results, any referrals, and their responses to these questions.

The patients' first appointment will take approximately 45-60 minutes (to account for onboarding), and all subsequent appointments (up to 4 screening test pairs, depending on the patient's study entry date) will take approximately 45 minutes to complete. Rolling recruitment of patients will occur over an 18-month period and will end when a minimum of 2 and a maximum of 4 SCREEN-Qmci test pairs are completed every 12 weeks. In older adults, with no diagnosis of MCI or dementia, measures of cognitive abilities, including verbal fluency, attention, and intelligence [100], and measures of executive functioning [101] remain stable for anywhere from 4 to 8 weeks or from 1 to 5 years between test and retest (controlling for the effects of normal aging [100]). To date, there are no clear guidelines on the optimal time between tests [102,103]. Streiner [104] recommends longer periods to avoid recall bias. Furthermore, greater practice effects are experienced with shorter test-retest intervals [62]. The 3-month interval was therefore selected to minimize such confounds and is justified given the stability of the constructs under investigation. A randomization process will determine the order of screen administration at each visit. The Qmci will be administered using a pen and paper. HCPs will be provided with identical tablets, preloaded with the SCREEN app software.

The GAS-10 will be administered just before and immediately after the administration of the first MCI screen (eg, the SCREEN) and immediately followed by the administration of the second MCI screen (eg, the Qmci) at each appointment. After completing the 2 MCI screens, the HCP will manually calculate the results for the Qmci, log in to the BrainFx portal to retrieve the SCREEN report, and review both sets of results with the patient. The Qmci cut-off score for distinguishing MCI from normal cognition is ≤67/100 [88]. The SCREEN does not include scoring guidelines for a cut-off score but identifies whether a score on any of the 7 tasks is an *area of challenge*.

To determine the sensitivity and specificity of the SCREEN in comparison with the Qmci, the results of both screens will be classified in binary format as healthy or not healthy, where *healthy* denotes SCREEN=no areas of challenge in all 7

activities and Qmci≥67 and *unhealthy* denotes SCREEN=1 or more areas of challenge and Qmci≤67. Consistent with consensus guidelines for screening for cognitive impairment [37,49,50], the research protocol will also require HCPs to refer patients to their primary care physician for further evaluation if they receive an abnormal score on the Qmci or significant concerns on the SCREEN. The SCREEN does not have a standardized cut-off score that can be used to classify results as abnormal. Therefore, in consultation with and on the recommendation of the SCREEN developers, for the purpose of the research protocol, a set of cut-off scores was developed to classify SCREEN results as normal (zero areas of challenge), some concerns (≤3 areas of challenge), or significant concerns (≥4 areas of challenge). All HCPs in this study will be OTs who are trained to assess individuals' abilities or disabilities through the use of standardized testing and functional observation. As a result, the study protocol includes a condition that referral decisions for physician oversight or further testing are the purview of the HCP and their clinical judgment. This became the proxy gold standard for a positive screen in this research study.

Following the review of the results at each appointment, the HCP will provide patients with a handout that summarizes recommendations for supporting cognitive health. If the SCREEN identifies any *areas of challenge,* the patient will also receive a handout developed by BrainFx containing tailored strategies to strengthen brain health and manage deficits in those areas.

Perceived Usefulness and Clinical Workflow Integration

Semistructured, in-depth interviews will be conducted, in person or by telephone, with HCPs, executive directors, and a subset of patients and their care partners throughout the study. Interviews will be audio-recorded and transcribed verbatim. Data collection will be guided by the *TTF theoretical model*, which emphasizes the importance of the fit between technologies and users' tasks in creating a perceived net benefit to use [89,105] (Figure 2). Standard questions to capture demographics, attitudes, and experiences data will also be asked at the beginning of each interview.

HCPs will complete a TTF questionnaire (Textbox 2) as part of their entry or exit interviews with a member of the research team, which will be scheduled 3 months after they enter the study and again within 1 month after they exit the study.

Figure 2. Task Technology Fit model.
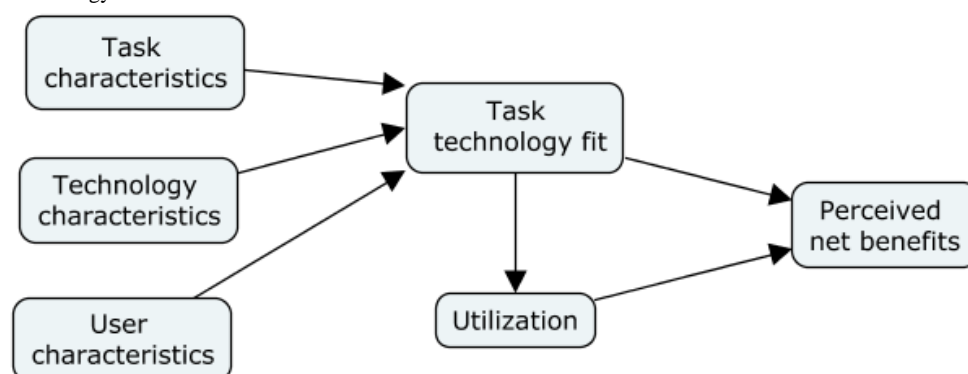
Textbox 2. Task Technology Fit questionnaire. Task Technology Fit questionnaire response options are as follows: 1=entirely disagree, 2=mostly disagree, 3=somewhat disagree, 4=neither agree nor disagree, 5=somewhat agree, 6=mostly agree, and 7=entirely agree.

Technology enhancements

- The quality of the information I receive from the BrainFx SCREEN and Report is enough to meet my clinical needs.

- The BrainFx SCREEN and Report provides me with the right data I need to better support patients and caregivers.

- I am able to quickly locate the results of the BrainFx SCREEN on a patient chart.

- The data elements on the BrainFx Report are easy to understand or it is easy to find out.

User satisfaction

- Technical support to access the BrainFx app was always available when I needed it.

- I can count on the BrainFx system to be "up and running" and available when I need it.

- The tablets were subject to unexpected or inconvenient downtimes, which makes it harder for me to do my work.

- The BrainFx app was subject to frequent problems.

- It was easy to learn the BrainFx system.

Task characteristics

- I frequently deal with nonroutine cases of older adults with cognitive issues.

- I frequently deal with routine cases of older adults with cognitive issues.

- Identifying cases of mild cognitive impairment usually takes more than one clinician.

- Sharing relevant and timely information with other care providers is important when diagnosing cognitive impairment.

Utilization

- The BrainFx system was convenient and easy to use.

- There was not enough training for me on how to administer the BrainFx SCREEN using the tablets.

- There was not enough training for me on how to use the BrainFx Report.

- BrainFx support took an interest in helping me to solve problems to avoid disruptions to my workflow.

Perceived net benefits to use

- My overall effectiveness in detecting mild cognitive impairment increased when I used the BrainFx SCREEN and Report.

- My ability to target interventions for individual patients and their needs was improved with the BrainFx SCREEN and Report.

- My ability to target interventions for individual caregivers and their needs was improved with the BrainFx SCREEN and Report.

- I waste less time interpreting test results and preparing interventions with BrainFx SCREEN and Report.

- I spend less time writing up charting cognitive test results with the BrainFx SCREEN and Report.

- The BrainFx SCREEN and Report provide better information to patients and their caregivers.

- The quality of my follow-up recommendations to patients and caregivers has improved with my use of the BrainFx SCREEN and Report.

Statistical and Analytic Plan

Descriptive and inferential analyses will be conducted using SPSS Statistics for Windows, Version 26 (IBM Corp). Qualitative analysis will be conducted using NVivo version 12 (QSR International Pty Ltd).

Descriptive and Inferential Analysis

Descriptive data will be described using frequencies and percentiles and compared using the chi-square test or Fisher exact test as necessary. Continuous data will be analyzed for central tendency and variability; categorical data will be presented as proportions. Normality will be tested using the Shapiro-Wilk test, and nonparametric tests will be performed using the Mann-Whitney U test. Statistical significance will be considered at a *P* value of .05, with 90% CI provided where appropriate. We powered the exploratory analysis to validate the SCREEN using an estimated effect size of 12%, with the understanding that Canadian prevalence rates are not available [29], and determined that we needed at least 114 participants. For test-retest reliability, using 90% power and a 5% type 1 error rate, we will require a minimum of 58 test results.

MCI test outcome data will be coded into a binary format of *healthy* or *unhealthy* (where unhealthy indicates a positive result on the test, ie, 1 or more *areas of challenge* on the SCREEN results, or a score of ≤67/100 on the Qmci) to account for the difference in categorical versus continuous outcome variables. For this reason, sensitivity and specificity will be determined using cross-tabulation rather than using the area under the curve

using receiver operating characteristic curves. A principal component analysis with varimax rotation will be used to better understand the derivation of components' contribution to screen test outcomes and to explore the differences between a conventional MCI screen (Qmci) and one that is intended to be more ecologically valid by assessing functional impairment (SCREEN). Binary logistic regression will examine the effects of variables such as age, education, self-reported comfort with technology, anxiety before and after completing the MCI tests, and sleep levels on the results. The internal consistency of both the SCREEN and Qmci will be assessed using Cronbach α. Test-retest reliability, the ability of a measurement instrument to reproduce results on 2 or more occasions (ceteris paribus), will be assessed using an intraclass correlation coefficient [106].

Qualitative Analysis

To assess the perceived usefulness of adopting the tablet-based SCREEN in a real-world clinical setting, HCPs, FHT executive administrators, patients, and their care partners will be interviewed upon entry and exit from the study. All HCPs and patients will be interviewed twice, and care partners will be sampled until saturation [107]. Interviews will be audio-recorded and transcribed verbatim. Two members of the research team will analyze the transcripts using NVivo and a mix of inductive and deductive analytic techniques to identify themes and insights. Deductive insights will be drawn from sensitization to the TTF model to explore the impact of the software and hardware platform on the process of screening for MCI in a primary care setting.

Results

This funded research was launched in January 2019, and enrollment was conducted in February 2020. Quantitative data collection was interrupted in March 2020 because of the COVID-19 pandemic and the shutting down of all nonessential in-person clinical visits; qualitative data collection was concluded in July 2020. The results are forthcoming.

Discussion

Summary

This research study will assess the psychometric properties and perceived usefulness of a novel tablet-based tool to screen for MCI in adults 55 years and older in the primary care setting. A fundamental objective of a screening test is to reduce morbidity or mortality in an at-risk population through early detection and treatment [108], with the anticipated benefit outweighing potential harm [58]. However, a rapid screening test for MCI might also assist time-strapped, cost-sensitive primary care physicians [109] in determining whether referral for a definitive battery of more expensive tests is warranted [110]. Screening for MCI and dementia is usually conducted through informant reports of functional impairment [14] and patient performance outcomes on tests with high sensitivity [58], with no consensus or guidelines on which are most effective [63,109-112]. Many of these tests are inappropriate for use in primary care because they are time-consuming to administer, insufficiently sensitive, ecologically invalid, or impacted by education or cultural bias. In addition, advances in the field of neurobiology are changing our understanding of MCI and testing, for instance, tests of object discrimination and familiarity may be better suited to detect mild dysfunction from MCI as they rely on intact functioning of the perirhinal cortex of the hippocampus, which is impaired in the earliest stages of MCI [25]. Identifying affordable, psychometrically tested screening tests for MCI that conform to clinical workflows and are easy to consistently administer and complete may initiate treatment if appropriate, help normalize and destigmatize cognitive testing for older adults, expedite referral, allow early access to programs and services that can support aging in place or delay institutionalization, and improve the psychosocial well-being of patients and their care partners by increasing access to information and resources that aid with future planning and decision making [113].

Limitations

The assessment of this novel screen for MCI will be executed within the constraints of limited financial resources. As such, it will methodologically constrain our use of a presumed *gold standard* test for MCI with the participant population, which in many studies involves a neuropsychological evaluation. In fact, the presence or absence of a gold standard MCI screening test is the subject of some debate [112]. The absence of an established gold standard has resulted in the use of proxies, such as a validated, sensitive test for the same condition [107,108].

Although patient participation in the study is voluntary (there is no randomization or selection for particular traits), we anticipate that those with concerns about their cognition and those more comfortable with the use of tablet technology may be more likely to self-select into the study. Our data collection and statistical analysis will account for both the potentialities.

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Abbreviations

ADL: activities of daily living
EMR: electronic medical record
FHT: family health team
GAS: Geriatric Anxiety Scale
HCP: health care provider
IADL: instrumental activities of daily living
LBB: Living Brain Bank
MCI: mild cognitive impairment
MMSE: Mini-Mental State Exam

MoCA 8.1: Montreal Cognitive Assessment 8.1
Qmci: Quick Mild Cognitive Impairment
TTF: Task Technology Fit
ZBI: Zarit Burden Interview

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<u>Protocol</u>

Personalized Analytics and a Wearable Biosensor Platform for Early Detection of COVID-19 Decompensation (DeCODe): Protocol for the Development of the COVID-19 Decompensation Index

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Abstract

Background: During the COVID-19 pandemic, novel digital health technologies have the potential to improve our understanding of SARS-CoV-2 and COVID-19, improve care delivery, and produce better health outcomes. The National Institutes of Health called on digital health leaders to contribute to a high-quality data repository that will support researchers to make discoveries that are otherwise not possible with small, limited data sets.

Objective: To this end, we seek to develop a COVID-19 digital biomarker for early detection of physiological exacerbation or decompensation. We propose the development and validation of a COVID-19 decompensation Index (CDI) in a 2-phase study that builds on existing wearable biosensor-derived analytics generated by physIQ's end-to-end cloud platform for continuous physiological monitoring with wearable biosensors. This effort serves to achieve two primary objectives: (1) to collect adequate data to help develop the CDI and (2) to collect rich deidentified clinical data correlating with outcomes and symptoms related to COVID-19 progression. Our secondary objectives include evaluation of the feasibility and usability of pinpointIQ, a digital platform through which data are gathered, analyzed, and displayed.

Methods: This is a prospective, nonrandomized, open-label, 2-phase study. Phase I will involve data collection for the digital data hub of the National Institutes of Health as well as data to support the preliminary development of the CDI. Phase II will involve data collection for the hub and contribute to continued refinement and validation of the CDI. While this study will focus on the development of a CDI, the digital platform will also be evaluated for feasibility and usability while clinicians deliver care to continuously monitored patients enrolled in the study.

Results: Our target CDI will be a binary classifier trained to distinguish participants with and those without decompensation. The primary performance metric for CDI will be the area under the receiver operating characteristic curve with a minimum performance criterion of ≥ 0.75 ($\alpha = .05$; power $[1 - \beta] = 0.80$). Furthermore, we will determine the sex or gender and race or ethnicity of the participants, which would account for differences in the CDI performance, as well as the lead time—time to predict decompensation—and its relationship with the ultimate disease severity based on the World Health Organization COVID-19 ordinal scale.

Conclusions: Using machine learning techniques on a large data set of patients with COVID-19 could provide valuable insights into the pathophysiology of COVID-19 and a digital biomarker for COVID-19 decompensation. Through this study, we intend to develop a tool that can uniquely reflect physiological data of a diverse population and contribute to high-quality data that will help researchers better understand COVID-19.

Trial Registration: ClinicalTrials.gov NCT04575532; https://www.clinicaltrials.gov/ct2/show/NCT04575532

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Introduction

During the COVID-19 pandemic, novel digital health technologies have the potential to improve our understanding of SARS-CoV-2, improve health care delivery, and produce better outcomes. In addition to digital technologies, there is a need for a high-quality COVID-19 research data repository that allows academic, public health, and translational researchers to make discoveries that might otherwise not be possible from data silos. Given the breadth and specialization of digital technologies that will be utilized during the COVID-19 pandemic, it is likely that there are research questions that can only be answered by integrating and analyzing data generated through multiple technologies. The National Institute of Biomedical Imaging and Bioengineering and National Cancer Institute of the National Institutes of Health (NIH) issued a request for proposals and awarded contracts [1] for the development of digital health solutions to address the COVID-19 pandemic by enabling new studies on these technologies. Data generated by digital health technologies could potentially advance the public health response, facilitating underlying approaches that might improve planning for future epidemics and pandemics.

In response to the request for proposals, physIQ collaborated with the NIH to deploy a method of collecting an immense volume of physiological data on patients with COVID-19 and develop a COVID-19 biomarker or index that could facilitate early detection of decompensation. In other words, the goal is to identify when an individual starts transitioning from being SARS-CoV-2–positive to having acute COVID-19. Such early identification would allow clinicians to intervene early and possibly prevent acute clinical events including hospitalization. This study aims to develop and validate a COVID-19 decompensation index (CDI) in a 2-phase manner and build on existing wearable biosensor–derived analytics generated by physIQ's end-to-end cloud platform for continuous physiological monitoring with wearable biosensors.

The development of a CDI is believed to be key to managing and mitigating the severity of a patient's illness, especially COVID-19 where little is known about the progression of the disease. Using an easy-to-wear biosensor (patch), which provides streamed physiological data for analysis by state-of-the-art analytics, could yield significant advantages during in-person, telephonic, or survey-based patient assessments, which are the basis for remote patient monitoring solutions today [2]. Most remote patient monitoring solutions have yet to harness recent advancements in biosensor devices and machine learning technologies and thus do not allow for intelligent continuous patient monitoring. Furthermore, any data that are collected from patients are typically funneled through already overburdened clinical providers. This may be the reason why most remote monitoring solutions for COVID-19 are limited to temperature and pulse oximetry spot checks. In fact, there is no evidence that such spot checks are an efficacious strategy; rather, they are used only because they are familiar variables to health care professionals and are sampled at a manageable frequency [3]. This is especially true considering that previous studies suggest that <50% of hospitalized patients with COVID-19 have a fever upon admission [4,5], and studies on other viral infections have reported that a significant increase in heart rate can be detected approximately 2 days prior to a fever [6]. Early warning signs of COVID-19 are probably being missed because of focusing only on limited spot checks rather than early changes in the overall cardiopulmonary status, as reflected by the combination of variables such as respiration rate, heart rate, heart rate variability, physical activity levels, and other metrics that can be derived from biosensor data [7].

The equitable deployment of digital health solutions is equally as important as developing a digital biomarker or index. Populations that are underserved in health care also have less access to advanced digital health solutions owing to various social determinants of health [8]. The development of a tool that can uniquely address a barrier to care, reflect the physiological data of diverse populations, and contribute to a trove of high-quality data that would help researchers in better understanding COVID-19 in all populations is of paramount importance [9].

While this study is exploratory, we expect parameters including respiratory rate and heart rate to be predictive of decompensation, considering that they may vary in the degree to which they are predictive for any individual. We hypothesize that a combination of many biosensor-derived physiological features will best capture the heterogenous characteristics of decompensation across the population. Our digital biomarker development approach will harness the availability of a large number of continuous physiological features that characterize all aspects of physical function and can reflect decompensation (heart rate, respiratory rate, heart rate variability, activity, sleep, arrhythmias, skin temperature, and others).

Our study responds to the need for novel technologies to manage the COVID-19 pandemic and aims to develop and validate a CDI by using physIQ's pinpointIQ platform in a diverse population of adults with COVID-19. This effort will achieve two primary objectives: (1) to collect adequate data to enable the development of the CDI and (2) to collect rich deidentified clinical data correlating with outcomes and symptoms related to COVID-19 progression. Our secondary objectives include the evaluation of feasibility and usability of pinpointIQ, the digital platform on which data are gathered, analyzed, and displayed.

Methods

Study Design

This is a prospective, nonrandomized, open-label, 2-phase study. This study design was chosen because the primary focus of the study, in addition to data collection for the NIH digital data hub, is the development of a digital biomarker for early detection of COVID-19 decompensation. This initially requires the determination of the model structure and predictor variables (phase I), followed by validation and performance assessments of the CDI (phase II). Phase I will involve data collection for the NIH digital data hub as well as the collection of data to support the preliminary development of the CDI. In doing so, "decompensation events" will be identified during the 28-day participant monitoring period. A "decompensation event" is defined as a hospitalization event due to COVID-19 during which a patient achieves a maximum World Health Organization ordinal scale for clinical improvement (WHO OSCI) score of ≥3 [10]. A WHO OSCI score of 3 corresponds to "hospitalization, no oxygen therapy" [10]. Health records will be obtained from the care facility on any clinical event for final adjudication as a COVID-19 decompensation event. Once adjudicated, the event is added to the superset of decompensation events to drive the development of a CDI model. Once a critical number of decompensation events occur in the study sample, the event and nonevent data will be combined and partitioned into training and testing subsets to enable the development of the initial CDI.

Phase II will also involve data collection for the NIH digital data hub and will contribute to continued refinement and validation of the CDI as additional decompensation events are recorded. While this study will focus on the development of a CDI, the pinpointIQ platform will also be evaluated for feasibility and usability while clinicians deliver care to continuously monitored patients enrolled in the study.

Participants

Participants will be recruited from two pools of patients at University of Illinois Health: (1) patients who test positive for COVID-19 in an outpatient setting and (2) patients who were hospitalized with a diagnosis of COVID-19 and subsequently discharged for home convalescence. This will yield a convenience sample. To be enrolled in the study, patients must meet the following eligibility criteria: they must be aged ≥18 years, test positive for COVID-19, be able to respond manually to a survey on a provided smartphone, and complete the informed consent process. Participants would then be enrolled in the pinpointIQ could platform and trained on the system.

Data Collection

Upon enrollment, the participant will be shipped a kit that includes biosensor patches, a locked Android smartphone, a charger, pulse oximeter, and a quick start Guide. Participants are remotely enrolled through electronic consent through a trial management platform. The research associate trains the participant on patch application and the phone app survey response. The patient wears the patch for 28 consecutive days at 5-7–day intervals (corresponding to the battery life of the biosensor). Participants can independently change their chest-worn patch. Once the participant has the biosensor applied and is enrolled on the platform, physiological data will immediately begin streaming to the cloud for analytic (applied machine learning) purposes and for clinical monitoring (Figure 1). The pinpointIQ platform is a secure, scalable, device-agnostic, cloud-based software product. The platform performs continuous collection and processing of high-fidelity physiological data.

Figure 1. Study protocol. ED: emergency department, HR: heart rate, RR: respiratory rate, ECG: electrocardiography, UIH: University of Illinois Health. ©2021 physIQ.
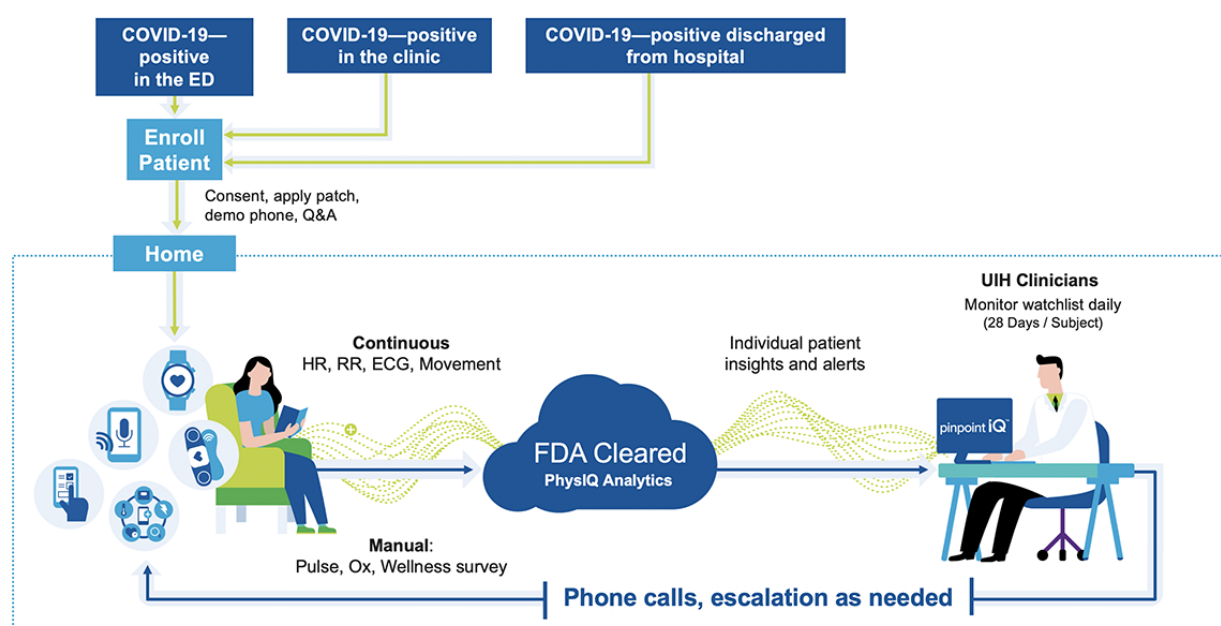
This continuous patient remote monitoring platform, pinpointIQ, includes Food and Drug Administration (FDA)–cleared analytics that can provide early indications of nonspecific patient deterioration, facilitate data collection, and notify general clinician-defined events. This closed-loop monitoring platform is comprised of the following components, each of which will be used in this study.

The biosensor is VitalPatch (VitalConnect Inc), which is an FDA-approved wireless, battery-operated wearable biosensor worn on the torso to acquire 125-Hz electrocardiography signals, 0.25-Hz impedance, 50-Hz triaxial accelerometric measurements, and 0.25-Hz skin temperature data. A library of analytics on the pinpointIQ platform is applied to the raw sensor data to derive a collection of vital signs and physiological features, including heart rate, respiration rate, heart rate variability, activity level, sleep-wake determination, and atrial fibrillation detection.

A smartphone is provided to the participant. PhysIQ developed an Android smartphone app that serves as the gateway for real-time data acquisition via bluetooth from the biosensor. It also provides an interface for patient-reported outcome surveys

(Figure 2). The app runs on a dedicated locked smartphone that is configured only to run the app, which has been validated to reliably interface and collect data from the biosensor. The app interacts with the biosensors in real time and uploads data directly to the pinpointIQ platform over a secure cellular network connection. The app also provides patients with indications for proper data collection and escalating alerts of potential data lost, including connectivity issues, low battery, low memory, and unanswered surveys.

To ensure consistent gathering of patient-reported outcome data and spot check peripheral oxygen saturation measurements, digital surveys with health status questions and a reminder to spot check pulse oximetry measurements will be provided to the participants twice daily. Responses will be manually entered into the smartphone app by the participant and be presented as a response in the portal watchlist to the health care professional. While not the primary physiological indicators in this study, these data will enrich and annotate the continuous physiological data collected from the biosensor. These responses are automatically uploaded to pinpointIQ and are immediately flagged as complete on the participant's dashboard (Figure 3).

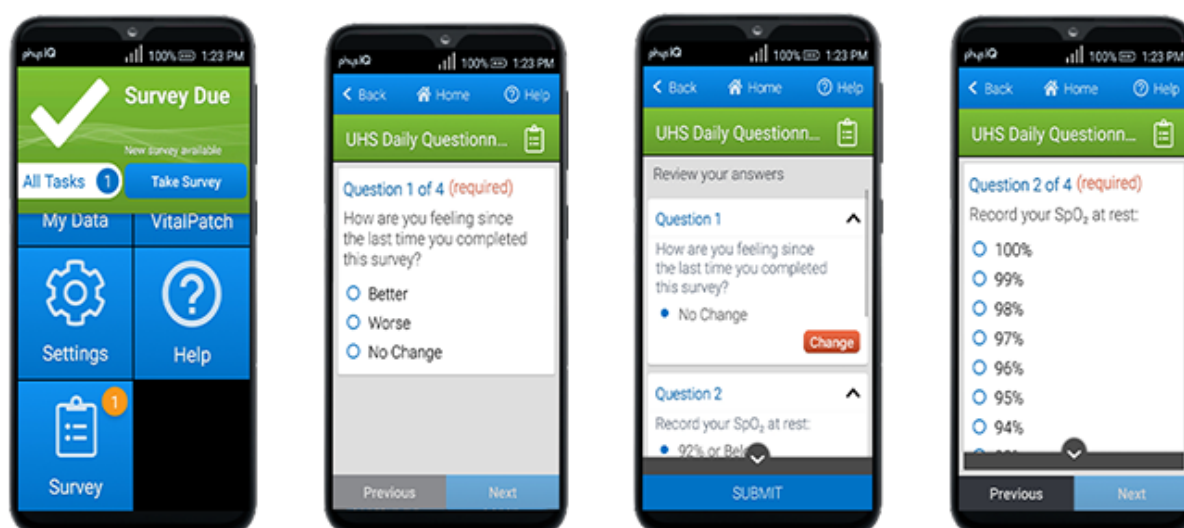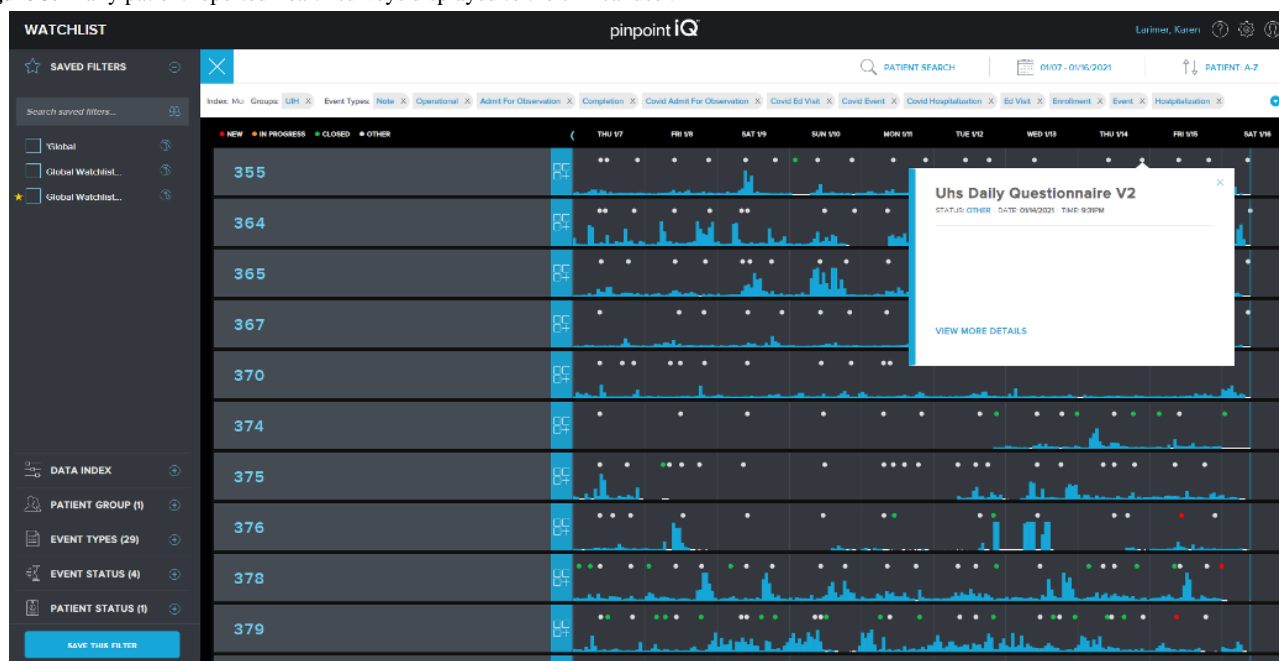**Figure 2.** Smartphone app and an example survey.

Figure 3. Daily patient reported-health surveys displayed to the clinical user.

Two FDA-approved analytics modules will also be used. The first one is the physIQ heart rate and respiration module, which is a cloud-computing, all-software product that utilizes biosensor input data to derive the heart rate, heart rate variability, and respiration rate. In addition, the heart rate monitoring module includes an atrial fibrillation detection output. The second one is the physIQ personalized physiology analytics module, which is a cloud-computing, all-software product that utilizes biosensor data to compute a multivariate change index (MCI). The MCI is a multiparameter algorithm that establishes a personalized physiological baseline for each patient and monitors for subtle changes from that baseline over time. While the MCI is cleared for subtle physiological changes, we aim to develop an index specifically for the early detection of COVID-19 decompensation (ie, the CDI).

Additionally, the clinical portal component of pinpointIQ provides tools for viewing biosensor data and analytics results, which also drives clinician-defined events as well as application programming interface and software development kit tools for accessing and exporting data and analytics data for research and analysis. The clinical portal and alerts rules engine provide a web-based user interface portal to manage and monitor a specific study or patient population.

Clinicians can review a list of all patients using the watchlist view of the secure, web-based portal. As illustrated in Figure 4, the watchlist can be filtered by groups, patient status, and specific patient identifiers. In addition, the portal allows the assignment of devices (phones and sensors), scheduling of surveys, and modification of patient profiles. Starting from the watchlist, clinicians can access specific patient records on the patient dashboard to examine data in detail, including patient responses to surveys, point measurement values, data records on physiological features, raw biosensor data (eg, electrocardiograms and accelerometry measurements), markers, and clinician notes.

"Clinician-defined events" are also displayed as markers on the watchlist for quick review by clinical users. Clinician-defined events are driven by rules that target specific changes in one or more physiological features over time. Defining rules that would trigger events for participants allows clinical users to identify patients who need attention. PinpointIQ's rules engine ingests physiological feature data and applies clinician-defined thresholds and persistence criteria to trigger "events" that warrant clinician review or response. Clinician-defined events include, for example, tachycardia, tachypnea, bradycardia, and atrial fibrillation.

Individual patient dashboards would clinicians to view continuously acquired biosensor data from each participant, as well as the occurrence of autogenerated clinician-defined events and clinical notes entered by clinicians over time (Figure 5).

For the target study population, physIQ will apply the full suite of clinical and operational rules currently in production. These rules have a basic template with validated thresholds but can be modified on the basis of clinician needs. The combination of rule outputs, physiological features, and clinical data (spot check measurements, survey results, and demographics) will drive the development of CDI.

Figure 4. Watchlist and patient dashboard.

Figure 5. Clinical user's patient dashboard.

Study Outcomes

Our target CDI will be based on a machine learning model to distinguish between participants with and those without a decompensation event. The primary performance metric for CDI will be the area under the receiver operating characteristic curve (AUC) with a minimum AUC performance criterion of ≥0.75 (α=.05; power [1–β]=0.80).

The secondary outcomes will include the evaluation of the feasibility of using the pinpointIQ solution as a tool for health care professionals to determine when a participant undergoes decompensation (acute COVID-19) and manage the study populations on the basis of physIQ-validated rule sets and analytics. Feasibility and usability are the primary constructs that will guide the secondary outcomes. Feasibility will be assessed by evaluating the degree to which the monitoring program could be delivered to the participants, assessment of the intended effects of the program on participant outcomes, and the degree to which this program could be utilized with existing means [11].

Overall clinical usability will be determined on the basis of a combination of survey compliance, biosensor data quality, and data availability metrics, as well as load on clinical resources. Survey compliance will be measured by determining the proportion of completed electronic patient-reported outcome surveys and pulse oximetry measurements, obtained using the smartphone app, in accordance with the study protocol. Biosensor data quality assessments will be made using a signal quality index, which would indicate when the acquired biosensor data are usable for deriving accurate physiological features. Data availability will be measured using a biosensor-based "pseudo-compliance" approach that will determine the percentage of data collected relative to the theoretical amount of data that could be acquired. This will be carried out using the first and last timestamps extracted from acquired biosensor data to define the theoretical amount of data that could be collected continuously and then calculating the ratio of the actual amount of data collected to the theoretical amount.

Furthermore, we shall obtain data on participant sex or gender and race or ethnicity, which could impact differences in the CDI performance, as well as the lead time—time to predict physiologic decompensation due to COVID-19—and its relationship with the ultimate disease severity in accordance with the WHO OSCI [10].

Sample Size and Statistical Analysis

In phase I, we will combine physIQ's existing personalized analytics, biosensor-derived analytics or aggregates, and clinical rules as input variables to derive the CDI. Cases of COVID-19 decompensation recorded in phase I will inform the final set of input variables to derive the CDI. Our goal is to develop a CDI that relies solely on biosensor-derived physiological features. However, readily available fixed variables such as gender, age, and weight will be examined to determine their impact on the performance of the CDI model. The full set of biosensor-derived features that we intend to analyze as input variables to CDI will be derived from continuous 1-minute measurements of heart rate, respiratory rate, heart rate

variability, sleep-wake determination, step rates, activity levels, and other outputs of physIQ's personalized physiology analytics algorithm.

On conclusion of phase I, all COVID-19 decompensation events (positive) and nonevents (negative) will be combined to assess the performance of the CDI model using the AUC as the performance metric.

A "clinical event" is defined as an escalation of care from home-based remote monitoring to a higher level of care. For example, if during monitoring, a nurse identifies that a patient is becoming sicker and needs acute care, this event would be considered a clinical event. Health records will be gathered from the care facility on any clinical event for final adjudication as a COVID-19 clinical event. The adjudication consists of review of the electronic health record of the participant experiencing the clinical event and 2 emergency department physicians independently deciding on whether the event was a "COVID-19 clinical event" or "non–COVID-19 clinical event." If the physicians' opinions do not agree, the case is further reviewed by a third emergency department physician, and a final decision is made. A COVID-19 clinical event is a "decompensation event" if a patient achieves a maximum WHO OSCI score of ≥3 while hospitalized.

We assume an event rate of 7.5% on the basis of recent readmission rates for patients with COVID-19. To achieve a target CDI performance of an AUC of ≥0.75 with α=.05 and power (1–β)=0.80, we require a sample of 12 positive cases and 148 negative cases for a total sample size of 160 cases. Our proposed sample size of 400 cases in phase I will enable us to partition the data into development (for training) and holdout (for performance assessment) subsets. We intend to use 60:40 partitioning for training and testing, which amounts to 18 positive cases and 222 negative cases for training the CDI model, and 12 positive cases and 148 negative cases for assessing the performance of the CDI model. We anticipate utilizing more events than the minimum required number for performance measures such that heterogeneous COVID-19 decompensation characteristics, as reflected in biosensor-derived analytics, are captured.

The CDI developed in phase I will be deployed in phase II. Based on the performance in phase I, a decision threshold will be defined for use during the deployment of the CDI model in phase II. On conclusion of phase II, the final COVID-19 decompensation event detection performance of the CDI will be validated through secondary AUC analysis. Additionally, exploratory analysis of both lead time to COVID-19 decompensation-related hospitalizations and predictivity of the severity of the decompensation event will be performed. Event time will be defined as the admission date, and severity measures will be based on the WHO OSCI score.

Overall CDI decompensation event detection performance and lead time statistics will be examined across the study population as well as within subgroups. The data will be stratified on the basis of sex or gender and race or ethnicity into subgroups to determine if there are differences in performance and detection lead times among the groups. A sample size of 1200 cases has been chosen for phase II to ensure the capture of data across a

diverse population on the basis of known COVID-19–related hospitalization rates for the sex or gender and race or ethnicity subgroups of interest.

Data Management

After enrollment, each participant will be assigned a unique identifier to be used in the platform. Data will be entered by research staff and clinicians, and data accuracy will be verified by the principal investigator. Data quality control measures include queries to identify missing data and the assessment of outliers and discrepancies. All databases are password-protected. Other cloud security measures include role-based access controls for all URL routes in the application programming interface and within the platform. Patients who withdraw from the study will no longer be monitored and will resume usual care.

Owing to the minimal-risk nature of the study, no external observational study monitoring board is required. The principal investigator and research staff will monitor data internally and meet weekly to ensure the study is proceeding as intended.

Results

Data collection for phase I has been concluded in end-January 2021 with a preliminary analysis. COVID-19 events captured in phase I will inform the final set of input variables to determine the CDI. Data collection for phase II will begin immediately with anticipated completion in September 2021. We anticipate the completion of study data analysis in November 2021. The final results will be disseminated through scientific publications. Data will also become available through the NIH.

The study protocol has been approved by the institutional review board of the University of Illinois, Chicago. Written informed consent will be obtained from all study participants by the study staff responsible for recruitment. Important protocol modifications will be conveyed to investigators, the institutional review board, regulators, journals, and trial participants. Participant identities will not be disclosed for any public purpose or for publication, nor will they be disseminated outside of the study team.

Discussion

There is a need for a high-quality COVID-19 research data set that can allow academic, public health, and translational researchers to make discoveries that might otherwise not be possible with small, limited data sets. Novel digital technologies should be leveraged to provide scalable, robust platforms to gather and analyze data quickly and efficiently. The use of machine learning techniques on a large data set of patients with COVID-19 can provide valuable insights into the pathophysiology of COVID-19 and reveal a digital biomarker for physiological decompensation due to COVID-19.

In addition, the highly communicable nature of COVID-19 demands a remote patient monitoring solution. While remote patient monitoring programs for various diseases have been evaluated over the years and have yielded mixed results, the literature demonstrates the lack of consistent positive findings, which leave potential users uncertain of their value [12]. Nonetheless, the demands emerging due to COVID-19 on our health system's resources require a solution that is scalable and designed to protect clinicians. Through this study, we plan to develop a tool that can uniquely reflect the physiological data of a diverse population and contribute to a trove of high-quality data that will help researchers better understand COVID-19.

Authors' Contributions

All authors participated in conceiving, writing, and reviewing the protocol and the manuscript.

Conflicts of Interest

KL, SW, and JS own shares in and are engaged in paid employment at physIQ.

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Abbreviations

AUC: area under the receiver operating characteristic curve
CDI: COVID-19 decompensation index
FDA: Food and Drug Administration
MCI: multivariate change index
NIH: National Institutes of Health
WHO OSCI: World Health Organization ordinal scale for clinical improvement

Protocol

Determining the Efficacy of Electronic Cognitive Behavioral Therapy for Generalized Anxiety Disorder Compared to Pharmaceutical Interventions: Protocol for a Quasi-Experimental Study

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Abstract

Background: Generalized anxiety disorder (GAD) is an extremely prevalent and debilitating mental health disorder. Currently, the gold standard treatment for GAD is cognitive behavioral therapy (CBT) and/or pharmacotherapy. The most common medications used to treat GAD are selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors. While CBT is the gold standard treatment for GAD, it is costly, time-consuming, and often inaccessible. Fortunately, the electronic delivery of CBT (e-CBT) has emerged as a promising solution to address these barriers. e-CBT has shown to offer comparable results to in-person CBT while improving accessibility for patients and time efficiency for clinicians.

Objective: This study aims to investigate the treatment efficacy of e-CBT compared to and in conjunction with pharmacotherapy for GAD.

Methods: This study will use a quasi-experimental design to allow patients the freedom to choose which treatment modality they would like to receive. Participants with a diagnosis of GAD will be enrolled in 1 of 3 possible treatment arms: (1) e-CBT, (2) medication, or (3) a combination of e-CBT and medication. The e-CBT program will include a 12-week psychotherapy program delivered through the Online Psychotherapy Tool—a secure, cloud-based, digital mental health platform. The treatment efficacy of e-CBT will be compared with that of medication alone and medication in combination with e-CBT.

Results: The study received ethics approval in April 2019 and participant recruitment began in June 2019. Participant recruitment has been conducted through social media advertisements, physical advertisements, and physician referrals. To date, 146 participants (e-CBT: n=53; medication: n=49; combination: n=44) have been recruited. Data collection is expected to conclude by June 2021, and data analysis is expected to be completed by October 2021. Linear regression (for continuous outcomes) and binomial regression (for categorical outcomes) analysis will be conducted using interpretive qualitative methods.

Conclusions: If either the efficacy of e-CBT is shown to be comparable to that of medication or the effects of both treatments are augmented when used in tandem, these findings could have major implications on the mental health care system. e-CBT is a more accessible and affordable treatment that could increase mental health care capacity 4-fold if proven viable.

Trial Registration: ClinicalTrials.gov NCT04478526; https://clinicaltrials.gov/ct2/show/NCT04478526

International Registered Report Identifier (IRRID): DERR1-10.2196/27772

Introduction

Background and Rationale

An estimated 450 million people suffer from mental and/or behavioral disorders globally [1]. Anxiety disorders are some of the most common mental health disorders, with generalized anxiety disorder (GAD) being the second most prevalent among them [2,3]. As the demand for treatment increases, mental health care systems globally are becoming overwhelmed and in need of accessible, cost-effective, time-friendly solutions [4].

Currently, the gold standard treatments for GAD are pharmacotherapy and/or psychotherapy [5]. The recommended first-line pharmacotherapies are selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) [5]. Regarding psychotherapy, 12-20 sessions of individual cognitive behavioral therapy (CBT) is the first-line treatment [5]. Individual CBT is effective at improving patient quality of life and decreasing psychological distress in times of crisis, with long-term effects being seen [5-9].

While these pharmacotherapies and CBT are generally effective, neither are without their drawbacks. In terms of pharmacotherapy, a large stigma, potential adverse effects, polypharmacy, and personal reasons deter many patients from opting for this treatment. Regarding individual CBT, high costs, long waiting lists, privacy concerns, and treatment times only available during regular work hours often make it inaccessible. Due to these limitations, there is an urgent need to create a treatment modality for GAD that can be accessible and cost-effective without sacrificing the quality of care and treatment efficacy.

The delivery of CBT asynchronously through the internet (e-CBT) appears to be a viable solution to address the limitations of CBT. e-CBT has been proven to be clinically efficacious, increase treatment adherence, yield high treatment satisfaction, and offer comparable results to in-person CBT [10-17]. Given the structured nature of CBT, predesigned content can be provided to patients, allowing them to access it anywhere at any time, saving health care providers time and costs, while increasing care capacity. While e-CBT has been shown in the literature to be effective in treating anxiety symptoms, the method of delivery has largely been through self-help, with patient-therapist interaction occurring through email [11-15]. While self-help programs can be beneficial, therapist-patient engagement is associated with increases in treatment effectiveness [18-21]. Moreover, email as the primary form of

communication between therapist and patient is both insecure and nonscalable. Therefore, a secure, scalable, and therapist-guided delivery of e-CBT is needed. While using a different platform still requires clinicians to provide individual feedback (similar to email), the scalability comes from the overall clinic-like management and automatic distribution of materials to patients following the completion of their assignments.

While it is known that e-CBT offers comparable results to in-person CBT when treating GAD, it has yet to be investigated whether a combination therapy of e-CBT and pharmacotherapy offers an augmented benefit to the individual. Additionally, an investigation of the efficacy of pharmacotherapy versus e-CBT through a secure platform has not been conducted to date. The potential of discovering a new gold-standard combination therapy for the treatment of GAD could have significant implications in the health care field, with greater accessibility for patients and time-efficiency for health care providers.

Objectives

In this study, a secure and scalable e-CBT program will be delivered to individuals with GAD. This program will be delivered through the Online Psychotherapy Tool (OPTT), which is a secure, cloud-based platform designed specifically for the online delivery of psychotherapy [10,22-27]. There will be 12 e-CBT modules that mirror in-person, individual CBT content. Participants will be offered either e-CBT, medication, or a combination of e-CBT and medication. The following project aims to investigate the efficacy of e-CBT in the treatment of GAD compared to and in conjunction with current pharmacotherapy strategies. By using OPTT, we hypothesize that this psychotherapy intervention will improve patient quality of life and decrease symptom severity in individuals with GAD independent of medication use.

Methods

Study Design

This study will use a quasi-experimental design to allow participants the freedom to choose which treatment they would like to receive. This research design aims to be naturalistic by mimicking the decisions made by patients and physicians regarding their autonomy to choose a course of treatment. The treatments provided within the study also aim to replicate evidence-based best practice clinical guidelines for the treatment of GAD. All procedures have been approved by the Queen's

University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB) (Multimedia Appendix 1, Multimedia Appendix 2).

Participants

A total of 165 patients (e-CBT: n=55; medication: n=55; combination: n=55) aged 18-65 years will be recruited at Queen's University from outpatient psychiatry clinics at Kingston Health Sciences Centre sites (Hotel Dieu Hospital and Kingston General Hospital), Providence Care Hospital, family doctors, physicians, clinicians, and self-referrals in Kingston, Ontario, Canada. Interested participants will meet with a research coordinator who will provide them with a study letter of information that they will read before obtaining informed consent. Additionally, it will be explained to the participants that they will not always have access to their therapist and that the program is not to be used as a crisis resource. Once informed consent is obtained, a psychiatrist on the research team will evaluate the participants through secure video appointments. During these appointments, a diagnosis of GAD will be confirmed using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [28].

Inclusion criteria include being between 18 and 65 years of age at the start of the study, a diagnosis of GAD according to the DSM-5, the competence to consent to participate, the ability to speak and read English, and consistent and reliable access to the internet. Exclusion criteria include active psychosis, acute mania, severe alcohol or substance use disorder, and/or active suicidal or homicidal ideation. Additionally, participants will be excluded if they are receiving another form of psychotherapy, as this could have a confounding effect on the efficacy of treatment. Participation in the study will be discontinued if the participant is noncompliant with their treatment program. Regarding medication, noncompliance will be defined as stopping the medication altogether or skipping more than 3 days of doses in a row. With e-CBT treatment, noncompliance will be defined as missing more than 2 weeks of e-CBT sessions. If a participant is deemed to be in an acute crisis by self-report or by the psychiatrist in charge of their care, their treatment will be halted and they will be directed to the proper resources (eg, emergency department, crisis lines, etc). If deemed eligible for the study, participants will be presented with all 3 arms of the study by the psychiatrist, who will discuss the recommended treatment plan. In collaboration with the psychiatrist, the participant will decide which of the treatment arms they would like to take part in.

Procedures

At baseline, participants successfully enrolled in the study will complete a demographic questionnaire and the following clinically validated symptomatology questionnaires: the Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form (Q-LES-Q-SF), the 7-item Generalized Anxiety Disorder Questionnaire (GAD-7), and the 42-item Depression Anxiety Stress Scale (DASS-42). All participants will complete the questionnaires biweekly (at weeks 0, 2, 4, 6, 8, 10, and 12) for the duration of treatment and at a 6-month follow-up. Participants in the e-CBT or combination arms will complete these questionnaires directly through OPTT. For participants

in the medication arm, the questionnaires will be completed during their appointments. Once the treatment has been decided upon by the participant in collaboration with the psychiatrist, treatment will commence according to the arms explained below. Participants in the combination arm will begin the e-CBT program and pharmacotherapy simultaneously.

e-CBT Protocol

All e-CBT modules are designed to mirror standard in-person CBT for GAD. The basis of the therapy is to help participants understand the interconnectivity of their thoughts, behaviors, emotions, physical reactions, and environment. This is achieved through presenting information, learning coping skills, and practicing these skills through homework. These coping skills will include actions such as deep breathing and meditating, goal setting, thought recording, and activity schedules. Through the course of this program, participants will work on refocusing their beliefs and thoughts to more realistic states in which they can better cope with their anxiety. By improving thought processes, participants will have the ability to better react to events in their environment and develop coping strategies.

Participants will complete approximately 30 e-CBT slides each week through the OPTT platform. Each session is expected to last approximately 50 minutes. The slides will highlight different topics each week and include general information, an overview of skills, and homework. The homework included in each session will be submitted through OPTT and reviewed by a therapist assigned to the participant. Therapists will provide personalized feedback every week to their participants within 3 days of submission. Participants will have access to these online sessions at any point throughout the week and can complete them in multiple blocks or all at once. Weekly homework submission for feedback will be mandatory before being eligible for the next session. Feedback will be reviewed by one of the psychiatrists on the team before submission to the participants.

Therapist Training

All therapists on the research team have experience in psychotherapy delivery and are trained by a psychiatrist involved in the project. Additionally, all therapists learn the specifics of the modules covered in treatment, along with the standard care pathway. The therapists are a combination of medical graduates and residents, graduate students, and trained research assistants. Before working with any patients, therapists will provide practice feedback on simulated sessions that will be analyzed by the psychiatrists on the team to ensure that the quality of care is adequate. All therapists will be supervised by the lead psychiatrist on the research team who is an expert in online psychotherapy delivery. Moreover, homework feedback is only sent to the patient after it is read, edited, and approved by the supervisor. Any issues regarding OPTT are handled through OPTT technical support, which can be accessed at any time.

Medication Protocol

Participants in the medication or combination arm will attend biweekly medication reconciliation appointments with their psychiatrist at the clinic. During the intake appointment, participant medication history (including any current

medications) will be collected. If a participant is taking medication for GAD that is not one of the recommended ones in the protocol, they will be switched to a suggested drug. It is required that a participant's medication remain unchanged for 6 weeks before the start of the study and during the study. The psychiatrist will suggest medications according to Canada's best practice guidelines for the treatment of GAD. The pharmacotherapy protocol is summarized in Figure 1.

Figure 1. Flowchart of the 12-week generalized anxiety disorder pharmacotherapy protocol. SNRI: selective norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.
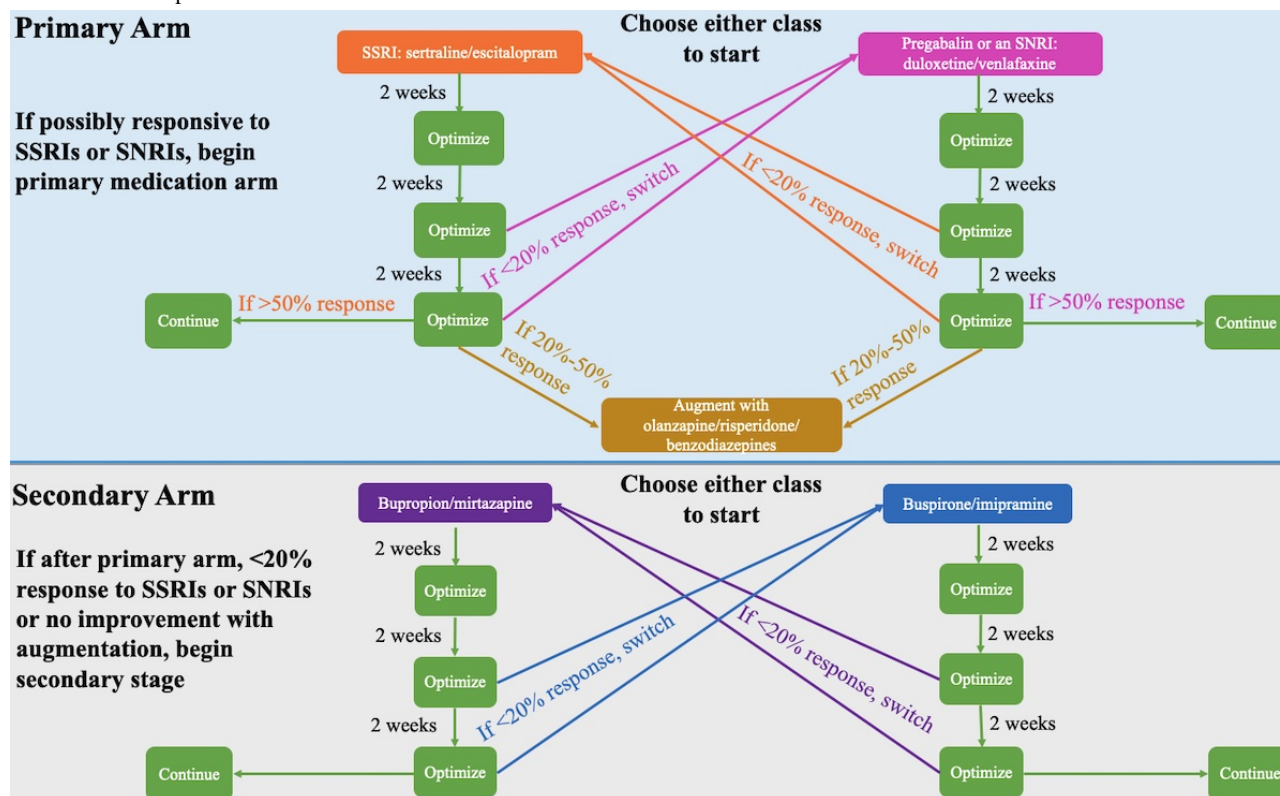
If a participant has never taken an SSRI or SNRI, they will commence the primary medication arm. The 2 classes of medications within the primary arm will be described to the participant, and with the recommendation of the prescribing psychiatrist the participant will begin either an SSRI (sertraline or escitalopram) or pregabalin/SNRI (duloxetine or venlafaxine). If the participant has previously been deemed unresponsive to either an SSRI or an SNRI/pregabalin, they will commence the primary medication arm. The participant will start the medication class that they have not been previously deemed unresponsive to (eg, if previously unresponsive to sertraline, the participant will commence the SNRI class). Previous unresponsiveness will be defined as anxiety symptoms not improving after treatment with the maximum tolerated dose of the specific medication for a duration of 8 weeks. If a participant is deemed unresponsive to both an SSRI and an SNRI/pregabalin, they will commence the secondary medication arm. The 2 classes of medications within the second arm will be described to the participant and, with the recommendation of the prescribing psychiatrist, they will begin either bupropion/mirtazapine or buspirone/imipramine.

At the participant's second appointment (2 weeks on the medication), their medication will be maintained and optimized, regardless of whether a response is reported. At the third appointment (4 weeks on the medication), the medication will be optimized if a partial response is reported or switched

according to the "medication switch protocol" if no response is reported. Partial response will be defined as an improvement of ≥20% in GAD-7 score compared with baseline. If the medication is switched (<20% improvement in GAD-7 score compared with baseline), the 6-week protocol will recommence with the new medication. At the fourth appointment (6 weeks on the medication), the dosage will be optimized if the participant is responding well to the medication and reports an improvement in GAD-7 score of >50% if within the primary medication arm or ≥20% if within the secondary medication arm compared with baseline. If this is the case, the participant will remain on that medication for the remainder of the 12-week study. If the participant does not present an improvement of >20% in their GAD-7 score compared with baseline, the medication will be switched according to the "medication switch protocol" and the 6-week protocol will recommence. If the participant is in the primary medication arm and reports a 20% to 50% improvement in GAD-7 score compared with baseline after 6 weeks on the new medication, the medication will be augmented with either olanzapine, risperidone, or benzodiazepines. Benzodiazepines have shown efficacy as adjunctive therapy in the treatment of anxiety; they have especially been helpful with decreasing level of agitation. Adjunctive olanzapine and risperidone demonstrated efficacy in patients who remained symptomatic after 6 weeks of antidepressant therapy [29].

Medication Switch Protocol

If a participant is unresponsive to medication after 4 or 6 weeks of administration (<20% improvement in GAD-7 score compared with baseline), their medication will be switched to another class. If the participant has a history of nonresponse to any of the 4 medication classes, these classes will be removed as treatment options. If a participant started in the primary or secondary medication arm and has not previously demonstrated nonresponse to the second class of medications within that arm, they will be switched to the second class of pharmaceuticals within that arm. If a participant started in the primary arm and was previously unresponsive to the second class of pharmaceuticals within that arm, they will begin the secondary medication arm if necessary.

Ethics and Data Privacy

All procedures have been approved by the Queen's University HSREB. For privacy purposes, participants are only identifiable by an ID number on the platform and hard copies of the consent forms with participants' identities are stored securely on-site and will be destroyed 5 years after study completion. Participant data are only accessible by the care providers directly assigned to that participant and only anonymized data are provided to the analysis team members. Participants have the option to withdraw from the study at any point and request for their data to be removed from the analysis. However, since the collected data are considered a medical record, they will not be permanently deleted for 10 years after treatment.

The online platform used for the study (ie, OPTT) is compliant with the Health Insurance Portability and Accountability Act, Personal Information Protection and Electronic Documents Act, and Service Organization Control 2. Additionally, all servers and databases are hosted in Amazon Web Services Canada's cloud infrastructure, which is managed by MedStack to assure that all provincial and federal privacy and security regulations are met. OPTT does not collect any identifiable personal information or internet protocol addresses for privacy purposes. OPTT only collects anonymized metadata to improve its service quality and provide advanced analytics to the clinician team. OPTT encrypts all data, and no employee has direct access to participant data. All encrypted backups are kept in the S3 storage that is dedicated to Queen's University, located in Kingston, Ontario, Canada.

Data Analysis

Initially, all data will be examined for missing, nonsensical, and outlying variables. Missing data will be treated as missing and not imputed (ie, analyzed on a per-protocol basis). The participant population of this study was intentionally oversampled to account for dropouts/withdrawals. Based on previous research, an anticipated dropout rate of up to 30% was factored in. Using the GAD-7 score as the primary outcome, a 30% change is considered clinically significant. Therefore, a sample size of 55 participants in each arm of the study would be sufficient for detecting significant results with $P=.05$ and a power of 0.95. Data collection will occur biweekly and at a 6-month follow-up. Using Mann-Whitney U tests, demographic information can be compared between participants who complete the program and those who withdraw prematurely in the hopes of identifying possible differences between the 2 groups. Moreover, an intention-to-treat analysis will be conducted to evaluate the clinical effects of treatment on participants who withdraw prematurely. Linear regression analysis (for continuous outcomes) and binomial regression analysis (for categorical outcomes) will be used to identify variables associated with the outcome measures (GAD-7, DASS-42, and Q-LES-Q-SF). This will occur over the 4 measurement time points while controlling for demographic variables, including age and gender. Additionally, differences between study arms will be analyzed.

Other quantitative measures for the e-CBT group will be gathered by extrapolating recorded information directly through the OPTT application (ie, the number of logins per day, the amount of time spent logged in, etc). Qualitative measurement analyses will be done to inquire about the role of personal, social, and cultural factors in enabling or constraining the use of e-CBT. Findings will identify factors related to the utility, feasibility, and accessibility of e-CBT from the perspectives of users and providers. Interpretive qualitative methods are ideal for gathering in-depth descriptions of user experience and meaning.

Results

The study received ethics approval from the Queen's University HSREB in April 2019, and the recruitment of participants began in June 2019. Participant recruitment has been conducted through social media advertisements, physical advertisements, and physician referrals. To date, 146 participants have been recruited (e-CBT: n=53; medication: n=49; combination: n=44). Data collection is expected to conclude by June 2021, and data analysis is expected to be completed by October 2021. Linear regression will be used to analyze continuous outcomes, and binomial regression will be used to analyze categorical outcomes.

Discussion

GAD is a prevalent mental illness that is overwhelming the mental health care system. Innovative, efficacious, and accessible treatments are needed to address the issues with current treatment options. Developing an online psychotherapy clinic with predesigned therapy modules can drastically increase care capacity without sacrificing the quality of care. Investigating the effectiveness of an e-CBT program compared to pharmacotherapy and a combination of the 2 can provide valuable insight into new treatment developments. Outcomes of this study will be shared as a preprint on bioRxiv.org for the rapid dissemination of findings. We will also hold multiple online workshops for other clinicians interested in implementing this approach and provide technical and academic support to deploy this solution in their respective practices. This will ensure that the findings can be efficiently incorporated into clinical practice. If feasible, an online psychotherapy clinic can provide significant time and financial savings to the health care system while providing an equitable and accessible method of treatment delivery for patients.

Conflicts of Interest

NA and MO have cofounded the care delivery platform in use (ie, OPTT) and have ownership stakes in OPTT Inc.

Multimedia Appendix 1
GUIDED report checklist.
[PDF File (Adobe PDF File), 80 KB - resprot_v10i5e27772_app1.pdf]

Multimedia Appendix 2
TIDieR report checklist.
[PDF File (Adobe PDF File), 236 KB - resprot_v10i5e27772_app2.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
DASS-42: 42-item Depression Anxiety Stress Scale
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
e-CBT: electronically delivered cognitive behavioral therapy
GAD: generalized anxiety disorder
GAD-7: 7-item Generalized Anxiety Disorder Questionnaire
HSREB: Health Sciences and Affiliated Teaching Hospitals Research Ethics Board
OPTT: Online Psychotherapy Tool
Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form
SNRI: selective norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor

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Protocol

Influence of Stress, Gender, and Minority Status on Cardiovascular Disease Risk in the Hispanic/Latino Community: Protocol for a Longitudinal Observational Cohort Study

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Abstract

Background: Hispanic/Latino sexual and gender minorities (SGM) are the fastest growing ethnic group of SGM in the United States. Cardiovascular disease (CVD) is a leading cause of morbidity and mortality among Hispanics/Latinos. SGM inequities in CVD risk have been identified as early as young adulthood, and minority stress has been identified as a potential mediator. Yet, the small number of ethnic or racial minority participants in SGM studies have precluded the examination of the intersections of sexual orientation, gender identity, and race and ethnicity.

Objective: Minority stress models conceptualize relationships between stressors in minority groups and health outcomes. In this study, we will (1) examine the influence of sexual orientation and gender identity on CVD risk among all *Hispanic Community Health Study/Study of Latinos* (HCHS/SOL) participants at visit 3 (2021-2024; N~9300); (2) model pathways from sexual orientation and gender identity to CVD risk through stigma, discrimination, and stress in a 1:2 matched subcohort of SGM and non-SGM participants at visit 3 (n~1680); and (3) examine the influence of resilience factors on sexual orientation or gender identity and CVD risk relationships among subcohort participants at visit 3 (n~1680).

Methods: This study will leverage existing data from the parent HCHS/SOL study (collected since 2008) while collecting new data on sexual orientation, gender identity, stigma, discrimination, stress, coping, social support, and CVD risk. Data analysis will follow the SGM minority stress model, which states that excess stigma against SGM populations leads to minority stress that increases CVD risk. In this model, coping and social support serve as resilience factors that can mitigate the impact of minority stress on CVD risk. Cross-sectional and longitudinal regression models as well as structural equation models will be used to test these relationships.

Results: This study was funded by the National Heart, Lung, and Blood Institute in March 2020. Recruitment is scheduled to begin in the first quarter of 2021 and continue through 2024.

Conclusions: Understanding the influence of stigma-induced stress on CVD risk among Hispanic/Latino SGM has significant implications for the development of culturally specific CVD risk reduction strategies. Study findings will be used to build on identified Hispanic/Latino cultural strengths to inform adaptation and testing of family and community acceptance interventions.

International Registered Report Identifier (IRRID): PRR1-10.2196/28997

Introduction

Background

Cardiovascular disease (CVD) is the second leading cause of death among Hispanic/Latino adults [1]. This population bears a heavy burden of obesity, diabetes, poorly controlled hypertension, and other cardiovascular risk factors [2]. Recent studies have identified heterogeneity in cardiovascular risk among Hispanic/Latino adults by heritage group, gender, acculturation, and duration of US residency [3,4]. However, variability in cardiovascular risk factors has not been systematically examined by sexual orientation or gender identity.

The inclusion of sexual orientation measures in national, population-based surveys such the National Health Interview Survey, the National Health and Nutrition Examination Survey, and the Behavioral Risk Factor Surveillance Survey (BRFSS) have provided data on the elevated prevalence of cardiovascular risk factors among sexual minorities, including smoking [5-7], obesity [6-8], high blood pressure [6], and glycosylated hemoglobin [6]. An analysis of data from the National Longitudinal Study of Adolescent to Adult Health identified sexual orientation inequities in cardiovascular risk behaviors (eg, smoking), as well as clinical measures (eg, blood pressure) and biomarkers (eg, C-reactive protein), beginning in young adulthood [9].

The BRFSS is the only national population-based survey to have published data that includes a module to assess gender identity. BRFSS data indicate transgender adults experience disparities in weight [7], smoking [10], and myocardial infarction [11]. The aforementioned studies have also identified variations in cardiovascular risk among sexual and gender minorities (SGM) by sex assigned at birth (eg, male, female), gender identity (eg, transgender woman, cisgender woman), and sexual identity (eg, gay, bisexual) [5,6,8]. However, the small number of ethnic minority SGM in these samples have precluded specific analyses within Hispanic/Latino SGM, even though Hispanic/Latino SGM are the fastest growing ethnic group of SGM in the United States [12].

Rationale

Psychosocial stressors play an important role in CVD risk [13]. A global investigation of the determinants of CVD outcomes, in 52 countries over 7 continents, found that psychosocial stress was a powerful predictor of myocardial infarction, comparable in impact to smoking [14,15]. Baseline data from the *Hispanic Community Health Study/Study of Latinos* (HCHS/SOL) found

that a composite score for psychological distress, including depressive symptomatology and trait anxiety, was significantly associated with obesity for women, diabetes for men, and smoking for all participants [16].

Stigma and discrimination are common psychosocial stressors for minority groups and are associated with a range of negative health outcomes, including increased risk for CVD [17-21]. A recent nationally representative sample of 489 SGM reported prevalent harassment or threats (57%) and violence (51%) because of their sexual orientation or gender identity [22]. The HCHS/SOL Sociocultural Ancillary Study found that most Hispanics/Latinos (80%) reported exposure to ethnic discrimination during their lifetime [23]. While exposure to ethnic discrimination varied based on education, income, and acculturation, lack of sexual orientation and gender identity measures in HCHS/SOL precluded examination by SGM status. Other research suggests that Hispanic/Latino SGM experience the unique stressors of both racism and ethnocentrism within SGM communities and rejection of their sexual orientation and/or gender identity by their Hispanic/Latino families and communities [24].

Resilient coping and social support may mitigate the impact of psychosocial stressors on CVD risk. Hispanic/Latino cultural values are hypothesized to engender strong social supports that buffer health risks [25-27]. For example, lower acculturation and foreign-born nativity, often used as proxies for stronger cultural values, are associated with lower CVD prevalence [28]. However, SGM Hispanic/Latino individuals may lose access to these cultural buffers if they are rejected by their families or communities, or forced to conceal their sexual orientation or gender identity [24]. Connection to SGM community may mitigate minority stress for Hispanic/Latino SGM [29,30]. However, whether this connection reduces CVD risk for Hispanic/Latino SGM has not been studied.

Conceptual Framework

This study, *Stress Gender and Minority Status in the Study of Latinos* (SGM SOL), aims to advance scientific knowledge of how stigma at the intersection of ethnic identity, sexual orientation, and gender identity impacts CVD outcomes for Hispanic/Latino SGM. It draws on two complementary conceptual frameworks: intersectionality theory and the minority stress model. Intersectionality addresses how the stress of holding multiple stigmatized identities, such as being a racial/ethnic minority, SGM, and/or an immigrant, may compound inequities [31,32]. Intersectionality theory guided our decision to measure multiple social identities including

sexual orientation and gender identity, socially ascribed race, and immigration background. In keeping with a fundamental tenet of intersectionality theory—that social identities are mutually constituted—we plan to use adapted measures of stigma, discrimination, and social stress that are inclusive of multiple simultaneous identities without requiring participants to attribute experiences to a particular identity [33]. The minority stress model posits that stigma and discrimination create excess minority stress for SGM populations that result in health inequities, and that these inequities can be mitigated by resilience factors, such as positive coping and social support [34-36].

SGM SOL aims to assess relationships among CVD risk and stigma, discrimination, stress, and coping and social support by comparing SGM with non-SGM Hispanic/Latino adults, thereby testing relationships theorized by the minority stress model, as depicted in Figure 1.

Figure 1. Conceptual framework and study aims for the SGM SOL (Stress Gender and Minority Status in the Study of Latinos) study. CVD: cardiovascular disease.
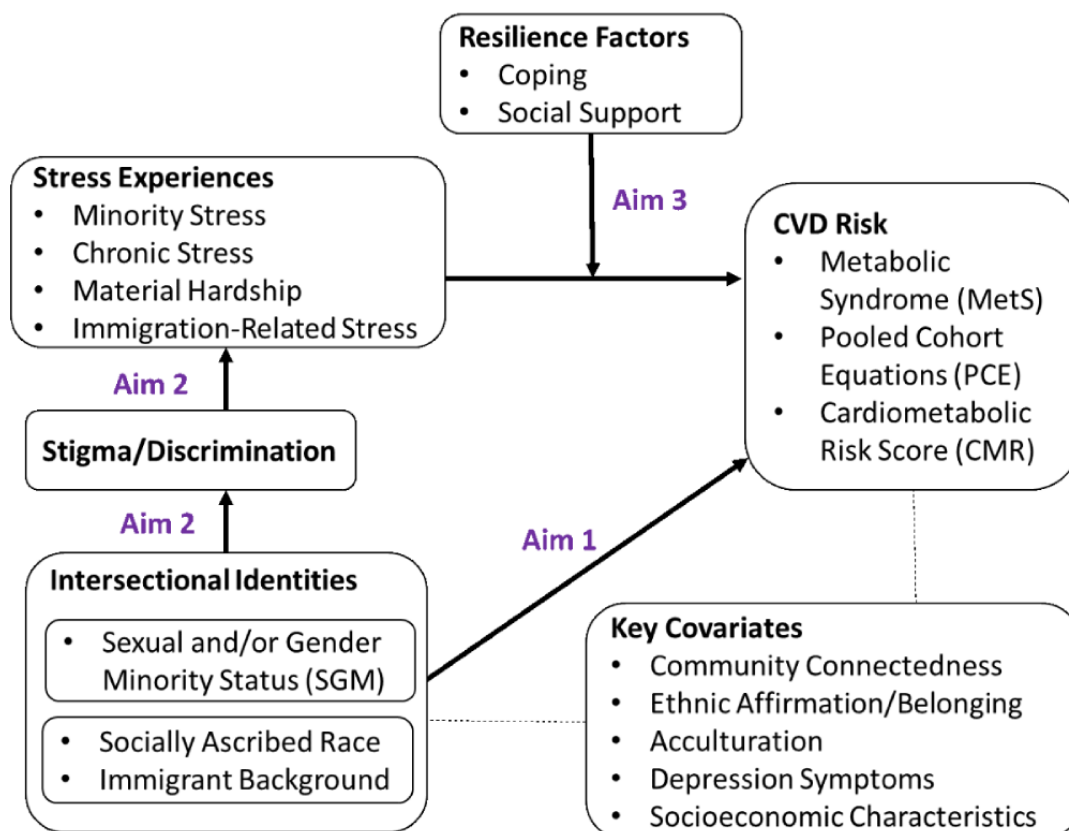
Objectives

The primary aims of this study are to (1) examine the influence of sexual orientation or gender identity on CVD risk during visit 3 of HCHS/SOL (N~9300); (2) model pathways from sexual orientation or gender identity to CVD risk through stigma, discrimination, and stress in an HCHS/SOL subsample (n~1680); and (3) examine the influence of resilience factors on sexual orientation or gender identity and CVD risk relationships in the HCHS/SOL subsample (n~1680).

Methods

Setting

SGM SOL builds on the infrastructure of HCHS/SOL, a multicenter, longitudinal, observational cohort study designed to evaluate prevalence, incidence, and risk and protective factors for cardiovascular disease and other chronic conditions among Hispanic/Latino adults in the United States. It is the largest well-characterized longitudinal cohort study of diverse self-identified US Hispanic/Latinos with 16,415 adults (aged 18-74 years) enrolled at baseline. Using a 2-stage probability sample, households and participants were randomly selected using stratification and oversampling at each stage in 4 US sites—the Bronx, NY; Chicago, IL; Miami, FL; and San Diego, CA [37]. Full details about the study design have been previously published [37,38].

Study Design and Population

SGM SOL is a longitudinal observational cohort study of HCHS/SOL adults who will participate in visit 3. HCHS/SOL collected in-person data in 2008-2011 (visit 1), and 81% of eligible participants (n=11,623) returned for visit 2 (2014-2017). We expect 80% of the visit 2 participants to return for visit 3. Thus, we project approximately 9300 visit 3 participants. Based on national data, which indicate that 6.1% of the Hispanic/Latino population in the United States identify as SGM [39], we anticipate that 560 HCHS/SOL participants will meet at least one of the SGM inclusion criteria.

Inclusion Criteria

All visit 3 participants are asked 4 screening questions pertaining to sexual orientation or gender identity: (1) sex assigned at birth; (2) current gender identity, including the age at which gender identity first differed from sex assigned at birth, if applicable; (3) any history of an intersex condition; and (4) any history of same-sex attraction, including age of first same-sex attraction, if applicable. SGM status is operationalized as reporting a current gender that is different from one's sex assigned at birth, reporting any history of an intersex condition, or reporting any history of same-sex attraction.

Study Procedures

As shown in Figure 2, the first aim will be addressed using the entire HCHS/SOL visit 3 cohort (N~9300) who complete the screening measures related to sexual orientation or gender identity. The second and third aims will be addressed by enrolling 560 SGM and 1120 non-SGM who are matched 2:1 to the SGM participants by site, age, and sex assigned at birth (n~1680). All study procedures have been approved by the central institutional review board (IRB) at the University of North Carolina Chapel Hill and by the local IRBs of all participating institutions.

Figure 2. SGM SOL (Stress Gender and Minority Status in the Study of Latinos) measures added to the core HCHS/SOL (Hispanic Community Health Study/Study of Latinos) measures in visit 3, by aim. SOGI: sexual orientation or gender identity, CVD: cardiovascular disease, hsCRP: high-sensitivity C-reactive protein.
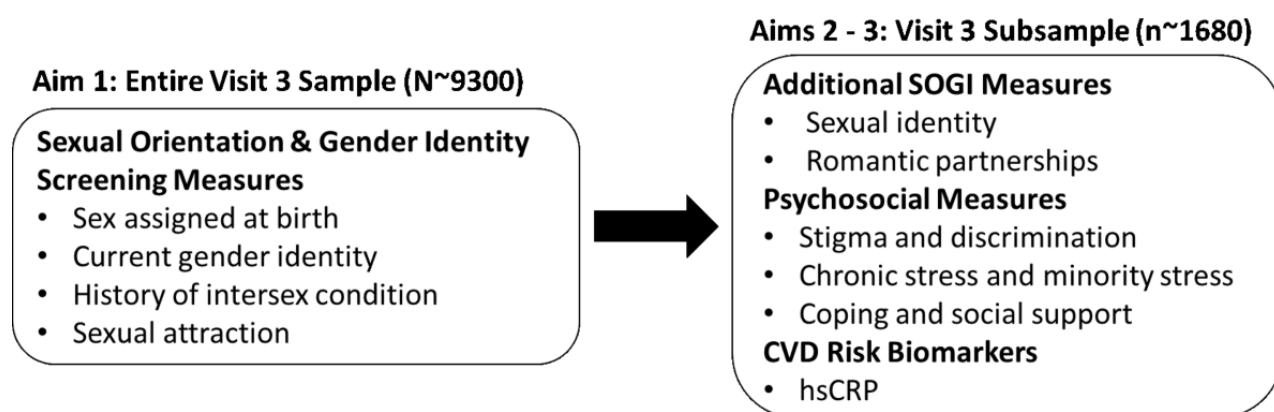
Recruitment

Recruitment for the SGM SOL cohort is being coordinated with the existing recruitment activities for HCHS/SOL visit 3. At the end of their scheduled visit 3 assessment, all current participants who screen as SGM are invited to participate in SGM SOL. A matched subsample of participants who screen as non-SGM are invited to participate at the end of their visit 3 assessment. Matching is based on sex assigned at birth (female, male), age (<50, 50-59, ≥60 years), and site (the Bronx, Chicago, Miami, San Diego). An algorithm embedded within the HCHS/SOL visit 3 electronic data management system indicates whether a participant should be invited to take part in the SGM SOL ancillary study. All individuals who agree to participate in SGM SOL will complete the informed consent process.

Data Collection

At visit 3, all participants complete the 4 SGM screening questions and psychosocial questionnaires and have a fasting blood sample and anthropometry measures taken. All HCHS/SOL questions are asked in the participant's language of preference. Questionnaires are administered by bilingual staff who are centrally trained and certified in interviewing techniques. The SGM SOL matched cohort subsample completes

an additional 30-minute structured interview and laboratory testing for high-sensitivity C-reactive protein. The structured interview includes additional questions on sexual orientation and gender identity as well as detailed questions regarding stigma, discrimination, stress, and coping and social support. Individuals who are interested in participating but unable to do so at the time of their visit 3 assessment are given the option to complete the SGM SOL interview via phone at a later date.

Measures

All new SGM SOL study measures are listed in Table 1, organized by visit and topic area. We also list related measures for visit 3 or previously collected at visits 1 or 2. All HCHS/SOL visit 3 participants will complete the measures listed in Table 1 in the visit 3 column as well as the 4 SGM screening questions. The SGM SOL study participants will complete the additional measures listed in Table 1 in the new measures column. Except where noted below, all study instruments have existing, validated Spanish translations. In the few cases where translations were not available, items were translated into Spanish by culturally knowledgeable bilingual staff, then back-translated by different culturally knowledgeable bilingual staff members to ensure accuracy [40]. Below, we describe each of the main measures listed in the conceptual framework.

Table 1. SGM SOL (Stress Gender and Minority Status in the Study of Latinos) measures and related HCHS/SOL (Hispanic Community Health Study/Study of Latinos) measures at visits 1, 2 and 3.

Constructs	New SGM SOL measures	HCHS/SOL measures		
		Visit 3 (2020-2023)	Visit 2 (2014-2017)	Visit 1 (2008-2011)
Sexual and/or gender minority screening measures	Sex assigned at birth	—[a]	Interviewer-ascribed sex	Interviewer-ascribed sex
	Current gender identity, age when gender identity differed from sex assigned at birth, if applicable	—	—	—
	Intersex/DSD[b]	—	—	—
	Sexual attraction, age of first same-sex attraction, if applicable	—	—	—
Additional sexual orientation measures	Sexual identity, including age of first sexual minority identity, if applicable	—	—	—
	Romantic partners, age of first same-sex partnership, if applicable	—	—	—
Race and immigration background	"Street" race (ie, race ascribed by others)	—	US citizenship, immigrant visa status	Self-reported race, Hispanic/Latino background, place of birth, parents' place of birth
	—	Years in the United States	Years in the United States	Years in the United States
Stigma and discrimination	Identity stigma (adapted for all identities)	—	—	—
	Everyday Discrimination Scale - short form (adapted for all identities)	—	—	—
Stress experiences	Minority Stress - Rejection Anticipation subscale (adapted for all identities)	—	—	—
	Chronic stress	—	Chronic stress	—
	Material hardship	—	—	—
	Immigration-related stress	—	—	—
Resilience factors	Brief Resilient Coping Scale	—	—	—
	Interpersonal support evaluation list	—	Interpersonal support evaluation list	—
CVD[c] risk	PCE[d]: sex assigned at birth, age, street race, total cholesterol, HDL-C[e], SBP[f], hypertension treatment, type 2 diabetes, and tobacco use	Tobacco use; medications for hypertension, hyperlipidemia, and/or diabetes	Tobacco use; medications for hypertension, hyperlipidemia, and/or diabetes	Tobacco use; medications for hypertension, hyperlipidemia, and/or diabetes
	MetS[g]: waist circumference, blood pressure, triglycerides, HDL-C, fasting glucose, medications for hypertension, hyperlipidemia, and/or diabetes	Waist-hip ratio, blood pressure	Waist-hip ratio, blood pressure	hsCRP[h], waist-hip ratio, blood pressure
	CMR[i]: blood pressure, glycosylated hemoglobin, hsCRP, waist circumference	Total cholesterol, HDL-C, LDL-C[j], triglycerides, fasting glucose	Total cholesterol, HDL-C, LDL-C, triglycerides, fasting glucose	Total cholesterol, HDL-C, LDL-C, triglycerides, fasting glucose
Potential confounders and covariates	LGBT[k] Minority Stress Scale - Community Connectedness subscale (adapted for all)	Years in the United States	Years in the United States	Years in the United States
	Multigroup Ethnic Identity Measure - Affirmation and Belonging subscale	—	Short Acculturation Scale for Hispanics	Short Acculturation Scale for Hispanics

Constructs	New SGM SOL measures	HCHS/SOL measures		
		Visit 3 (2020-2023)	Visit 2 (2014-2017)	Visit 1 (2008-2011)
	—	Income, employment, education, marital status	Income, employment, education	Income, employment, education, occupation, marital status
	Hormone use, including for gender affirmation	—	Female hormone use	Female hormone use

aNot applicable.

bDSD: differences of sex development.

cCVD: cardiovascular disease.

dPCE: pooled cohort equation.

eHDL-C: high-density lipoprotein cholesterol.

fSBP: systolic blood pressure.

gMetS: metabolic syndrome.

hhsCRP: high-sensitivity C-reactive protein.

iCMR: cardiometabolic risk score.

jLDL-C: low-density lipoprotein cholesterol.

kLGBT: lesbian, gay, bisexual, and transgender.

Exposure Variables

The National Institutes of Health define SGM populations as "individuals who identify as lesbian, gay, bisexual, asexual, transgender, Two-Spirit, queer, and/or intersex. Individuals with same-sex or -gender attractions or behaviors and those with a difference in sex development are also included" [41]. Several best practice recommendations for measuring sexual orientation and transgender-inclusive gender identity have been published [42]. The Gender Identity in US Surveillance (GenIUSS) group recommends the 2-step method of measuring sex assigned at birth and current gender identity separately [43]. No consensus exists on measurement of intersex status and no federal surveys include it [44]. The Sexual Minority Assessment Research Team recommends assessment of 3 dimensions of sexual orientation: attraction, behavior, and identity [45] (Table 1).

SGM Screening Measures Among All Visit 3 Participants

In addition to the GenIUSS group, the Center of Excellence for Transgender Health [43] recommends a 2-step measure to ascertain transgender status. The measure has been validated with a variety of populations in both English and Spanish [46-49]. The items include (1) "What sex were you assigned at birth, meaning on your original birth certificate? (a) Male, (b) Female;" and (2) "What is your current gender identity? (a) Male, (b) Female, (c) Transgender Male, (d) Transgender Female, (e) Gender nonbinary, (f) Some other identity." To measure intersex status, we ask, "Have you ever been told by a doctor that you have a difference of sexual development or an intersex condition?" This item is adapted from a measure recommended by the Williams Institute and tested online [43,44]. To measure sexual attraction, we ask, "People are different in their sexual attraction to other people. Which best describes your feelings? Are you attracted (a) Only to females, (b) Mostly to females, (c) About equally often to males and females, (d) Mostly to males, (e) Only to males, (f) I have never felt sexually attracted to anyone at all." This item has been used in multiple national surveys in English and Spanish [50].

Additional Sexual Orientation Measures Among the Ancillary Study Subsample at Visit 3

Sexual orientation identity is measured using an item that has been validated in a variety of populations in English and Spanish across multiple federal population-based surveys [49-51]. The item reads, "Do you think of yourself as (a) Not gay or lesbian, that is straight; (b) Gay; (c) Lesbian; (d) Bisexual; (e) Something else." Sexual orientation behavior is measured using a modified item from the General Social Survey [50] that reads, "In your lifetime, have your romantic partners been (a) Males only, (b) Females only, (c) Males and Females, (d) I have not had romantic relationships."

Race and Immigration Background

We measure socially ascribed race, that is, the race that is usually ascribed to the participant by others, using 2 items previously used in the Latino National Health and Immigration Survey and the Pew National Survey of Latinos [52]. The first measures self-reported skin color, a physical characteristic often used to ascribe race to individuals. The second measures self-reported "street race" or what race participants think others attribute to them based on their appearance. These measures have been shown to predict inequities in health status, regardless of self-identified race [53]. Immigration background was ascertained at visit 1 where participants identified their country of birth and their parents' country of birth. Respondents provided their self-reported Hispanic/Latino background as Cuban, Dominican, Mexican, Puerto Rican, Central American, South American, mixed, or other.

Potential Mediators

Stigma and Discrimination

We measure stigma using the Identity Stigma Scale, which asks respondents to agree or disagree along a 4-point Likert scale to a series of 6 questions beginning with the stem, "These next statements refer to 'a person like you'; by this I mean persons who have the same gender, race, sexual orientation, nationality, ethnicity, and/or socioeconomic class as you. I would like you

to respond on the basis of how you feel people, in general, regard you in terms of such groups" [54]. Response options include items such as "Most people believe a person like you cannot be trusted" and "Most people look down on people like you." Previously, HCHS/SOL included 2 items measuring perceived discrimination of Hispanic/Latinos adopted from Gil et al's Acculturative Stress Index [55]. The Everyday Discrimination Scale is a widely used measure that assesses experiences of discrimination, and the short form has been used in the Chicago Community Adult Health Study [56]. The benefit of both measures is that they have been adapted to apply to stigma and discrimination experiences for any identity without requiring the respondent to attribute the experience to any specific identity or preset list of identities, consistent with intersectionality theory. Lastly, we include one additional question adapted from the BRFSS Reactions to Race Module to measure discrimination in a health care setting [57].

Stress Experiences

Minority stress is measured using a 6-item adaptation of the Rejection Anticipation subscale of the LGBT Minority Stress Scale [58]. To make this scale applicable to all participants while focusing on stress related to sexual orientation or gender identity, we replaced "because I am LGBT" with "because of my sexual orientation or gender identity" in the stem of the question. The scale includes questions such as, "I stay on guard and alert because something bad might happen to me because of my sexual orientation or gender identity." Participants respond using a 5-point Likert scale. The 8-item Chronic Burden Scale was assessed at visit 2 [59] and is being reassessed among the ancillary study subsample as a measure of chronic stress [60]. Using established scales available in Spanish and English, material hardship [61] and immigration-related stress [62] are measured as forms of stress unrelated to sexual orientation or gender identity.

Moderators

Resilience Factors

Coping is measured using the 4-item Brief Resilient Coping Scale [13] in which participants use a 5-point Likert scale to report how well each item describes their actions. Social support is measured by the Interpersonal Support Evaluation (ISEL) [63,64]. The ISEL contains 12 items, available in English and Spanish, which assess the perceived availability of social support on a 4-point scale ranging from "definitely false" to "definitely true." All items are summed to yield a total score (range 0-36). Longitudinal assessment is possible since ISEL was also measured during visit 2.

Key Covariates

Community connectedness may affect both stigma and minority stress [30,65,66]. For example, individuals who are connected to marginalized communities may experience and/or have more awareness of stigma. The same individuals may also experience less stress because their connections allow for access to greater social support. We measure community connectedness using a subscale of the LGBT Community Connectedness scale adapted for all identities. For example, we replaced "I feel connected to other LGBT people" with "I feel connected to other people who

share my sexual orientation or gender identity." Participants agree or disagree with items along a 5-point Likert scale. To be consistent with intersectionality theory, we also measure connection to ethnic minority communities using the Affirmation and Belonging subscale of the Multigroup Ethnic Identity Measure [67]. In this measure, participants agree or disagree along a 4-point Likert scale with items such as, "I have a strong sense of belonging to my own ethnic group." Because acculturation has known effects on CVD risk [27,68,69], and we hypothesize that it may also be related to SGM stigma, we are assessing the number of years participants have lived in the United States. The HCHS/SOL already collects measures of additional socioeconomic characteristics such as education, employment, income, occupation, and marital status.

CVD Risk Outcome Measures

CVD risk is multifactorial, including risk behaviors (eg, smoking), risk biomarkers (eg, blood pressure), and other risk factors (eg, diabetes). SGM SOL aggregates risk behavior, biomarkers, and other factors to assess CVD risk, operationalized as the following three outcomes: (1) the American College of Cardiology Pooled Cohort 10-Year Atherosclerotic Cardiovascular Disease Risk Assessment Equation (PCE) [70], (2) the modified International Diabetes Federation Metabolic Syndrome (MetS) [71], and (3) the cardiometabolic risk score (CMR) [72]. We outline each measure and the rationale for inclusion below.

The PCE uses a complex algorithm to estimate the risk of heart attack or stroke over the following 10 years for adults aged 40-79 years [70,73,74]. The measures used to calculate this risk include sex assigned at birth, age, socially ascribed race, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), hypertension treatment, type 2 diabetes, and tobacco use. We include the PCE measure for all participants because it is commonly used in clinical practice and is likely to have real-world applicability. Consistent with prior clinical [75] and research use [76], the PCE will be operationalized as a dichotomous variable in which participants with PCE score >7.5% will be considered to have high CVD risk.

The MetS is a cluster of anthropometric, hemodynamic, and metabolic disturbances that have been associated with CVD morbidity and mortality [77]. Our assessment is similar to the International Diabetes Federation [71] and consistent with prior HCHS/SOL studies that defined MetS as meeting 3 or more of the following criteria: (a) waist circumference ≥102 cm in men and ≥88 cm in women; (b) blood pressure ≥130 mm Hg SBP and/or ≥85 mm diastolic blood pressure (DBP) or treatment for previously diagnosed hypertension; (c) triglycerides ≥150 mg/dL or treatment for this lipid abnormality; (d) HDL-C <40 mg/dL in men and <50 mg/dL in women or treatment for this lipid abnormality; and (e) fasting glucose ≥100 mg/dL or previous type 2 diabetes diagnosis [2]. We use this measure in order to compare outcomes with prior HCHS/SOL studies that use this measure [2,78,79].

The CMR is designed to characterize overall functioning across multiple measures of cardiovascular risk [72], similar to the MetS and consistent with concepts of allostatic load [72]. To

compare to prior studies among sexual minorities, we are creating a cumulative biological risk score by counting the number (range 0-5) of biological markers that meet a clinically defined high-risk criterion [21]. The criteria for high risk are defined as: (a) SBP ≥140; (b) DBP ≥90 mmHg; (c) glycosylated hemoglobin ≥6.4%; (d) C-reactive protein ≥3 mg/dL; and (f) waist circumference ≥102 cm for men and ≥88 cm for women. Individuals will receive a value of 1 if they are above the risk threshold. While this measure is similar to the MetS, we include it because it has been used to examine sexual orientation disparities among young adults and may be more appropriate for the <50 years age group than traditional CVD measures [9,21]. We are analyzing the CMR only as a continuous variable since there is no established cut-off value for high risk [80].

Data Management, Quality Assurance, and Quality Control

Each site recruits, consents, and collects data for approximately 420 participants (140 SGM and 280 non-SGM) for the SGM SOL ancillary study. Data collected at the sites and entered into the web-based data management system are identified by participant and staff ID numbers. Measures taken to ensure the security of the data include, but are not limited to requiring valid IDs and passwords to access the web-based data management system, using a firewall and user logins to shield the local area network from web users, and using secure sockets layer standard to provide encryption and user authentication. The data management system includes procedures to support efficient, high-quality data acquisition, tracking, and quality assurance. When there is active data collection, the Coordinating Center prepares monthly reports to track enrollment and data quality.

Staff Training

Site personnel completed central training on sexual and gender minority cultural awareness, SGM SOL research protocols, and data collection instruments. Since collection of data on sexual orientation and gender identity was new for HCHS/SOL staff, we made every effort to raise cultural awareness and ensure comfort with the questions. Site principal investigators and all site personnel were invited to an SGM cultural awareness training that included a discussion of concepts and terminology related to sexual orientation or gender identity. The interactive training included opportunities to match terms with definitions, discuss relevant case scenarios, and ask questions in a judgement-free confidential manner. More than 50 personnel completed this training. This training was recorded and made available on the study website for future refresher training or to train new staff. Subsequently, personnel engaged in data collection or supervision completed study-specific training to increase familiarity with the questions, model appropriate ways to respond to potential participant questions, and provide opportunities to practice.

Statistical Analysis

General Approach

The complex sampling design and sampling weights specific to this study will be incorporated into the final analyses using SUDAAN (RTI International), Stata (StataCorp), and Mplus (Muthén & Muthén). Skewed variables will be log or square root transformed for modeling, and we will account for the matched study design for aims 2 and 3 in the analysis. Variables with a substantial number of missing values (ie, >5%) will be explored to determine if they are associated with any exposure or outcome variables. If we find more than 10% missing data, we will use multiple imputation including auxiliary information about the missingness. In addition, we will conduct a series of sensitivity analyses to evaluate the robustness of conclusions drawn from the primary models to departures from missing at random assumption by comparing the magnitude of the primary effect. All models will assess for linearity of covariates and use polynomials in case of departure. We will specify two-sided tests and .05 significance level.

Analyses for Aim 1

Once data collection is complete, we will use logistic regression models to determine if SGM have higher prevalence of CVD risk than non-SGM Hispanic/Latino adults at visit 3 (N~9300). We will estimate adjusted prevalence rates [81] for PCE and MetS and its ratios comparing SGM versus non-SGM. Linear regression models will be used to estimate and compare the mean CRM between SGM and non-SGM. All models will be stratified by sex assigned at birth and control for age, Hispanic/Latino background, site, and key covariates listed in Table 1, including key intersectionality covariates—immigration background and socially ascribed race. If sample sizes allow, rather than dichotomize by SGM and non-SGM, we will conduct the primary analyses (PCE, MetS, and CMR) by gender identity and by sexual orientation, separately.

In order to determine if SGM have a greater increase over time in CVD risk than non-SGM adults, we will use generalized estimating equations and available repeated measures (visits 1, 2 and 3). We will model mean values for each outcome separately (PCE risk score, MetS count score, and CRM count score) over time by including SGM and age, and test the effect of SGM while adjusting for site, Hispanic/Latino background, and key covariates from Table 1. We will stratify by sex assigned at birth and include an interaction term between age and SGM to test whether the patterns of change over time are the same for SGM and non-SGM. A logit link function in the GEE model will be used for binary outcomes (PCE and MetS). We will conduct exploratory analyses by gender identity and sexual orientation if sample size allows.

Analyses for Aim 2

To determine if SGM status has significant indirect effects on CVD risk via stigma, discrimination, and stress, we will fit models for each continuous outcome score (PCE, MetS, CRM) separately among the SGM SOL subsample (n~1680). First, using linear regression models we will test whether (1) stress, stigma, and discrimination differ by SGM status; (2) the effect of stress, stigma, and discrimination (measured as separate constructs) on CVD risk is significant; and (3) the total effect of SGM status on CVD risk is significant. We will then use structural equation models to estimate the direct effect of SGM status on continuous CVD risk outcome scores (ie, PCE, MetS, CRM) and the indirect effects through stress, stigma, and discrimination, separately. The structural part of the model will have the outcome regressed on SGM status, one variable at a

time (stress, stigma, and discrimination) and other covariates. For stress, the measurement part of the model will include 4 scales (chronic stress, minority stress, material hardship, and immigration-related stress). If sample size allows, we will conduct analyses by sex assigned at birth (male vs female), gender identity (cisgender vs transgender/nonbinary) and sexual orientation (lesbian, gay, bisexual, heterosexual).

Analyses for Aim 3

We will use linear regression models to test whether the effect of minority stress on continuous CVD risk outcomes is modified by (1) high resilient coping (brief scale >17) and (2) high social support (ISEL-12 >17). Models will include separate interaction terms for minority stress × coping and minority stress × social support controlling for covariates described above (and not including SGM status as the main effect). To derive the model, we will first determine the smallest number of covariates to control in the model by assessing their effects on the association of minority stress with CVD risk outcomes. We will retain covariates in the model when the change in the regression coefficient for minority stress is larger than 10%. Then, we will fit the model including the interaction term; we will consider $P<.10$ as evidence of interaction in each model. We will repeat the primary analyses stratifying by SGM to explore whether minority stress modifies the association in SGM and non-SGM, and whether these effect modifications are different.

Sample Size

The aim 1 analysis will include the entire visit 3 sample (N~9300) with approximately 560 meeting our criteria for SGM. With the 1:2 match, 560 SGM and 1120 non-SGM participants will be available for analyses of aims 2 and 3. To ensure adequate power, we have conducted power analyses for aims 2 and 3 using a smaller sample size of 1125 (375 SGM and 750 non-SGM). Previous HCHS/SOL ancillary studies have successfully recruited >70% of eligible participants and the lower bound for our sample of SGM participants (n=375) represents 67% of likely SGM participants in HCHS/SOL visit 3.

Power

For aim 1, we assume a total sample size of 9300 with 375 SGM participants (most conservative), power=0.8, variance inflation factor=2, and α=.05. For stratified analysis, we focus on our smallest subgroup (males) who comprise 36% of the sample. Based on these conservative assumptions, the power in both overall and stratified analyses is over 0.8 to detect prevalence ratios as small as 1.2 given a CVD risk factor prevalence ranging from 35% for the MetS to 63% for the PCE and as low as 20% for some age-sex subgroups [2,3]. For stratified analyses, the minimum detectable mean is 0.35 SD among males. The power is over 0.8 to test for each outcome (PCE, MetS, CRM) separately whether the mean is different by SGM and whether the patterns of change over time are the same.

For aim 2, power analysis was performed in Mplus using Monte Carlo simulation (10,000 replicates) to test separately the mediated effect of stigma, discrimination, and stress scores between SGM and CVD risk factor z-scores, given a conservative sample size of 1125, α=.05, and different effect sizes of direct paths based on Cohen's guidelines for R^2 (amount of explained variance in the outcome) [82]. We defined small, medium, and large effect sizes as 0.02, 0.13, and 0.26, given that we do not have estimates of the size of the indirect effects from the literature. We assumed the following parameters based on the literature [23,58,82]: minority stress (mean 2.08, SD 6.6 in Hispanics), discrimination (mean 1.5, SD 0.1), correlations between the SGM and CVD risk factors z-score ranging from 0.1 to 0.4, and residual variances of 0.95. The power is at least 0.9 for each effect (total, total indirect, and direct) from SGM to the CVD risk factors z-scores.

For aim 3, we performed a Monte Carlo simulation study in SAS to determine the minimum interaction term (in SDs) between high social support (ISEL-12 >17) and minority stress (continuous) on CVD risk factors z-scores assuming a conservative sample size of 1125, power=0.8, and α=.05. We generated 1000 samples and assumed the following parameters based on the literature [13,58,63]: minority stress (mean 2.08, SD 6.6 in Hispanics) and social support (range 0-36, mean ISEL-12 total 25.9, SD 6.6). The power is greater than 0.8 for an interaction term as small as 0.3 SD. Similarly, for resilient coping (range 4-20, mean 14.81, SD 2.95), the power is greater than 0.8 for an interaction term between high resilient coping and minority stress as small as 0.2 SD.

Results

This study was funded by the National Heart, Lung, and Blood Institute in March 2020. However, in-person examinations were paused due to the COVID-19 pandemic. Recruitment for SGM SOL is anticipated to begin in the first quarter of 2021 and continue through 2024.

Discussion

SGM SOL

Despite the heavy impact of CVD in Hispanic/Latino communities and the data that Hispanic/Latino populations are more likely to report being SGM, remarkably little research has focused on CVD in the Hispanic/Latino SGM population [83]. Leveraging the infrastructure of the existing HCHS/SOL cohort, SGM SOL will examine relationships among stigma, discrimination, minority stress, and CVD in this population [84]. Specifically, SGM SOL will test whether there are significant associations between minority stress and CVD and whether coping and social support mitigate the negative impact of minority stress, taking into consideration acculturation. SGM SOL will contribute to knowledge about the effect of psychosocial factors on cardiovascular health and advance scientific knowledge on how intersectional stigma and discrimination become embodied as health inequities.

SGM SOL is the first CVD study of this size in the fastest growing SGM ethnic group in the United States. While most existing studies of minority stress and CVD use cross-sectional designs [85], SGM SOL captures cross-sectional and retrospective longitudinal data, strengthening the ability to make causal inferences about the nature of stress-health relationships and the impact of coping and social support on these outcomes,

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providing key data for future interventions. Implementation of SGM SOL provides a template for low burden measurement of SGM status in other population-based studies as well as strategies for ensuring data collection staff are comfortable collecting data with multiply marginalized populations.

Understanding the influence of stigma-induced stress as well as resilient coping on CVD risk among Hispanic/Latino SGM adults has important implications for efforts aimed at improving health in this growing minority population. These advances in our understanding are key to our ability to identify ways clinical providers can more effectively tailor their care to meet the needs of Latino/Hispanic SGM populations. Additionally, results can be used to develop family and community interventions that reduce SGM-related stigma and build on identified Hispanic/Latino cultural strengths by adapting and testing family acceptance strategies [86] that have been only been tested among youth to date.

Limitations

It is possible that we will have fewer SGM participants than anticipated; therefore, we powered the study based on highly conservative estimates of the sample size. Maximizing sample size and power, aim 1 utilizes the full visit 3 HCHS/SOL cohort and will allow for exploratory analyses among specific SGM groups if the size of the SGM population is sufficiently large. Although HCHS/SOL is an excellent platform for a population-based study of Hispanic/Latino SGM health, the number of questions on sexual orientation and gender identity we could include for the entire cohort were limited by the need to reduce the burden on participants who are already completing 120 minutes of core data collection activities as part of visit 3. However, we will have more detailed information on sexual orientation and gender identity for all participants in the subsample. Hypothesized mediators (ie, stigma, discrimination, and minority stress) will be measured for the first time at visit 3, limiting the ability to assess temporality. However, CVD risk measures will be available for all 3 visits and measures of chronic stress for 2 visits. By assessing age at which SGM participants identified their current sexual orientation and gender identity, we will be able to assess temporality for relationships between SGM status, chronic stress, and CVD outcomes.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Health Disparities and Equity Promotion Study Section (National Institutes of Health).
[PDF File (Adobe PDF File), 133 KB - resprot_v10i5e28997_app1.pdf]

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Abbreviations

BRFSS: Behavioral Risk Factor Surveillance Survey
CMR: cardiometabolic risk score
CVD: cardiovascular disease
DBP: diastolic blood pressure
GenIUSS: Gender Identity in US Surveillance
HCHS/SOL: Hispanic Community Health Study/Study of Latinos
HDL-C: high-density lipoprotein cholesterol
IRB: institutional review board
ISEL: Interpersonal Support Evaluation
MetS: metabolic syndrome
PCE: pooled cohort equation
SBP: systolic blood pressure
SGM: sexual and gender minorities
SGM SOL: Stress Gender and Minority Status in the Study of Latinos

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<u>Protocol</u>

Individual Differences and Features of Self-reported Memory Lapses as Risk Factors for Alzheimer Disease Among Adults Aged 50 Years and Older: Protocol for a Coordinated Analysis Across Two Longitudinal Data Sets

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Abstract

Background: Increasing evidence has promoted the clinical utility of self-reported memory problems for detecting early impairment associated with Alzheimer disease (AD). However, previous studies investigating memory problems often conflated the *types* of problems (ie, retrospective and prospective) with their *features* (ie, frequency and consequences). This bias limits the specificity of traditional measures of memory problems and minimizes their ability to detect differential trajectories associated with cognitive decline. In this study, we use a novel measure of self-reported memory problems that uses daily reports of memory lapses to disentangle *types* from *features* for analyzing the impact of each dimension in two longitudinal data sets. Furthermore, this study explores the individual difference factors of age and gender as potential moderators of the relationships between self-reported memory lapses and objective cognitive decline.

Objective: The aim of this study is to describe the protocol for a secondary data analysis project that explores the relationship between experiences of daily memory lapses and their associations with cognitive decline in middle-aged and older adults.

Methods: This study uses multilevel, coordinated analyses across two measurement burst data sets to examine the links between features and consequences of memory lapses (retrospective and prospective) and their association with objective cognitive decline. This study's sample (N=392; aged 50-85 years; n=254, 64.8% women) is drawn from two ongoing, nationally funded research studies: The Effects of Stress on Cognitive Aging, Physiology, and Emotion study and the Einstein Aging Study. Both studies assess the daily experience of memory lapses, including the type as well as the emotional and functional outcomes, and objective measures of cognition, such as processing speed and episodic memory. We will use multilevel modeling to test our conceptual model demonstrating that differences in frequency and types of memory lapses show differential trends in their relationships with cognitive decline and that these relationships vary by the age and gender of participants.

Results: This project was funded in August 2019. The approval for secondary data analysis was given by the institutional review board in February 2020. Data analysis for this project has not yet started.

Conclusions: The early and accurate identification of individuals most at risk for cognitive decline is of paramount importance. Previous research exploring self-reported memory problems and AD is promising; however, limitations in measurement may explain previous reports of inconsistences. This study addresses these concerns by examining daily reports of memory lapses, how these vary by age and gender, and their relationship with objective cognitive performance. Overall, this study aims to identify the key features of daily memory lapses and the differential trajectories that best predict cognitive decline to help inform future AD risk screening tools.

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Introduction

Background

Alzheimer disease (AD) is insidious in its onset, with clinically detectable cognitive decline only emerging late in the trajectory [1,2]. Once an individual reaches a diagnostic threshold of cognitive impairment, the functional ability is already negatively affected and a critical period for intervention has been missed [3,4]. Therefore, the period during which cognitive testing is within normal limits but subtle cognitive changes are noticed by older adults, particularly in complex real-world environments, is a crucial target for the prevention or delay of AD onset in individuals at highest risk [2,5]. Self-reports of memory decline, particularly episodic memory, are the earliest and most central deficit of AD [6,7], appearing up to 15 years before objective cognitive deficits [1], and are of high clinical relevance due to the associated functional consequences [8]. Furthermore, report of a cognitive concern is a required criterion for diagnosing mild cognitive impairment (MCI), and problems with memory are specifically associated with the highest risk of progression from MCI to AD [9].

Self-reported Memory Problems and AD Risk

A growing body of evidence demonstrates the importance of memory problem reports in the risk profile for cognitive decline and AD. Cognitively intact older adults who report memory problems are up to four times more likely to develop AD over time than their peers who do not endorse problems [10-15]. Although several longitudinal studies demonstrate an increased risk of AD among older adults with self-reported memory problems, associations between objective cognition and reported memory problems are inconsistent [16,17]. Individuals who report memory problems are a decidedly heterogeneous group; only a subgroup is actually experiencing very early, subtle changes in their objective cognitive functioning that may indicate AD [18]. To distinguish insidious AD symptomology from memory problems because of other causes, it is important to better characterize the earliest cognitive symptoms, specifically examining the relationships between specific features of different types of reported memory problems (eg, prospective and retrospective memory lapses; Figure 1) and objective cognitive outcomes, and to further consider how age and gender (potential contributors to self-schemas that may influence reporting) affect these relationships.

Figure 1. Features of memory lapses by the type of memory problem.

	Prospective memory lapses	**Retrospective memory lapses**
Frequency	How often individuals forget planned activities (eg, taking medications)	How often individuals forget past events or information (eg, someone's name)
Consequences	Forgetting planned activities is irritating or interferes with activities	Forgetting past events or information is irritating or interferes with activities

Daily Self-reported Memory Problems

Traditional measures of memory problems (eg, "Do you have problems with your memory?") are inherently prone to response bias as they often require respondents to report experiences or changes with their memory functioning over long time periods or record a momentary snapshot of global functioning [19]. Historically, these measures do not distinguish between two important *features* of memory problems: the *occurrence* (ie, *frequency*) of problems and their *consequences*, namely, emotional (eg, worry, sadness) or functional (eg, reduction in activities). First, it is critical to understand how often individuals have memory problems. The frequency of memory problems, particularly in daily life, is related to the objective measures of

memory and is higher in individuals with amnestic MCI than in healthy controls [20,21]. In addition, better cardiovascular fitness is associated with fewer forgetting episodes through the hippocampal volume, thereby suggesting a role for brain health in the experience of forgetting [22]. However, the frequency of memory problems is difficult to estimate accurately, given the extended time frames for reporting. Current measures tend to include consequences in questions about the frequency of memory problems, conflating the two and potentially reducing the predictive validity of reported memory problems on objective cognitive outcomes and the risk for AD. When self-reports of memory problems co-occur with general concerns about memory [23] or lower performance in independent activities of daily living (IADL) [15,24,25], the risk of future

cognitive decline and AD is higher than with memory problem reports alone. Self-reported problems with remembering appointments and managing finances are better predictors of cognitive decline than other types of cognitive problems, such as paying attention to a television program [25,26]. Importantly, memory lapses associated with higher levels of consequences may also indicate that an individual is beginning to experience more severe memory problems, that is, memory problems associated with greater functional impairment. Memory problems *of consequence* may be better early indicators of cognitive decline. Assessing memory problems in naturalistic settings using a method that can uncouple occurrence from exposure would allow earlier detection of impaired memory. However, traditional memory lapse measures do not dissociate the consequences of memory problems from the frequency of their occurrence.

In addition to failing to separate frequencies and consequences, few measures assess different *types* of memory problems. Lab-based work suggests that self-reports of retrospective memory problems, or forgetting events from the past, may reflect decrements in the episodic memory, whereas self-reports of prospective memory problems, or forgetting future intentions, may be more closely related to executive functioning deficits [27,28]. Furthermore, prospective memory is associated with several factors key to successful aging, including IADL performance [29,30], quality of life [31], and medication adherence [32]. Although some multi-item assessments include both retrospective and prospective memory problems (eg, memory functioning questionnaire [33] and prospective and retrospective memory questionnaire [34]), these are rarely implemented in large population-based studies examining cognitive decline [35,36]. Given the evidence supporting the differential relationship of memory problem type (ie, retrospective vs prospective) with a variety of cognitive [27,28] and functional outcomes [30,37], it is important to examine how the frequency and consequences of different types of memory problems affect long-term cognitive performance.

Influences of Age and Gender on Self-reported Memory Problems

Another important factor influencing the association between self-reported memory problems and objective cognitive decline is variation because of individual differences. Age and gender are primary nonmodifiable risk factors for AD, but neither of these have been extensively examined for their potential impact on the expression of reported memory problems or their cognitive outcomes [38]. Most research exploring self-reported memory problems is focused exclusively on older adults (ie, ≥65 years) because of the increase in AD risk with age. However, AD neuropathology is known to accumulate over years or even decades before diagnosis [39]. Cognitively intact middle-aged adults who report experiencing memory lapses exhibit structural brain differences consistent with AD as well as poorer memory performance than their peers [40,41]. Age may also play an important role in reports of memory problems because cognitive demands vary at different life stages (eg, before and after retirement), and different meaning is attributed to memory problems during middle age compared with later in life [42]. Depending on the operationalization of memory

problems (eg, frequency and consequences), some studies have found no age effects [43,44], others have found an increase in self-reported memory lapses with age [45,46], and other have found differing nonlinear relationships across middle- and older age [47,48]. Thus, examining the features (ie, frequency and consequences) of different types (ie, retrospective and prospective) of memory problems is key to explicating these aging-related trends.

Although some memory problem features may increase with age, it is unclear how specific memory problems change over time or whether there are differential consequences from middle age to the oldest ages [12]. Older adults may be prone to reporting more serious consequences to memory problems considering increases in frequency over time [49]. Changes in memory performance may elicit anxiety regarding possible cognitive decline or AD or cause a loss of confidence in the ability to perform household activities or IADL [50]. In contrast, it is also possible that the consequences of memory problems decrease with aging, as individuals adapt to changing memory performance and develop appropriate compensation strategies [51]. Changes in memory are expected events among older adults [52]; therefore, they may be less emotionally and functionally burdened by their forgetting than their younger counterparts.

Regarding gender differences, women have a different risk profile for cognitive decline compared with men, including up to twice the risk of developing AD over their lifetime [53] and a more precipitous decline after the onset of a clinically identifiable deficit [54,55]. Gender differences in the rates of self-reported memory lapses are largely unknown; one early study found a higher prevalence in women [56] and another study found a higher prevalence in men [45]. Recent evidence suggests that women may report a greater frequency of memory lapses than men with similar objective cognitive performance [57]. This result may be attributed to a greater overall somatic symptom reporting by women [58]; however, it is critical to distinguish differential symptom reporting in women from illness or disease risk. Major depressive disorder, for example, is more common in women, but profiles of depressive symptom reporting demonstrate no gender differences [59]. The potential differences in the frequency and consequences of reported memory problems by gender are unknown, as are their associations with cognitive decline and AD.

Conceptual Framework

The conceptual model guiding this study (Figure 2) is based on the identified need to disentangle two different aspects of memory problems: *occurrence* (ie, frequency) from functional and emotional *impacts* (ie, consequences), and gauge their unique contributions to the prediction of objective cognitive decline. This conceptual model additionally includes the key individual difference measures of age and gender, which may affect the expression and strength of the relationship between memory problems and cognitive performance. We propose to separate these features of memory problems by measuring memory lapses that occur on a daily basis using intensive, diary assessments that allow participants to provide more details about the memory lapses as they occur in their natural environment.

Figure 2. Conceptual model of this study's aims.
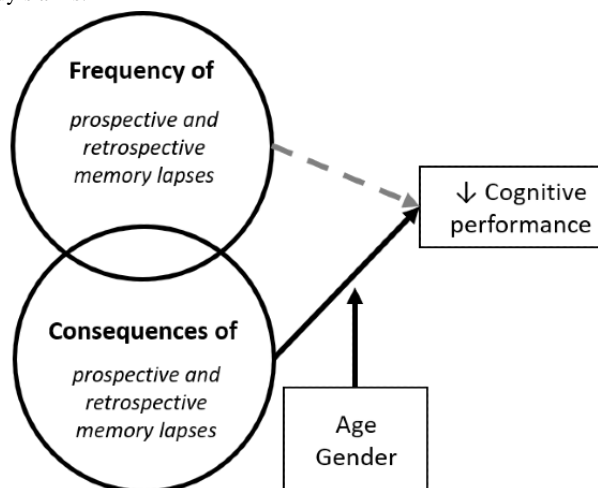
Study Aims

The overall aims of this study are to examine how features of different types of memory lapses relate to objective cognitive performance and whether these associations depend on age or gender. Using a construct-level replication framework across two longitudinal data sets, we will examine the following aims:

- Aim 1: To test whether the frequency or consequences of different types of daily memory lapses (retrospective and prospective) predict decline in cognitive performance. We hypothesize that the consequences of memory lapses, rather than frequency, will better predict future cognitive decline.
- Aim 2: To identify age and gender differences in frequency and consequences of different types of daily memory lapses. We hypothesize that older adults will report more frequent memory lapses but rate these lapses as lower in consequences relative to middle-aged adults. For gender, we hypothesize that women will report more frequent memory lapses and rate memory lapses as having greater consequences compared with men.
- Aim 3: To test whether age or gender moderates the predictive utility of frequency or consequences of different types of daily memory lapses on cognitive decline. We hypothesize that age and gender will moderate the relationship between memory lapses and objective cognitive decline such that cognitive decline will be greatest for women and older adults reporting memory lapses with the highest level of consequences.

Methods

Overview

We will use multilevel modeling (MLM) in coordinated analyses in two measurement burst data sets funded by the National

Institute on Aging (NIA): the Effects of Stress on Cognitive Aging, Physiology, and Emotion (ESCAPE) study [60] and the Einstein Aging Study (EAS) [61]. These data sets include intensive measurement components that are repeated multiple times across longer time frames, providing both daily data to capture the features of different types of daily memory lapses and long-term cognitive change on objective assessments (Multimedia Appendix 1 presents an overview of data collection protocols in ESCAPE and EAS). Critically, the application of MLM to intensive measurement designs such as ESCAPE and EAS permits the evaluation of within-person (ie, differences at the day level) and between-person variations (eg, individual differences), with the key addition of modeling *developmental change*. As participants in these ongoing studies are evaluated repeatedly across years, MLM can further address differences in developmental trajectories, including identifying the profiles of those individuals most at risk for developing cognitive impairment.

Sample Characteristics

Participants in this study must meet the following criteria for inclusion: age 50 years or older, no clinically significant objective memory impairment (ie, MCI or dementia) at baseline, and completion of at least two burst assessments for the longitudinal analysis (Figure 3 shows the flowchart of the current analytical sample in this study). The samples and design characteristics of the data sets are listed in Table 1. The ESCAPE and EAS data sets are recruited through systematic random sampling using a sampling frame from registered voter lists from Bronx, New York, and collected at an academic institution [60].

Figure 3. Sample size from the Effects of Stress on Cognitive Aging, Physiology, and Emotion study and Einstein Aging Study based on the inclusion criteria. EAS: Einstein Aging Study; ESCAPE: Effects of Stress on Cognitive Aging, Physiology, and Emotion.
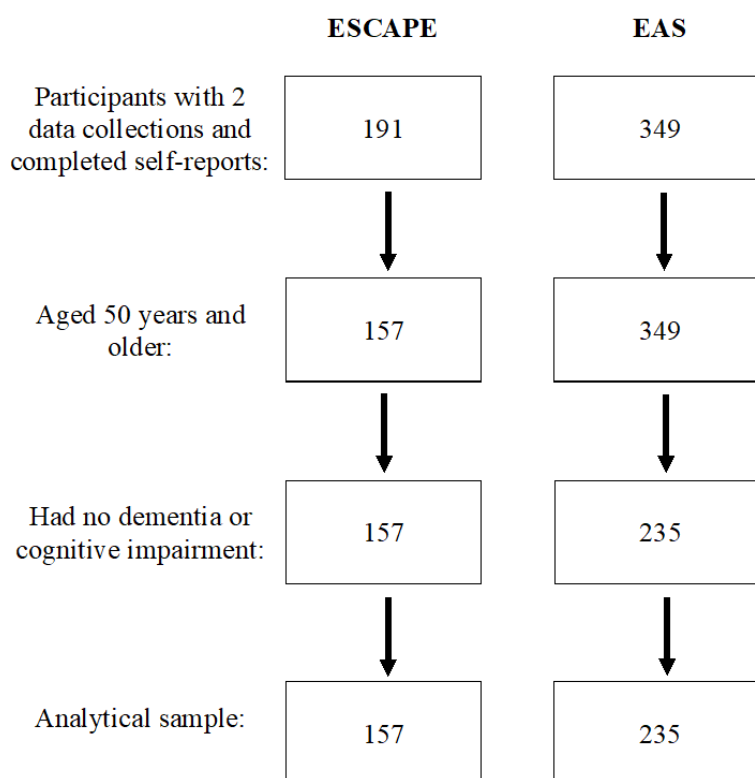

Table 1. Sample and design characteristics.

Characteristics	ESCAPE[a]	EAS[b]
Sample description		
Total sample, n	157	235
Age (years), range	50-65	60-85
Gender: women, n (%)	99 (63.1)	155 (65.9)
Race: Black, n (%)	44 (28.0)	87 (37.0)
Study design		
Daily assessments: possible days, n	14	14
Possible bursts, n	4	4
Possible number of occasions. n	8792	13,160

[a]ESCAPE: Effects of Stress on Cognitive Aging, Physiology, and Emotion.

[b]EAS: Einstein Aging Study.

Designs and Procedures of Selected Data Sets

The included data sets are uniquely suited to our planned analyses because of the use of a measurement burst design and inclusion a measure of daily memory lapses that can be separated into frequency, emotional consequences, and functional consequences by retrospective and prospective memory lapses. Participants in both studies completed electronic daily diaries using a study-provided smartphone that guided participants through data collection and provided a date and time stamp for each observation. These time stamps were critical to assuring that diaries were completed as instructed rather than at the end of the diary period (ie, backward filling) [62,63]. Each study also included extensive cognitive testing (traditional and ambulatory) and a questionnaire battery for physical health and psychological well-being. The primary differences among the study designs were the selection of lab-based assessments for cognition (Textbox 1), psychological well-being, and physical health. ESCAPE finalized the collection in 2019, and data collection in the EAS is ongoing.

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The daily diary design of these projects specifically supports our measurement approach for daily memory lapses. Participants report on their experiences with memory lapses at the end of the day report, and for any memory lapses experienced, they provide additional details on the impact of that lapse. Reporting at the end of the day, rather than over longer time windows, reduces a recall bias in reporting and allows a greater recollection of experiences and their impact.

Textbox 1. Objective cognition measures by study.

Episodic memory

- Effects of Stress on Cognitive Aging, Physiology, and Emotion (ESCAPE) study
  - Paired Associates
  - Spatial Location Memory
  - Auditory Verbal Learning Test

- Einstein Aging Study (EAS)
  - Logical Memory
  - Craft Story
  - Benson Complex Figure

Working memory

- ESCAPE
  - Operation Span
  - Backward Letter Span

- EAS
  - Backward Number Span

Other cognition

- ESCAPE
  - Shipley Vocabulary
  - Ravens Progressive Matrices

- EAS
  - Trails A/B
  - Digit Symbol
  - Wechsler Adult Intelligence Scale Vocabulary
  - Multilingual Naming Test
  - WAIS-III Block Design

Ethics Approval and Consent to Participate

Data collection in the EAS and ESCAPE data sets was approved by the institutional review board at the Albert Einstein College of Medicine, and participants provided written informed consent for participation. This study was approved by the Pennsylvania State University Institutional Board (STUDY00012793 [ESCAPE] and STUDY00017272 [EAS]). Informed consent for this project was waived by the institutional review board because of the exclusive use of secondary data sets.

Measures

Memory Lapses

Both data sets include a measure of daily memory lapses. Retrospective memory lapses are represented by lapses for names, words, past events or information, and where something was placed. Prospective memory lapses are represented by lapses for medications, appointments, chores, and finishing something that was started. For both types of lapses, the participants are asked two follow-up questions. The first asks about emotional consequences (ie, "How much did this bother you?") and the second asks about functional consequences (ie, "How much did this interfere with your activities?"). Both questions are rated on a visual analog scale ranging from 0 to 100.

Objective Cognition

Both data sets include a number of lab-based measures of objective cognition as well as novel ambulatory assessments of cognitive performance. The lab-based assessments include measures of episodic memory, working memory, executive functioning [64,65], vocabulary [66-68], spatial memory [69], and fluid intelligence [70].

Ambulatory objective cognitive tests were administered remotely via smartphones (Figure 4). Participants completed

several trials of these tests up to five times each day at a pseudorandomly determined time (spaced approximately 2-3 hours apart). At each assessment, the participants completed a processing speed and spatial memory test. The processing speed test uses the reaction time as an outcome. The spatial memory test uses an accuracy measure that quantifies the distance between the original and the participant's indicated locations of the dots. The reliability of these assessments exceeds 0.95.

Figure 4. Ambulatory cognitive tests administered via smartphone. Top three images are the spatial memory test (in temporal order), and the bottom image is the processing speed test.
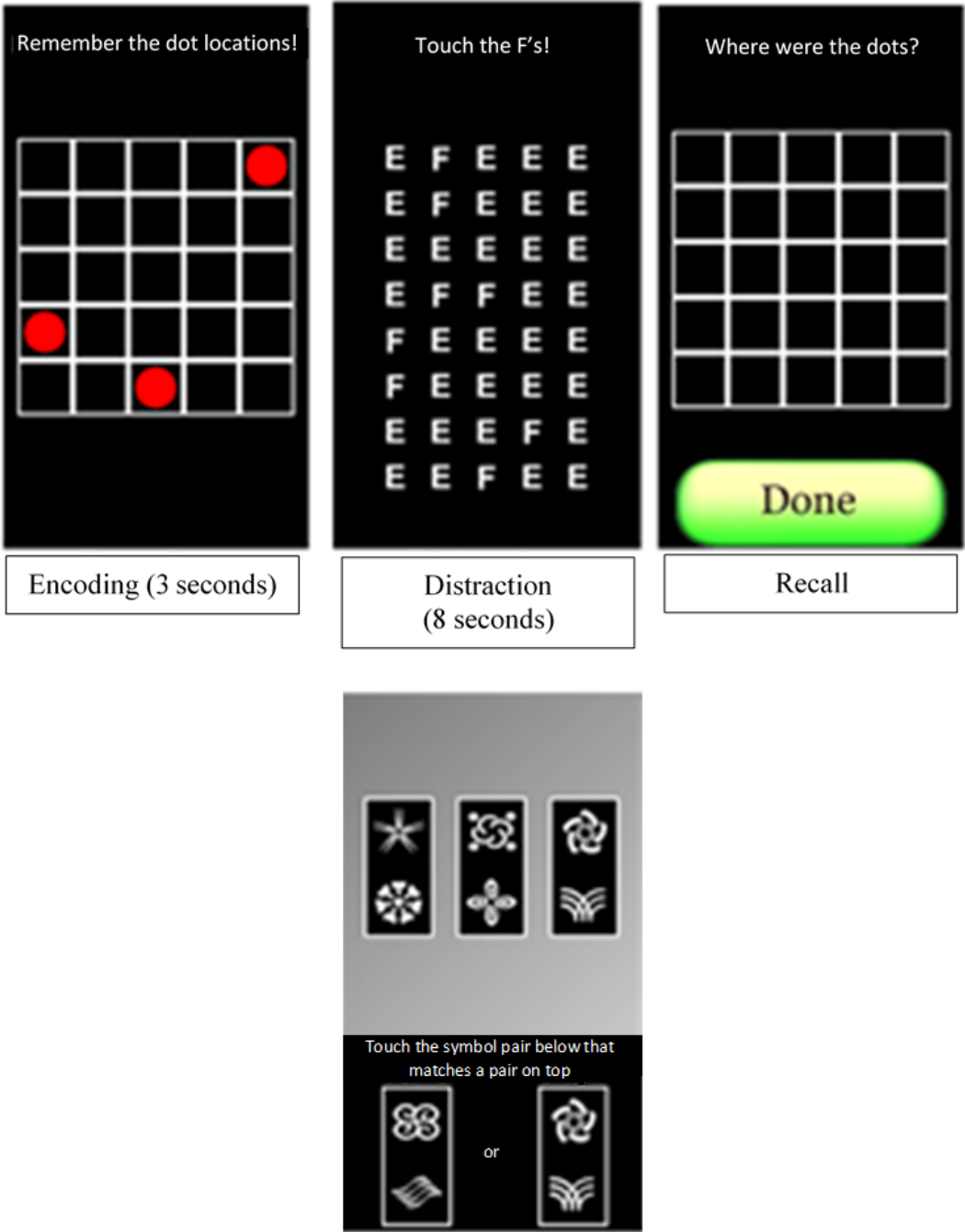
Covariates

Both studies include a detailed medical history questionnaire that can be used to identify medical conditions that may impact

memory functioning, including endocrine disorders (eg, diabetes), cardiovascular diseases (eg, hypertension), and chronic inflammation (eg, arthritis), as well as the measures of depressive and anxiety symptoms to account for contributions

of other psychological symptoms that are related to memory impairment.

Availability of Data and Materials

The EAS and ESCAPE data sets are available from the Albert Einstein College of Medicine, but restrictions apply to the availability of these data. These data sets were used under license for this study, and so they are not publicly available. However, data are available under reasonable request from the authors and with permission of the principal investigators of EAS and ESCAPE as well as their affiliated organizations.

Analysis Plan

We will use three-level MLM to examine which features of daily memory lapses (frequency or consequences of retrospective or prospective lapses) predict future cognitive decline (aim 1); the impact of age and gender on the frequency and consequences of different types of daily memory lapses (aim 2); and, finally, whether age or gender moderates the predictive utility of the frequency or consequences of daily memory lapses on cognitive decline (aim 3). MLM is appropriate when observations are nested, such as in this study's data sets (days in bursts and bursts in persons) [71]. The MLM approach offers an advantage over other types of analytic models for repeated measures data (eg, repeated measures analysis of variance) for two reasons. First, MLM allows us to make use of all available data through maximum likelihood estimation methods rather than excluding individuals who fail to complete some surveys or who drop out of the study at later waves. Second, we can also test for individual differences among our relationships of interest by including random effects. We will explicitly test the underlying hypothesis that the consequences of memory problems that individuals experience in their everyday lives are the most informative for predicting future cognitive decline. Although the frequency of memory lapses is a necessary condition for the consequences of those lapses, we hypothesize that frequent memory lapses are not a sufficient predictor of cognitive decline over time. Analyses will be conducted by JM and JRT with assistance from NLH.

General Approach to Analysis

Across both data sets, we will begin by examining daily correlates of memory lapses to identify the potential confounds in the daily assessments that should be accounted for across analyses. Significant daily predictors of memory lapses will be incorporated into primary analytic models to control for other processes that influence the daily reporting of memory lapses. Potential daily covariates uncovered in the literature include daily stress [72] and physical activity [73].

Operationalization of Daily Memory Lapses

Measures of daily memory lapses across both data sets follow the same general structure with minor differences, allowing us to draw equivalent operationalizations of frequency and consequences across different memory lapse types. For the *frequency* of memory lapses, we will compute the total number of memory lapses over the daily diary period separately for each type of memory lapse (ie, prospective and retrospective). To measure *consequences*, we will use both the average and the maximum ratings across the daily diary period. In addition, we

will separately examine the emotional and functional consequences for each of the different types of memory lapses.

Operationalization of Objective Cognitive Performance

Data from lab-based cognitive tests (eg, Shipley Vocabulary) will be scored using standardized methods. Moreover, data from ambulatory cognitive tests will be used to create scores reflecting each of the following indicators: average performance, upper quintile performance, lower quintile performance, and intraindividual variability. For all objective cognitive performance–based tests, we will first remove any anticipatory (<150 milliseconds) or delayed (>3 SDs above the mean) responses from distributions by examining response times for all trials [74]. After detrending the remaining data for practice effects as in our previous work [75], we will compute the average, lowest quintile, and highest quintile scores for each task for each individual at each burst. We will also compute residualized and raw intraindividual SDs as the indicators of variability in cognitive performance [76-78].

Approach to Coordinated Analysis

Coordinated analysis was selected for this study as it permits the efficient replication of results across data sets to generate stronger substantive conclusions. Moreover, it allows fitting individual models within each data set, testing of covariates, and comparison of the effects of interest across different samples and contexts [79-81]. Using equivalent parameterization ensures that models' effects reflect the same underlying constructs across data sets and standardized estimates will promote the comparison of effects across data sets. We will conduct data set–specific follow-up analyses that focus on additional measures of cognitive performance to ensure the replicability of findings across different operationalizations. All cognitive data will be examined for practice effects before analysis.

Aim 1

Using MLM, we will first examine whether the frequency or consequences of different types of memory lapses covary with cognitive performance over time. This analysis addresses whether at assessments when an individual has a higher frequency of memory lapses (or reports higher levels of consequences), do they have poorer cognitive performance? Next, to test the prospective prediction hypothesis, we will use autoregressive MLM models to test the temporal relationships and determine whether changes in daily memory lapses from previous occasions predict future changes in cognitive performance over time. All models will examine the different features and types of memory lapses.

Aim 2

Potential contributor differences in the experience of daily memory lapses are the individual's age and gender. We will explicitly examine the associations of age and gender with frequency and the consequences of different types of daily memory lapses. When the frequency of memory lapses of different types is the outcome, we will use multilevel Poisson regression models. Poisson regression is the most appropriate when the outcome is count data and when the counts are not normally distributed [82]. Both emotional and functional

consequences were rated on a Likert scale and can be appropriately represented using a normal distribution [83].

Aim 3

For our third aim, we will include age and gender as the moderators of the predictive utility of frequency and consequences of daily memory lapses for predicting changes in cognitive performance. We will extend the analyses in aim 1 to include an interaction term between age at baseline (or gender) and frequency, as well as age at baseline (or gender) and consequences, to predict cognitive performance. We will then examine age and gender moderation for the frequency and consequences of the different types of memory lapses.

Results

This project was funded by the NIA in August 2019 (see Multimedia Appendix 2 for reviews of current protocol) and was approved by the Pennsylvania State University Institutional Review Board (STUDY00012793 [ESCAPE] and STUDY00017272 [EAS]). Data analysis for this study has not yet begun, but data cleaning and preliminary analyses are expected to be completed by January 2021. All aim-specific analyses are expected to be completed by April 2023.

Discussion

Principal Findings

The early and accurate identification of individuals most at risk for cognitive decline, functional impairment, and increased risk of AD is critical for an early intervention. Older adults who report memory problems but do not have objective memory impairment are at a substantially higher risk of AD than those who do not report problems [1,84]. Despite previous work showing that reports of memory problems are sensitive to subtle cognitive decline [35,36], there are potential biases in traditional measures, such as perceptions of normative and nonnormative aging, which limit the clinical utility of these measures in the early detection of cognitive impairment. For example, younger adults are more likely to attribute forgetfulness to emotional difficulties or stress than older adults [42], whereas older adults are more likely to view memory problems as a normal part of aging and less concerning [44,52]. Alternatively, self-reported memory problems may be more salient to older adults [85], particularly given that the fear about AD is common among those who report memory problems [86] and/or have had a family experience with AD [86,87]. Differences between men and women follow a similar, contradictory pattern: some studies have found that women report more memory problems than men [35,53], whereas other studies found that reports of memory problems among men may be more predictive of functional impairment [38,45,88]. The lack of consistency between these results can likely be attributed to issues with traditional measures of self-reported memory problems that require individuals to recollect memory problems over months or years, aggregate

these experiences, and report on them without distinguishing the frequency of experiences from the outcomes associated with the experience (eg, impacts on emotional and daily functioning) [16,89,90]. To increase the specificity of self-reported memory problems, we must refine our measures to account for the frequency and consequences of different types of memory problems.

This study addresses these previous limitations in memory problem assessment by using daily diary data collected in two NIA-funded longitudinal daily diary studies and a novel measure of daily memory lapses. This measure includes retrospective and prospective types of memory lapses and is collected daily over multiple bursts for both studies, which permits the investigation of frequency of occurrence and consequences without relying upon recollection and minimizes potential bias. By disentangling the components of self-reported memory lapses (ie, features and consequences) using daily measures, this project seeks to improve the specificity of memory lapse measures for predicting cognitive decline over time; measures that capture these additional characteristics of memory lapses may be more sensitive for detecting subtle cognitive decline earlier in the aging trajectory. A major strength of this study is the inclusion of potential modifiers of age and sex. Given the conflicting evidence regarding the relationship between self-reported memory lapses and objective measures of cognitive decline, the examination of these individual difference measures is necessary to identify the indicators of future cognitive risk and model varying developmental trajectories. Finally, the design of this study, using two large, representative data sets with up to 30,000 days of data, provides the opportunity for both coordinated analysis and direct construct-level replication.

Conclusions

This study addresses the urgent need [84] to identify the indicators of future cognitive decline risk to inform the development of noninvasive AD risk screening tools and novel intervention targets. Identifying the components associated with the accurate prediction of reported memory problems is necessary to improve assessment specificity and the clinical utility of self-reported memory problems as a symptom. Daily measurements can capture different types of memory lapses that occur, their frequency, and their emotional and functional consequences. Examining these experiences earlier in the aging trajectory and considering individual differences (eg, gender) will establish more sensitive indicators of those adults most at risk, before the onset of functional decrements associated with cognitive decline. Early, easy-to-implement tools for the detection of AD risk are a key component of reducing individual and societal burden. These tools can provide the time needed for patients and families to plan for the future and mobilize resources, evidence to guide the enrichment of samples for future research, and the opportunity to develop tools for use in early intervention trials.

Acknowledgments

Authors' Contributions

JM and NLH conceptualized the study and drafted the manuscript. JRT drafted and revised the manuscript. All authors approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Overview of data collection protocols in the Effects of Stress on Cognitive Aging, Physiology, and Emotion study and Einstein Aging Study.
[PNG File , 30 KB - resprot_v10i5e25233_app1.png]

Multimedia Appendix 2
Redacted National Institute on Aging peer review of this protocol.
[PDF File (Adobe PDF File), 5758 KB - resprot_v10i5e25233_app2.pdf]

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Abbreviations

AD: Alzheimer disease
EAS: Einstein Aging Study
ESCAPE: Effects of Stress on Cognitive Aging, Physiology, and Emotion
IADL: independent activities of daily living
MCI: mild cognitive impairment
MLM: multilevel modeling
NIA: National Institute on Aging

Protocol

Interpersonal Perception of Time-Use Patterns in Romantic Relationships: Protocol for the IP-COUPLES Study

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Abstract

Background: Perceptual congruence has been defined as the level of agreement between partners on various aspects of their shared lives, including perceived engagement in individual and jointly performed activities. While the level of adjustment made by partners to such activities is thought to contribute to a couple's sense of mutuality, perceptions of time use concerning activity engagement has yet to be considered. As such, this study will determine the level of perceptual congruence between partners with respect to perceived time use in their respective and shared activities.

Objective: The primary objective of the IP-COUPLES study is to determine the similarities and differences between partners in terms of their perceptual congruence with respect to independent and jointly performed activities. This study will also examine the association between independent and joint activities in terms of perceptual congruence of time use and the strength of this association.

Methods: This descriptive observational study includes 100 couples from Western Switzerland who are recruited using snowball sampling methods. The Life Balance Inventory (LBI), a self-report questionnaire that captures activity configuration congruence, will measure independent and joint perceptions of both time use allocated to daily activities and corresponding satisfaction. Due to COVID-19, the protocol can be administered virtually by the primary investigator. The mean scores of perceptual congruence variables will be used for analysis, namely perceived congruence of time use in terms of independent and jointly performed activities. For the first objective, an independent *t* test will be used for each variable to compare the mean score between activities on the LBI. For the second objective, the correlations between the mean scores for these activities will be calculated for each variable using the Pearson correlation.

Results: The IP-COUPLES study protocol was developed in 2019 and 2020. Enrollment began in June 2020. Data collection will continue until October 2021 to account for time needed for recruitment due to the COVID-19 pandemic crisis. Analysis and presentation of results are expected in 2022.

Conclusions: This study is exploratory, as it is the first to our knowledge to investigate how perceived time-use patterns with respect to independent or jointly performed activities are similar or different among romantic couples. By investigating the interpersonal perception of time-use patterns among couples, the IP-COUPLES study is an important first step to understanding how romantic partners' daily activities are contributing to the level of satisfaction as a partner and as a couple and to the sense of mutuality between partners in a romantic relationship.

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Introduction

A romantic relationship has been described as a particular form of social interaction between 2 individuals where one of the aims is a mutually satisfactory relationship [1,2]. However, to achieve such satisfaction is a complex process, often requiring behavioral and psychological adjustments to ensure each partner's respective needs and preferences are met in this relationship [3-5]. The notion of "we-ness" has been raised in social psychology in reference to a couple's sense of mutuality. A sense of mutuality often emerges from shared time and experiences over the course of a relationship [6]. However, it is important to clarify that "we-ness" is an interpersonal entity that encompasses both partners [7]. Moreover, "we-ness" also reflects the reciprocity between partners and the ability to accurately and cogently consider the other partner's perspective [8]. Not surprisingly, researchers have postulated couples with a high degree of "we-ness" are more likely to have a more satisfying relationship where the ability to adjust to one another's needs is thought to be a contributing factor to satisfaction [8]. Romantic partners who are better able to connect with their partner's respective experiences report higher rates of marital satisfaction [9,10]. In fact, such connectivity between partners is thought to support the unicity of the couple where patterns in their behavior and communication develop, as reflected in their shared activities or "patterns of doing." While we expect shared ways of doing to be unique to each couple [11], it remains unclear as to how such patterns are reflected in a relationship. In other words, we have yet to fully understand "time use" in a coupled relationship, namely what activities are jointly done as a couple and what activities are independently done by each partner. We aim to further understand how romantic partners respectively and jointly perceive time allocated for independent and shared activities and the sense of satisfaction associated with such perceptions. Such research sets the stage for further study of how couples independently and jointly adjust their activities when navigating changes, such as the onset of medical conditions in one or both partners and the corresponding impact on the relationship and sense of "we-ness."

Time-Use Patterns Among Couples

Kaufmann, a French sociologist, argued that a coupled relationship emerges from the formulation of shared or coconstructed routines [1,2,12]. Hence, such routines are thought to be reflected in a couple's time-use patterns. These patterns are defined as how people "spend and structure their time" within their everyday lives [13]. For those in coupled relationships, we expect time-use patterns to be reflected in both separate and joint activities [14-18]. Thus, everyday activities performed jointly as a couple are thought to contribute to the sense of unicity or mutuality of the relationship in question [11]. Mutuality between partners can also emerge when a partner

adequately adjusts to the needs of the other partner, including those activities one does independently. In fact, each activity, whether independent or done jointly, must consider both the expectations and needs of each partner. Hence, a romantic relationship can require the synchronization of time-use patterns and corresponding activities between partners [13,19]. However, each partner may have a different perspective when it comes to synchronization and the time allocated to such activities. Each partner may have to adjust to the needs of the other partner in terms of the time allocated for particular activities, while also considering his or her own needs.

Previous research examining time-use patterns among romantic couples suggested such patterns can either positively or negatively impact a relationship. For instance, it has been suggested that the time spent together as a couple has a direct influence on the perceived quality of the romantic relationship [18,20]. Joint or collaborative engagement in daily activities, especially those that involve new experiences, have been shown to contribute to the well-being of respective partners [17,19,21] as well as feelings of mutuality as a couple [13,22,23]. Some researchers have suggested couples should spend more time on joint activities [17,19], particularly those activities that are more social or leisure in nature [13,17,19]. Based on the analysis of time diaries of 4043 Belgian couples, Glorieux et al [17] reported that couples spent approximately 53% of their total time together with no significant differences between couples who were married and unmarried, although no information was provided about the duration of the relationship. Sleeping, eating, and watching television were the most commonly identified joint activities. Interestingly, shopping and leisure activities were largely conducted independently. Most shared time was spent in the home, during meals, evenings, and the weekends [17]. Genadek et al [18] found female same-sex couples spent more time on joint activities compared to both heterosexual and male same-sex couples. These results suggest time spent on joint activities can influence the quality of the relationship, which may also correspond to perceived mutuality and to "we-ness." Thus, when partners synchronize their time-use patterns, such synchronization requires each partner to allocate enough time for the other partner's needs for independent activities as well as jointly performed (couple) activities. While it is thought that a couple's mutuality can be strengthened when a partner shares a similar perception in terms of these activities, we do not in fact know the impact of perceptual congruence with respect to time use on their relationship. Hence, examining and understanding similarities and differences in perceived time-use patterns between partners with regard to activities is important given what is known about the impact of time use on relationship quality [13,19,22]. Many studies of time-use patterns [24-26] have considered individuals as singular entities in terms of analyzing their everyday activities when in fact, daily life, for those in partnered (coupled) relationships, requires a complex interplay between individuals and their respective

patterns of engagement. Hence, this study will further our understanding of the similarities and differences between partners in terms of their perceived time use when it comes to their independent and joint activities. The study design and methods for the IP-COUPLES study (Interpersonal Perception of time-use patterns among COUPLES) are based, in part, on the paradigm of interpersonal perception (IP).

Interpersonal Perception (IP): Measuring Perceptual Congruence of Time-Use Patterns Among Couples

IP is defined in social psychology as "reciprocal perceptions" between individuals with regard to various topics, such as affect [27], feelings [28], food preferences [5], job satisfaction, or political opinions [28], between at least two individuals and the degree of congruence between these perceptions [29,30]. Perceptual congruence refers to the degree of agreement between partners' perceptions [31]. It is "…the association between partners' perception of one another" [32]. These perceptions are crucial for the relationship [5,32]. As such, the more partners are congruent in their perceptions of the other partner's activities — for instance, they are able to perceive likes or dislikes in terms of time allocation — the higher their level of mutuality

and satisfaction with the relationship [8,11,31,32]. Studies have also suggested perceptual congruence between partners could be an indicator of problems in the relationship. For instance, each partner has a high degree of accuracy in terms of identifying the perceived needs of their respective partner, yet they are not able to meet these needs, thereby leading to lower rates of marital satisfaction [5,28].

Acitelli et al [33] were among the first to propose a model (see Figure 1) to measure perceptual congruence in a romantic relationship. They identified 3 key variables of perceptual congruence. The first is "perceived similarity," that is, the congruence between a partner's self-perception and his or her perception of the other partner, where one partner's own needs are projected onto the other partner [30]. In this way, there is assumed similarity, which refers to how one partner views the needs of the other partner as similar to oneself and thus, influences his or her perception of the respective partner. The second is "actual similarity," which refers to the actual congruence between each partner's self-perception, and the third is "understanding," which refers to the level of congruence between a partner's perception of the other partner and how the partner in question actually perceives himself or herself.

Figure 1. Reproduction of the model of perceptual congruence from Acitelli et al [33], presenting the 3 variables of perceptual congruence between partners in a romantic relationship. Arrows do not indicate a causal link but a correlation.
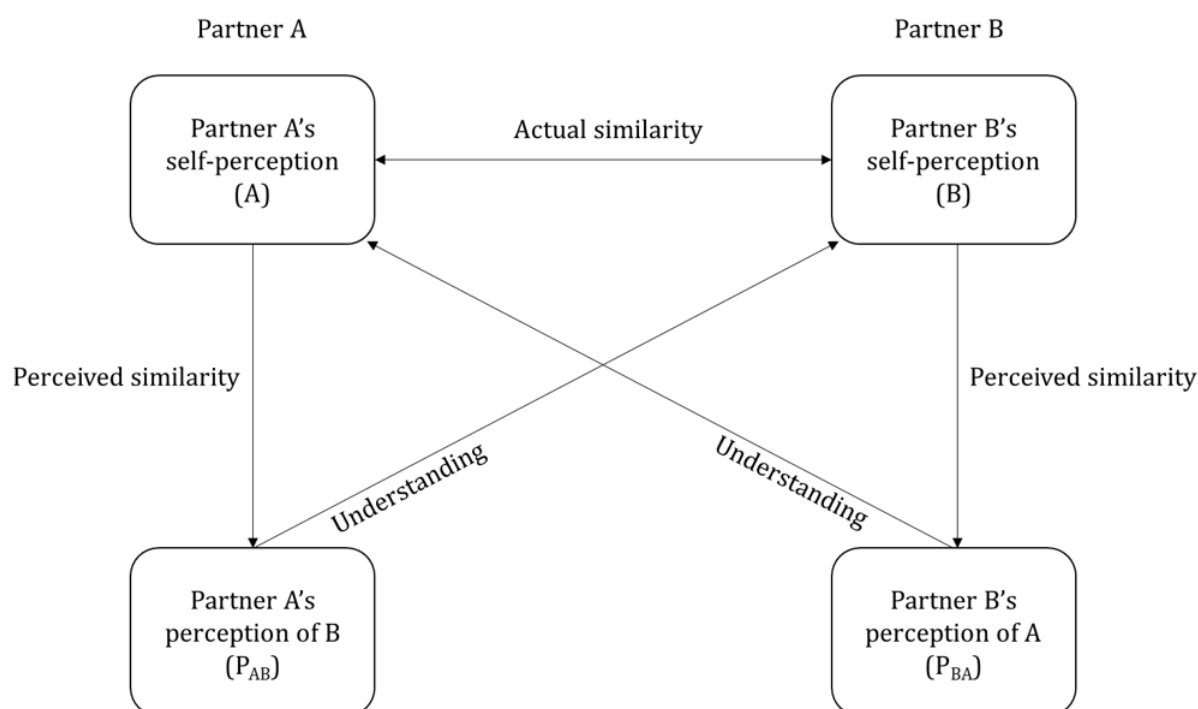
Using this model, studies of romantic couples have identified a significant link between the level of perceptual congruence and dyadic coping [34]. Dyadic coping of a couple is described as the level of interdependence required to address an external stressor. When one partner is experiencing distress, a response is often expected from the other partner. Research indicates that strong perceptual congruence between partners in their dyadic

coping strategies are related to a partner's respective level of satisfaction in the relationship [32].

Using the model put forward by Acitelli et al [33], the current study aims to build on our understanding of perceptual congruence among romantic couples by exploring the link between perceived time-use patterns in terms of individual and shared activities and the sense of mutuality in the relationship.

For this purpose, we operationalize time-use patterns using the Life Balance Model [35,36]. In this model, life balance is defined as the configuration of time allocated to activities that are "healthful, meaningful, and sustainable to an individual within the context of his or her current life circumstances" [20]. The key component of the Life Balance Model is activity configuration congruence (ACC). ACC emerges from time-use patterns, where both the amount of time and corresponding satisfaction (with the time) allocated to daily activities are considered. Optimally, ACC reflects a balance between "one's actual activity configuration in everyday life" and "one's desired activity configuration in everyday life" [37].

The aim of the IP-COUPLES study is to examine perceptual congruence of ACC between partners in a romantic relationship. More specifically, this study will examine the perceived ACC of "independent" activities, as reflected by each partner's ACC score on the Life Balance Inventory (LBI). Once this measure is completed, each partner will then complete his or her perceived ACC of "joint" activities. Finally, the couple will complete the LBI measure together. Consequently, this study will capture the following: (1) how each partner perceives his or her own ACC in relation to his or her own "independent" activities (LBI completed without the other partner), (2) how each partner perceives the ACC of his or her partner's activities that are performed independently (LBI completed without the other partner), (3) how each partner perceives the ACC of joint activities that are performed together as a couple (LBI completed without the other partner), and finally, (4) how each couple jointly perceives ACC of their jointly performed activities (LBI completed together as a couple).

We expect a sense of mutuality to be reflected in the level of perceived congruence between partners in terms of engagement in both independent and joint activities [15,17]. While it is thought that each partner in a romantic relationship must synchronize their time-use patterns to meet each other's needs, it remains unclear if and how perceptions of time use between partners are similar or different from one another as well as how these patterns are perceived as a couple. From our results, we will also determine the association between independent and joint activities in terms of perceptual congruence and the strength of this association. In fact, results may emphasize a need to distinguish between independent and joint activities when designing interventions that address perceived synchronization of time-use patterns between partners. The current study sets the stage for future research focusing on the effect of potential interventions on time-use patterns and mutuality or "we-ness."

Objectives of the Study

The aim of the IP-COUPLES study is to examine the perceptual congruence of ACC among partners that are in a romantic relationship. The primary objective of the IP-COUPLES study is to determine the similarities and differences between partners in terms of their perceptual congruence with regard to time use in both independent and joint activities. As well, this study will examine the association between independent and joint activities in terms of perceptual congruence between partners as well as the strength of this association.

Methods

Study Design

This protocol involves a descriptive observational study that will be undertaken in Western Switzerland. This methodology is observational, meaning the focus is on exploring a specific phenomenon at a given point in time, namely perceptual congruence within romantic couples. Participant recruitment began in July 2020, and the aim is to finish data collection by October 2021.

Sample and Recruitment

Previous studies on the notion of IP in coupled relationships were reviewed to determine the sample size necessary to achieve our intended objectives. To the best of our knowledge, no published studies have investigated time-use patterns in relation to the paradigm of interpersonal perception. We are aware that significant conclusions cannot be drawn due to the expected effect size. A post hoc calculation will be done to counterbalance this limitation. Kenny and Acitelli [28] included 238 married and unmarried couples to measure their perceptions with respect to well-being: feelings of closeness, feelings of caring, equity, enjoyment of sex, and job satisfaction. They calculated the correlation between the partners' actual feelings. The coefficients ranged from 0.47 (job satisfaction) to 0.20 (equity). Vanderbleek et al [38] explored the correlation between couple play and couple satisfaction and stability. From 30 couples, they found coefficients of correlation of 0.70 ($P<.01$) between couple play assessment (CPA) and the satisfaction scale, 0.69 ($P<.01$) between CPA and the communication scale, 0.65 ($P<.01$) between the CPA and the conflict resolution scale, and 0.52 ($P<.01$) between the CPA and the idealistic distortion scale. Finally, Tucker and Anders [39] included 61 undergraduate couples who were dating where they assessed each partner's attachment style, feelings about the relationship, and perceptions of the other partner's feeling about the relationship. The coefficients of correlation for each partner's perceptions of the other partner's feelings about the relationship ranged from a mean of 0.31 ($P<.001$) for men to a mean of 0.41 ($P<.001$) for women. From selected studies, we determined our sample size using Pearson correlation calculations. We calculated a conventional large effect size of 0.5 ($P<.05$). Using the GPower software [40], we determined a sample size of 180 participants or 90 couples. Hence, the current study aims to recruit 100 couples, which is 200 participants in total. The recruitment of an additional 10 couples accounts for potential attrition of participants. Applying a post hoc power analysis on this sample size, a size effect of 0.5 ($P<.05$) gives a power value of 96%. Hence, this sample size is large enough to confirm our hypothesized effect size. Because of difficulties of recruitment due to the COVID-19 pandemic, our plan is to conduct an intermediary analysis. For this analysis, we aim to have 72 couples (144 individuals) to undertake a post hoc calculated power value of 90%.

Participation in this study is voluntary. Western Switzerland is a French-speaking region, which is the primary investigator's native language. The choice to focus our sampling to this country is mainly due to the restrictions in place due to the

COVID-19 pandemic. While we recognize limiting our sample size to this geographic region has consequences on the generalizability of our results, ensuring the contextual elements are similar is important. For example, public health measures in place for this region are likely to affect time-use patterns and activity engagement, and we expect these to be similar for the sample. For participant recruitment, announcements have been published in local newspapers, in e-bulletins, and on websites of associations targeting those who are retired, as well as sports- or cultural-related associations. If necessary, advertisements will be placed in the professional networks of the primary investigator for snowball sampling, which are people who work in health-related fields, such as occupational therapy and social work. The advertisement outlines the title of the study, its objectives, the inclusion criteria, the implications for participants, and how the results will be used. Details are also provided about how to contact the main investigator (RB). Couples who agree to participate in this study contact this investigator by phone or email in accordance with their preference. A brief overview of the study is then provided verbally as well as in writing, including ethical procedures. Inclusion, exclusion, and dropout criteria are reviewed at this time. Couples in which one or both partners require assistance in daily activities are excluded from the current study. The need for assistance may pre-suppose a health issue that could mean that one or both partners are more vulnerable, which can impact the dynamics of the relationship. Ensuring participants are protected from COVID-19 has been considered in the study design. Web-based meetings are strongly encouraged with the main investigator (RB). Finally, informed consent is sent by post or email in accordance with the participants' wishes. Both partners are required to sign the consent form and return a copy to the main investigator.

Inclusion Criteria

The inclusion criteria are cohabiting coupled partners, married and unmarried, where each partner is 18 years or older at time of data collection; the respective partners must consider themselves to be in a romantic relationship; the 2 partners read, understand, and speak French; the partners have lived together in the same residence for at least 1 year; and the couple lives in Western Switzerland at the time of data collection.

Exclusion Criteria

The exclusion criteria are at least one partner has a disease or medical condition that requires assistance of the other partner or another caregiver with daily activities, at least one partner is under legal guardianship, and at least one partner does not give his or her consent to participate in the study.

Dropout Criteria

The dropout criteria are that partners are not able to physically separate from each other during the meeting (eg, move to another room) and therefore can hear each other's responses to the questionnaire, partners exchange answers during the course of data collection, worsening of a partner's health condition that requires the assistance of the other partner or caregiver with daily activities, and at least one partner revokes consent to the study.

Data Collection

Data collection is completed by the first author of the study. Participants are given 2 options with regard to the location for data collection. Originally, the study was designed for an in-person, face-to-face meeting at a physical location chosen by the couple [28]. Because of the COVID-19 pandemic, a videoconference platform (eg, Zoom) is being offered as an option. This virtual alternative prevents a physical meeting with people who may be at risk for COVID-19 or for whom it is impossible to do the meeting outside and safely.

The main questionnaire used in this study is the LBI [35]. The LBI was developed by Matuska, based on the Life Balance Model [37]. It measures the life balance of individuals with respect to time allocated for different daily activities and their level of satisfaction with how their time is allocated for such activities. The LBI tracks time allocation across 53 activities (eg, shopping, driving, participating in groups, relaxing, participating in outdoor activities, working, using a computer, taking care of oneself, playing music, reading). For each activity, participants are asked to indicate yes if they do or if they want to do the activity in question. A participant will indicate no if they do not do or if they do not want to do the activity. If they answer yes, participants are then asked to rate, using a Likert scale, if they are able to spend the amount of time they desire on the activity where "1" indicates less time than desired (ie, "always less than what I want") and "5" indicates more time than desired (ie, "always more than what I want"). The French version of the LBI has been validated [41] and will be used for the current study.

For the purpose of this study, the main investigator (RB) reads each question on the LBI and then lists the different options for participants to respond. To limit loss of data or misunderstanding, participants also have a printed copy of the questionnaire, so they can also read the questions and provide the answers as the questionnaire is administered by the investigator. The order of administration of the LBI is decided by partners at the outset of the initial meeting with the investigator, with one of the partners volunteering to go first. The partner who volunteers to start stays with the investigator (online), while the other partner moves far enough away, preferably to another room where he or she cannot hear any parts of questionnaires as they are administered. If there is no possibility to move to another room, the other partner will be asked to wear headphones (and to listen music if possible) so the sound is muffled.

The first partner to be administered the questionnaires will provide his or her sociodemographic information (eg, his or her age, education). At the second step, he or she completes the LBI a total of 3 times, using a different perspective each time: (1) self-assessment of his or her own ACC for activities that are independently performed, (2) his or her perceptions of how he or she thinks his or her partner would respond with respect to his or her own ACC for these activities, and (3) his or her perception of how he or she might answer when both partners are concurrently responding to the questionnaire concerning the perception of ACC for joint activities. When the first partner completes the LBI from these 3 perspectives, the other partner

then enters the room and follows the same steps. The other partner is also asked to leave the vicinity so as not to overhear administration and responses. In the final step, both partners are brought back together to complete the ACC jointly as a couple. They will also provide some further information about their relationship at this final step: the length of their relationship, the number of children they have together, the ages of the children, and how many children are still living with them.

If a couple withdraws or cannot complete any step of data collection, their data will not be included in the final analysis. As per previous studies, questionnaires will be completed by each partner individually to avoid any discussion between partners concerning their perceptual congruence on any of the activities [28,42].

Statistical Analysis

Statistics will be calculated using IBM SPSS version 25 [43]. For data coding, each couple will randomly be allocated a number. Partners in the couple will also be randomly allocated a letter, "A" or "B." The couple will be referred to as "C." For instance, we will refer to couple "1" as A1, B1, and C1; couple "2" as A2, B2, and C2; and so on. Prior to the analysis, the sample will be first described. The scores of LBI will then be reported as measures for the analysis that will aim to answer the study objectives. We will then do all calculations with the 3 variables of perceptual congruence, as described in the model by Acitelli et al [33]: (1) actual similarity, (2) perceived similarity, and (3) understanding of time-use patterns for activities performed independently and jointly, respectively. Because we expect to have a normally distributed sample, we will do parametric statistical tests.

Analysis

Prior to the analysis, the sample will first be analyzed in terms of their descriptive statistics. Intra- and interindividual central tendency and dispersion of scores will be calculated for (1) each partner's self-perception of his or her ACC for independent activities, (2) each partner's perception of the other partner's ACC for independent activities, (3) each partner's perception of the ACC for joint activities, and (4) each couple's perception of ACC for joint activities.

From the LBI scores, we will determine the different coefficients of the 3 variables that comprise perceptual congruence, as per Actelli et al [33] and the LBI (see Figure 2). Actual similarity between partners (AS_P) is the ratio between 1 partner's self-perception of ACC for his or her activities independently done and the other partner's self-perception of ACC for his or her activities independently done. The actual similarity between one partner and his or her partner (AS_C) is the ratio between one partner's self-perception of ACC for his or her activities independently done and the couple's self-perception of ACC for activities jointly done by partners. Perceived similarity between partners (PS_P) is the ratio between one partner's self-perception of ACC for his or her activities independently done and his or her perception of the other partner's ACC for his or her activities independently done. Perceived similarity between one partner and his or her couple (PS_C) is the ratio between one partner's self-perception of ACC for his or her activities independently done and his or her perception of the of ACC for activities jointly done by partners. Understanding between partners (U_P) is the ratio between one partner's perception of the other partner's ACC for his or her activities independently done and the other partner's self-perception of ACC for his or her activities independently done. Understanding between one partner and his or her couple (U_C) is the ratio between each partner's perception of ACC for activities jointly done by partners and the couple's self-perception of ACC for activities jointly done by partners.

Figure 2. Coefficients of perceptual congruence of time-use patterns among couples that are used for statistical calculations (adapted from the model of Acitelli et al [33]). ACC: activity configuration congruence; LBI: Life Balance Inventory.
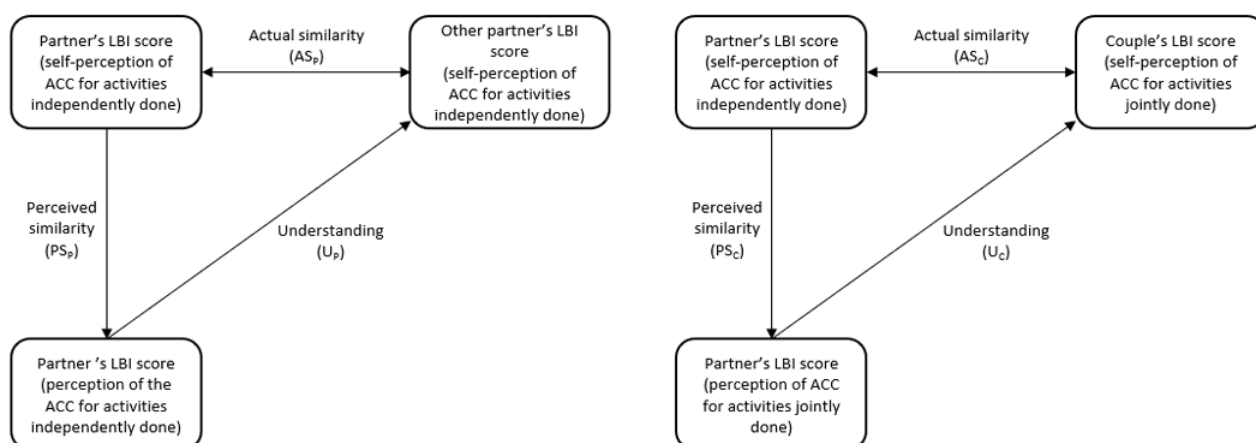
The first objective of the IP-COUPLES study is to determine if there are similarities and differences between partners' perceptual congruence of their independent and joint activities. The mean score of each variable of perceptual congruence will be calculated (1) between partners (AS_P, PS_P, and U_P) and (2) between each person and his or her partner (AS_C, PS_C, and U_C). Comparisons of mean scores will then be done using an independent t test: between AS_P and AS_C, between PS_P and PS_C, and finally, between U_P and U_C.

The second objective is to examine the association between independent and joint activities in terms of perceptual congruence and the strength of this association. Correlations will be calculated for each variable of perceptual congruence using Pearson correlation. Three correlations will be calculated: between AS_P and AS_C, between PS_P and PS_C, and between U_P and U_C.

Data Protection

All collected data will be anonymized. They will be kept for 10 years, in accordance with Swiss recommendations specific to data storage [44]. Data are stored on an encrypted external hard drive of the main investigator disconnected from any network. The data are only shared between members of the authorship team. No specific information is provided to participants nor between partners. They do not receive any analysis of their respective relationship. They can only access the final version of the study where the results are consolidated. The cantonal commission of ethics for research on humans gave its approval for the project (protocol number 2019-00847).

Results

The IP-COUPLES study protocol was developed in 2019 and 2020. Enrollment began in June 2020. Data collection will continue until March 2021, with ongoing adaptations due to the evolving COVID-19 pandemic crisis. Analysis and presentation of results are expected to be available in early 2022.

Prior Analysis

First, the sociodemographic description of the sample will be reported in table format. To facilitate readability, information that concerns all partners as individuals and couples will be presented in 2 tables. A bar graph will then be used to show the central tendency and dispersion of participant scores concerning (1) each partner's self-perception of his or her ACC for his or her independent activities, (2) each partner's perception of the other partner's ACC for his or her independent activities, (3) each partner's perception of the ACC for joint activities, and (4) each couple's perception of ACC for their joint activities. Coefficients of perceptual congruence variables will be presented in 2 tables. The first table will show the coefficients of perceptual congruence between partners' perceptions of ACC for independently done activities, and the second table will present coefficients of perceptual congruence between partners' perceptions of ACC for activities jointly done as a couple and those of the couple.

Study Objectives

Each study objective will be addressed in a separate table displaying the respective results.

Discussion

The current study aims to enhance our understanding of the relationship between mutuality of romantic couples and time spent (ie, time-use patterns), either independently or jointly, on performing everyday activities. This study is exploratory in nature, as it is the first to our knowledge to investigate how time-use patterns of couples and corresponding activities, whether independently or jointly performed, are similarly or differently perceived among partners in a romantic relationship. As previously noted, time-use patterns reflect couples' ways of doing, which contribute to the unicity of the couple. Findings from previous dyadic studies suggest interacting in daily life as a romantic couple affects the level of interdependence, which may be reflected in the activities in which partners engage [15,16]. In other words, the needs of each partner can influence the other's engagement in everyday activities. As such, the way partners perceive their respective partner's level of engagement in daily activities can influence how much they adjust to meet the needs of their partner. In some cases, they may even sacrifice their own needs in terms of their activities to accommodate the needs of their partner. Hence, the degree of adjustment or accommodation has been raised in previous research where the willingness of partners to adjust to each other's needs in terms of activities is thought to strengthen the sense of mutuality experienced by the couple [8,11,31,32]. The current study seeks to further understand the role of perceptual congruence of each partner in terms of engagement in these different types of activities, which remains unclear.

By investigating the interpersonal perception of time-use patterns within couples, the IP-COUPLES study will make an important contribution as to how romantic partners' daily activities contribute to feelings of satisfaction as a partner and as a couple and, in turn, the sense of mutuality between partners. By leveraging existing research on perceptual congruence and its related variables, we will be able to discern similarities and differences in how activities that are independently and jointly performed are perceived. Furthermore, we will go one step further in determining the extent to which each of these perceptions are related. We will also consider if there are significant differences between each variable of perceptual congruence, namely actual similarity, perceived similarity, and understanding [33].

This research sets the stage for future investigations that delve further into the perception of time-use patterns among couples. A next step in the IP-COUPLES study is to investigate the extent to which health-related changes in one or both partners can influence how daily activities are perceived by couples and, in turn, how it may influence feelings of mutuality between partners. Another study emerging from IP-COUPLES could subsequently investigate relationships between marital satisfaction and the degree of mutuality among couples and congruence with each partner's perceptions of time-use patterns as a couple.

The current study should be considered in light of certain limitations. The LBI questionnaire was designed for use by a single participant and not for joint responses as a couple per se. Given there are no questionnaires currently designed to capture joint activities and time use, including satisfaction with such time use, the LBI is the best tool available to be used for this purpose. Hence, our research team will carefully track and record any challenges that arise with regard to administering the LBI in this way. We expect our study will highlight the need to design and validate questionnaires that can be administered in this way, given what is known about co-performance of everyday activities.

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Another potential limitation is related to the COVID-19 pandemic. As a result of the pandemic and public health recommendations for social distancing, a large part of the world's population has been affected by changes in their daily activity patterns. In Switzerland, since March 2020, there has been alternating periods of public restrictions. Hence, responses by participants on the LBI may depend on the restrictions at the time of the interview. However, the focus of the current study is not so much on the activities, as it is on perceptual congruence. Nevertheless, partners may not be aware, or may be even more aware, of one another's activity patterns and engagement. As previously noted, couples recruited for this study are expected to be from the same geographic region in Switzerland. While this sampling approach limits the generalizability of the findings, similar public health measures are expected to be in place in this region. Continuing to collect data and track participants in the IP-COUPLES study with regard to navigating the current pandemic and the postpandemic period is being considered by the study team.

Acknowledgments

Conflicts of Interest

None declared

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Abbreviations

ACC: activity configuration congruence
CPA: couple play assessment
IP: interpersonal perception

LBI: Life Balance Inventory

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Protocol

Assessment of Outcomes of Immediately Loaded Dental Implants in Orofacial Cleft Patients: Protocol for a Single-Arm Clinical Trial

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Abstract

Background: Orofacial cleft, one of the most common congenital deformities, presents with a plethora of defects, subjecting the patient to a multitude of treatments from a young age. Among the oral hard tissue problems, absence of a maxillary permanent tooth in the cleft region either due to congenital absence or extraction due to compromised prognosis is a common finding. Conventionally, the missing tooth is replaced using a removable or fixed partial denture; however, the treatment modality does not satisfactorily meet patient expectations. The most recent decade has seen increasing use of dental implants in the cleft region; however, the outcome of an immediately loaded dental implant is still elusive for orofacial cleft patients.

Objective: This protocol is for a single-arm clinical trial aimed at determining the treatment outcome of immediately loaded dental implants in patients with a nonsyndromic orofacial cleft.

Methods: Patients meeting the set criteria will be sequentially enrolled until a sample size of 30 dental implants is met and will undergo the proposed treatment according to the predecided protocol. All patients will be followed up at the designated time intervals to record various clinical and radiographic parameters. Implant success will be defined based on the criteria elucidated by Misch et al in the Pisa, Italy Consensus. A quality-of-life assessment questionnaire will also be recorded at the end of patient's follow-up to determine their acceptance of the treatment.

Results: A total of 30 dental implants will be placed in patients with a nonsyndromic orofacial cleft. Obtained results will be statistically analyzed to determine the treatment outcomes and success.

Conclusions: This study will help determine the feasibility of immediately loaded dental implants in compromised bone sites such as those presented in cleft patients and will help in generating findings that can be used to fill the lacunae currently present in the holistic treatment of cleft patients.

Trial Registration: Clinical Trial Registry of India CTRI/2020/09/027997; http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=47659&EncHid=&userName=dental%20implants

International Registered Report Identifier (IRRID): PRR1-10.2196/25244

KEYWORDS

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Introduction

Background

Orofacial cleft is the most common congenital anomaly, with an incidence of 1 in 700 to 1 in 1000 live births across different populations [1]. India reports around 28,600 cleft cases every year with a prevalence of 1.09 in 1000 live births [2]. Cleft can be unilateral or bilateral, occurring either alone or a combination of lip and palate, with or without the involvement of the alveolar process. Complete clefting of the lip that involves the full height is often associated with cleft of the alveolus. In addition to compromised aesthetics and disoriented attachment of musculature leading to compromised functionality, these patients also suffer from various dental anomalies [3]. Tooth agenesis affecting the maxillary lateral incisor in the cleft region is the most commonly found anomaly followed by crowding and delayed development [4,5]. All of these defects in cumulation compromise the patient's quality of life, and each case poses a challenge for the multidisciplinary health care team due to the unique presentation.

Prosthetic rehabilitation plays a triple role of improving aesthetics, phonetics, and functionality of the patient [6]. Use of dental implants has increasingly become popular, as they help in maintaining the bone dimensions in the reconstructed region along with provision of improved aesthetics compared to conventional replacement options. Dental implant can be opted for only when the patient has reached skeletal maturity so as to avoid potential growth hindrance. Postinsertion, an implant requires a healing period of 3-6 months to firmly integrate with the underlying bone, which is then adequately loaded with a prosthesis. Considering the long treatment duration and compromised aesthetics already incurred by the patient, it is necessary to develop protocols that help reduce the rehabilitation time. Immediate implant loading is one such measure wherein acceptable initial implant stability enables

implant loading in as little time as 1 week. This would not only decrease time lapse in 2 consecutive rehabilitative procedures but also help improve the patient's psychological acceptance. Most studies presented have performed implant loading after the universally followed protocol of 6 months [7], while a few studies have also demonstrated loading after 3 months [8]. Only 1 study has been conducted so far that presented the results of immediate or early implant loading, but it was a retrospective analysis [8,9].

Aim

The aim of this study is to evaluate the clinical and radiographic success of immediately loaded dental implants in patients with an orofacial cleft.

Objectives

The objectives of the study are to evaluate the placed single dental implant in the cleft region for clinical and radiological parameters 3 months after dental implant placement; evaluate the placed single dental implant in the cleft region for clinical and radiological parameters 9 months after dental implant placement (6 months after definitive prosthesis); and evaluate and compare the placed single dental implant in the cleft region for clinical and radiological parameters 3 months and 9 months after dental implant placement.

Methods

A single arm, prospective clinical trial evaluating the clinical and radiological success of immediately loaded dental implants in orofacial cleft patients will be conducted at the GSR Institute of CranioMaxillofacial & Facial Plastic Surgery, Hyderabad, Telangana, India. Ethical clearance for the clinical trial has been obtained from the Institutional Ethical Committees of the associated institutes. A summary of the methodology is presented in Figure 1.

Figure 1. Summary of the research methodology. CBCT: cone beam computed tomography; IOPAR: intraoral periapical radiograph; ISQ: implant stability quotient; OHI-S: Oral Hygiene Index – Simplified; OPG: orthopantogram; QoL: quality of life; SABG: secondary alveolar bone grafting.
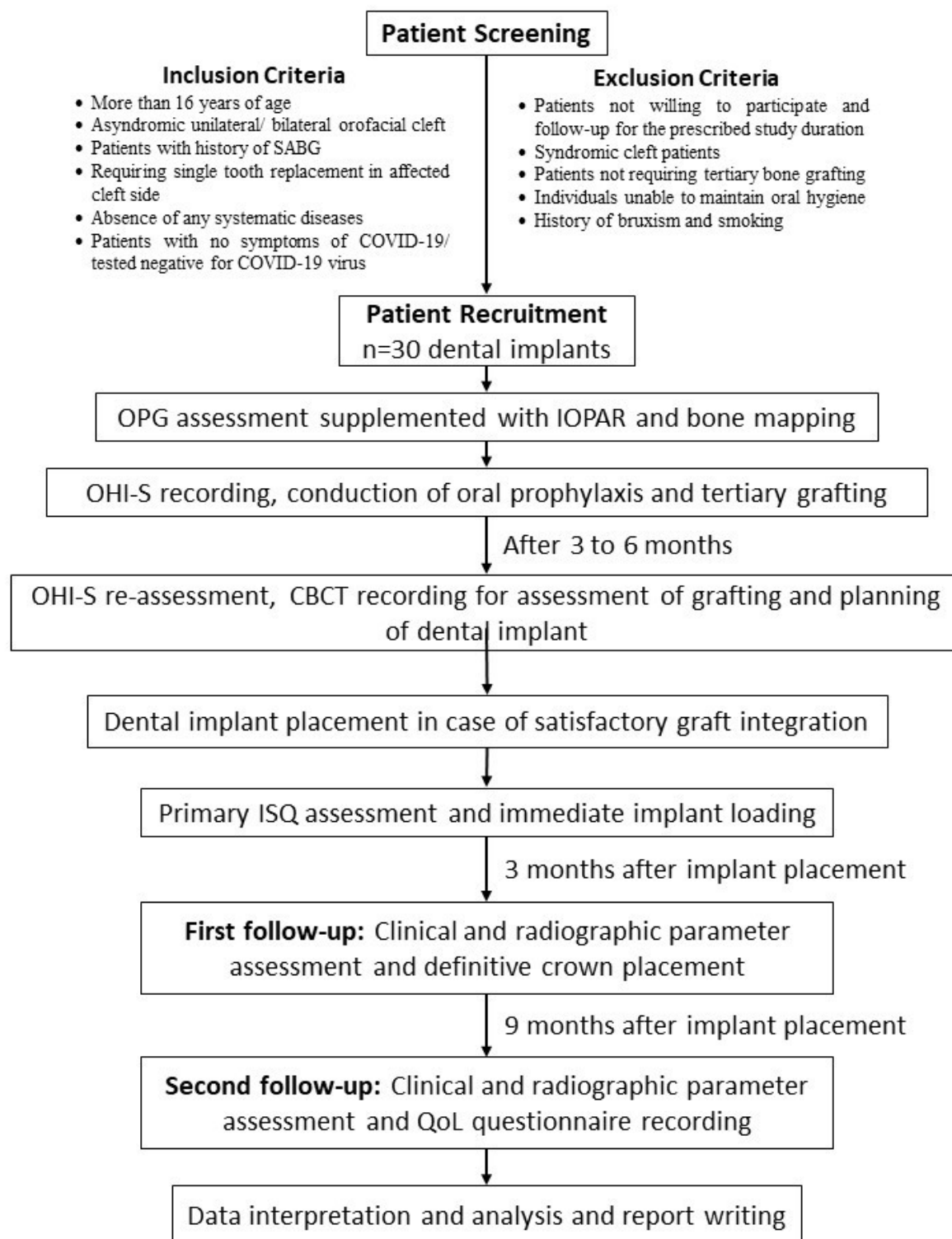
Sample Size Calculation

A recent study showed a success rate of 95% for dental implant–based treatment in cleft patients [10]. With a type I error of 5%, confidence interval of 95%, and 8% margin of error, a sample size of 28 dental implants was obtained. Considering 5% loss to follow-up, an additional 2 dental implants will be placed. Thus, a total sample size of 30 dental implants in sequential patients will be considered for the proposed study.

Patient Selection

Without gender bias, consecutive patients meeting the inclusion and exclusion criteria will be recruited until a sample size of 30 dental implants is met. Signed informed consent to be part of the study will be obtained from the patient or their parent or

guardian. Owing to the global COVID-19 pandemic, thorough COVID-19 history and consent will also be obtained. Institutional COVID-19 standard operating procedures will always be strictly followed. Before the beginning of treatment, each patient will be allotted a unique identification number to be used to designate them henceforth. Complete patient records including intra- and extra-oral photographs of the patients at all stages will be maintained, while maintaining confidentiality.

Inclusion Criteria

To be included in the study, patients will need to be older than 16 years, have an asyndromic orofacial cleft, have a unilateral or bilateral cleft alveolus, have undergone secondary alveolar bone grafting (SABG) between 9 and 12 years of age, require single tooth replacement of the lateral incisor/canine region only on the affected cleft side, not have any systemic diseases, and have no symptoms of COVID-19 or tested negative for SARS-CoV-19 virus.

Exclusion Criteria

Patients will be excluded when they are not willing to participate and follow-up for the prescribed study duration, have a syndromic cleft, do not require tertiary bone grafting, are unable to maintain oral hygiene (patients with a lack of manual dexterity or any kind of hand skeletal deformity), and have a history of bruxism and/or smoking.

Operative Assessment

All patients with a single tooth missing in the cleft area will undergo preoperative screening using an orthopantogram (OPG) supplemented with an intraoral periapical radiograph (IOPAR) and bone mapping to determine the need for tertiary grafting. Prior to tertiary grafting, all patients will have the Oral Hygiene Index-Simplified (OHI-S) recorded followed by conduction of oral prophylaxis [11]. Following standard procedure guidelines, bone grafting will be done by a single operator using either an autologous symphyseal bone graft or iliac bone graft, depending on the amount of bone required [12-14]. Before proceeding with implant surgery, the OHI-S will be re-assessed and compared with the previously recorded observations. This will help to determine the patients' attitudes towards oral health and their motivation towards maintaining oral hygiene. Cone beam computed tomography (CBCT) will be recorded 3-6 months after grafting to evaluate the integration of the grafted bone and plan implant placement. Before proceeding with implant surgery, the OHI-S will be re-assessed and compared with the previously recorded observations. In all patients, titanium dental implants (TitanGrade 4, blasted etched implant surface, Bredent GmbH Co, Senden, Germany) will be placed following a one-stage protocol. Additional bone graft material will be used to ensure complete bony coverage of the dental implant surface, if required. The implants will be placed slightly subcrestally, and the primary implant stability will be clinically evaluated by measuring implant stability quotient (ISQ) values using a Penguin[RFA] device. The obtained values will be interpreted as follows [15]: ISQ ≥70: high initial stability and suitable for immediate loading; ISQ 55-70: moderate stability; ISQ ≤55: low/questionable stability and not suitable for immediate loading. Following the immediate loading protocol, all implants

will be loaded with a provisional prosthesis made of autopolymerizing resin (ie, a provisional prosthesis will be placed within 7 days of dental implant placement) [16]. All patients will be educated about oral hygiene habits to ensure proper care of the placed implant and prosthesis along with use of a 0.12% chlorhexidine rinse for 30 seconds at least twice a day [17].

Follow-Up

All patients will undergo 2 clinical follow ups, 3 months and 9 months after implant placement. At the first follow-up after a period of 3 months following immediate implant loading, the provisional prosthesis will be removed, and clinical and radiological parameters will be measured. Clinical parameters will include probing depth, bleeding on probing, suppuration, pain or tenderness in the implant area, and implant stability using ISQ values. The implant will then be loaded with a definitive prosthesis, and a CBCT will be recorded. A second follow-up will be performed after 6 months of definitive prosthesis placement (ie, a cumulative period of 9 months following implant placement), and all parameters will be assessed as stated previously. At the end of the treatment, all patients will be asked to complete a quality of life (QoL) assessment questionnaire to determine the patient's perspective before and after dental implant treatment.

CBCT recordings will be done using a small sized field of view of approximately 50 mm in diameter, which has an effective dose of approximately 54μSv [18].

Radiograph Interpretation

All recorded radiographs (OPG, IOPAR, and CBCT) will be assessed by 2 investigators. Both the investigators are trained professionals in the field of prosthodontics and oral and maxillofacial surgery, respectively, and have experience of more than 15 years in patient rehabilitation. Before beginning the study, both investigators will be trained in interpreting CBCTs of previously recorded cases that are not related to the current study to practice consistent reading. Each investigator will reassess the recorded radiographs after 1 month to determine intraobserver variability. The findings of the 2 investigators will also be subjected to evaluation of interobserver variability.

Results

IBM SPSS version 23 and R 4.0.3 will be used for statistical analysis. Results will be aimed at determining the clinical and radiographic success of dental implants in patients with a nonsyndromic alveolar cleft. The Cox model of analysis will be used to determine the shared frailty of dental implants in case of bilateral cleft cases. The Kolmogrov-Smirnov test will be applied to determine the normality of the data. Depending on the data distribution, t tests, Wilcoxon tests, and chi-square tests will be utilized to determine statistical significance of clinical and radiological parameters assessed at 3 months and 9 months post implant placement. Binary logistic analysis will be done to compute the predictors of the outcome. CBCTs recorded after dental implant placement will be quantitatively compared to determine the presence of any significant variation in the marginal bone levels. Qualitative assessments of the

radiographs will be done to determine the presence of periapical pathology and any other abnormal radiographic findings. Intra- and inter-observer variability in radiographic assessments will be evaluated by using the Kappa statistic. Statistical significance will be set at $P<.05$.

Implant success will be defined based on the guidelines given by Misch et al [19] in the Pisa, Italy Consensus and as presented in the patient record sheet. Statistical comments on the implant survival rate will be given by calculation of a life table analysis.

Patient Record Sheet

Overview

Documentation of patient details forms an important part of diagnosis, treatment planning, and treatment outcomes. To avoid missing the recording of any details during a patient's examination, it is good practice to have a preformed record sheet that is well thought through and encompasses all the required parameters. This also helps in standardization of the protocol, making future comparisons easier.

Dental implant–based rehabilitation is a precision-driven treatment that requires a careful pretreatment examination and investigations to determine the implant position and dimensions. Essential components of a record sheet for dental implant–based treatment have been highlighted and documented; however, no such standardization has been developed for cleft patients [20]. Thus, the presented patient record sheet is developed with the specific aim of implant-based rehabilitation of orofacial cleft patients (Multimedia Appendix 1). It incorporates patient demographics and clinical and follow-up findings essential for successful treatment outcomes, as described in the following sections.

Patient Demographics

The first part consists of essential patient details such as name, age, gender, contact details, and patient ID along with the type of cleft and its characteristics.

Past Surgical and Other Treatment History

This section helps to determine the patient's previous medical history, associated complications, and any possible allergies. It also records the age of the patient at the time of SABG and the type of bone graft used. This forms an essential component of the record sheet as it helps in knowing the graft characteristics such as origin of the graft, time between grafting, and implant placement.

Prosthetic Considerations

This section focuses on intra-oral findings of the patient, highlighting the dental findings for the purpose of oral rehabilitation. This includes previous history of orthodontic treatment, age at which orthodontic treatment was done, missing teeth in the oral cavity, type of prosthesis previously used by the patient (if any), dentist's and patient's perceptions about the current prosthesis, and arch form characteristics.

Preoperative Assessment

This section records the findings concerning space of the edentulous ridge and corresponding OPG or CBCT findings.

Surgical Assessment

This section includes details concerning tertiary grafting and implant placement procedures.

Follow-Up Findings

In accordance with observations from previously conducted studies, important clinical and radiological parameters have been duly acknowledged in this section. This includes width of keratinized gingival, probing depths, and gingival and plaque index. It also records clinical findings such as bleeding on probing, suppuration, and pain or tenderness in the implant region. Recording of implant stability values using resonance frequency analysis (RFA) has been stressed since it is a noninvasive method and has shown good clinical results in healthy individuals. This is followed by recording of radiographic findings.

Implant Success

The last part enumerates the interpretation of the findings. Provision of this section avoids referring to multiple literature and provides a bird's eye view of the important interpretations in a single frame [19].

QoL Assessment Questionnaire

A QoL assessment questionnaire for the cleft population will be used to record their pre- and post-treatment experience with dental implant–based treatment.

Discussion

Orofacial cleft is one of the most common developmental anomalies with a high global (1 in 700 to 1 in 1000 live births) and Indian (1.09 in 1000 live births) prevalence. In 1991, Verdi et al [21] were the first to employ the use of dental implants in cleft patients. In their findings, they stressed the need for cortical bone and adequate bone height in the required rehabilitation region for successful treatment. Since then, dental implants have been widely used for prosthetic rehabilitation of cleft patients with varying success rates (95.8% to 98.6%) [7,22,23]. In one of the biggest databases published by de Barros et al [24], the authors reported a high survival rate of 98.4% at the end of a 1-year follow-up period. Thus, dental implants provide a promising rehabilitative option for orofacial cleft patients.

All studies conducted so far have warranted a healing period of 3-6 months before undertaking the loading of the placed implant in the cleft site. The grafted bone in the cleft region is shown to have stable bone mineral densities during the period of 3-6 months following grafting, and thus, placing a dental implant in the grafted bone after 3 months of healing is considered adequate for successful treatment [25]. Until now, only 1 work published in 2011 has commented on the potential success of immediately loaded dental implants in orofacial cleft patients, but it was a retrospective analysis [8].

RFA is a relatively new and popular noninvasive technique for evaluating primary implant stability [15]. Due to the lack of immediate loading of dental implants in cleft patients, this technology still hasn't found its application in such patients. Until now, the field of immediately loaded dental implants in

cleft patients has been a barren land with no research conducted at the global level including India, despite the high prevalence of the deformity.

Success of dental implants is not only dependent on the achieved primary stability and subsequent osseointegration but also dictated by the soft tissue condition in the implant region. Cembranos et al [26], in their retrospective analysis of 47 implants, highlighted the importance of periodontal profile assessment along with measurements of bone levels to determine the success of implant-based treatment in cleft patients. Clinical and radiological evaluations of implant and adjacent sites in the form of probing depths, plaque and gingival indices, and marginal bone loss were also given importance in a similar analysis undertaken by Alberga et al [10].

Considering the global prevalence of deformity and lack of research in the field of immediately loaded dental implants in cleft patients, this study is formulated with an aim of evaluating the clinical and radiographic success of dental implant at the cleft site in orofacial cleft patients. At the same time, the proposed work also emphasizes the importance of having a preformed patient record sheet and need for recording various clinical and radiographic parameters and thus, has formulated a dentist-friendly and comprehensive record sheet that will be utilized in the study.

Apart from providing patients with enhanced functionality, replacement of the missing tooth will also enhance a patient's aesthetics and their subsequent self-perception. During any rehabilitative procedure, it is important to know how the patient feels about it and what changes they see in their life pre- and post-treatment. This can be successfully evaluated using a QoL questionnaire. According to Burckhardt and Anderson [27], a QoL questionnaire encompasses details concerning material and physical well-being; relationships with other people; social, community, and civic activities; personal development and fulfilment; and recreation. QoL provides a meaningful way of determining the patient's psychological improvement and making pre- and post-treatment comparisons.

Scope

This study will help identify the success of immediately loaded dental implants for orofacial cleft patients and bring the same to regular clinical practice. Dental implants are a fixed treatment option that represent better functionality and aesthetics over conventional alternatives. Immediate loading of dental implants will not only prevent loss of the generated bone due to early functional stimulation but will also provide immediate aesthetic improvement, leading to an enhanced level of self-confidence of the patients. In cumulation, this will help increase patient's and dentist's acceptability of the treatment along with substantially reducing the treatment time and costs for such patients who have already undergone prolonged treatments since a young age.

Limitations

Being a unique study, the proposed sample size is small compared to the huge prevalence of the deformity. Thus, studies with a larger sample size will be required in the future to give a statistically stronger result. Also, the study is not a case-controlled trial since the bone characteristics found in a cleft patient are difficult to replicate in a healthy individual. Any attempts to do so will lead to an increasing number of bias-related factors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Patient record sheet.
[DOCX File , 90 KB - resprot_v10i5e25244_app1.docx]

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Abbreviations

CBCT: cone beam computed tomography
IOPAR: intraoral periapical radiograph
ISQ: implant stability quotient
OHI-S: Oral Hygiene Index - Simplified
OPG: orthopantogram
QoL: quality of life
RFA: resonance frequency analysis
SABG: secondary alveolar bone grafting

Protocol

Promoting the Mental Health of University Students in China: Protocol for Contextual Assessment to Inform Intervention Design and Adaptation

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Abstract

Background: Chinese students are extremely vulnerable to developing mental illness. The stigma associated with mental illness presents a barrier to seeking help for their mental health.

Objective: The *Linking Hearts—Linking Youth and 'Xin' (hearts)* project is an implementation science project that seeks to reduce mental illness stigma and promote the mental health of university students in Jinan, China. The Linking Hearts project consists of 3 components. In this paper, we outline the protocol for the first component, that is, the contextual assessment and analysis of the mental health needs of university students as the first step to inform the adaptation of an evidence-based intervention to be implemented in Jinan, China.

Methods: Six local universities will participate in the Linking Hearts project. A total of 100 students from each university (n=600) will engage in the contextual assessment through self-report surveys on depression, anxiety, stress, mental health knowledge, and mental health stigma. Quantitative data will be analyzed using several descriptive and inferential analyses via SPSS. A small number of participants (144 students and 144 service providers) will also be engaged in focus groups to assess the socio-environmental contexts of university students' health and availability of mental health resources. Qualitative data will be transcribed verbatim and NVivo will be used for data management. Social network analysis will also be performed using EgoNet.

Results: Linking Hearts was funded in January 2018 for 5 years. The protocol of Linking Hearts and its 3 components was approved by the research ethics boards of all participating institutions in China in November 2018. Canadian institutions that gave approval were Ryerson University (REB2018-455) in January 2019, University of Alberta (Pro00089364), York University (e2019-162) in May 2019, and University of Toronto (RIS37724) in August 2019. Data collection took place upon ethics approval

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and was completed in January 2020. A total of 600 students were surveyed. An additional 147 students and 138 service providers took part in focus groups. Data analysis is ongoing. Results will be published in 2021.

Conclusions: Findings from this contextual assessment and analysis will generate new knowledge on university students' mental health status, mental health knowledge, and resources available for them. These findings will be used to adapt and refine the *Acceptance and Commitment to Empowerment-Linking Youth N'Xin* intervention model. The results of this contextual assessment will be used to inform the adaptation and refinement of the mental health intervention to promote the mental health of Chinese university students in Jinan.

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Introduction

Background

Young people constitute a particularly vulnerable population for the onset of major mental illness [1]. In China, the prevalence of depression and anxiety among children and youths aged 13-26 years ranges from 16% to 24% [2]. The prevalence of depression among Chinese university students is even higher, at approximately 20%-30% [3,4]. A meta-analysis of 10 cross-sectional studies, which together engaged over 30,000 Chinese medical students, reported the prevalence of depression at 29%, anxiety at 21%, suicidal ideation at 11%, and eating disorders at 2% [5]. These statistics suggest that university students in China are experiencing considerable mental health challenges. Academic pressure, achievement expectations, study stress, living away from home amidst many life changes, and ineffective coping strategies were found to be associated with mental distress and psychological disorders such as internet addiction, anxiety, and depression [2-4]. Targeted prevention, early identification, and intervention are critical in light of the increasing evidence on the association between the duration of untreated mental disorders and negative clinical outcomes [6]. In recent years, China has undertaken a significant service reform to expand mental health services beyond specialized hospitals. China's second National Mental Health Work Plan (2015-2020) reconceptualizes mental health services in terms of prevention and promotion, treatment, and rehabilitation, and calls for integrated approaches of intergovernmental collaboration, active participation of community organizations, and proactive engagement of families and employers in promoting collective mental well-being [7]. The National Mental Health Work Plan emphasizes understanding, acceptance, and compassionate support for people living with mental illnesses, which is well aligned with the needs of university students. However, China's existing mental health care systems are faced with numerous complex challenges that impede effective and responsive mental health promotion, prevention, and care. One of the major challenges is related to low or delayed to help-seeking among individuals and families affected by mental illness. Evidence shows that nearly 92% of the individuals diagnosed with mental disorders in China never sought mental health care [8-11]. Delayed help seeking is associated with the stigma of mental illness and low mental health literacy [12,13].

Further, evidence indicates that lay people in China, regardless of education levels, have limited understanding of mental illness and often assign causes of mental illness to individual personality traits and social skills [8]. In addition, mental health services, largely provided at specialized hospitals, are overstretched, and there exists a shortage of trained mental health professionals. All these factors pose tremendous challenges in the health care system to meet the population's growing mental health needs [8]. One study found that 78% of the university health services are managed by student affair offices responsible for civil education and that mental health education is often marginalized [14]. Taken together, finding alternative strategies to meet Chinese university students' mental health needs on campus and in the community is an important priority.

Applying Evidence-Based Interventions in New Contexts

A number of evidence-based strategies have been used in the past to address system-level challenges, promote mental health, reduce stigma, and build capacity in individuals. One particular approach is the use of acceptance and commitment therapy (ACT), which is an evidence-informed, transdiagnostic intervention approach that is grounded on mindfulness [15]. ACT has previously been used with Chinese Canadian populations to reduce depression and adapted to promote mental health and reduce stigma for Asian men [16]. Given the congruency in the ACT processes of acceptance and value-oriented actions with Chinese cultural beliefs, ACT may be a useful intervention approach for adoption by the Chinese university population in Jinan, China.

Another approach that may be effective is group-based empowerment psychoeducation (GEP). This evidence-based approach is an adoption of traditional psychoeducation, whereby education extends beyond the provision of health information to include dialogue and critical reflection on the structural determinants of health and approaches that promote collective empowerment and capacity building among participants [17]. GEP has been successfully utilized in Chinese Canadians and other ethnoracial diasporic communities in previous studies [16]. GEP and ACT work in tandem to promote both individual and collective empowerment, and they reduce the stigma in Chinese university students in Jinan, China [11].

A growing body of evidence suggests that effective application and uptake of an evidence-based intervention must be informed by the contextual needs of the intended new users of the intervention [18,19]. The *Contextual Assessments and Analysis*, co-designed by the original intervention team and the knowledge user team, can provide critical information about the "who," "what," and "how" that are essential to ensure that the adapted intervention is relevant and effective to meet the sociocultural contexts of the intended end users and local stakeholders [20]. The use of mixed methods of quantitative and qualitative data collection and frequent dialogue enables the newly formed intervention team to identify the relevant needs for the users of the intervention, availability of resources and infrastructures, and acceptability of the intervention and implementation approaches [18].

The Linking Hearts Project

The *Linking Hearts—Linking Youth and 'Xin' (hearts)* project is an implementation research undertaken by a Canada-China research partnership. The Linking Hearts team consists of over 30 interdisciplinary Canadian and Chinese researchers. This project is guided by a socio-ecological approach with the theoretical assumption that people's experiences and health are influenced by factors at the individual, organizational, community, and societal levels. Since individuals shape and are shaped by their social contexts and environments, mental health challenges are too complex to be addressed from single-level analyses, and effective mental health interventions must consider multi-level contexts [21].

The objectives of Linking Hearts are to (1) improve access to quality mental health care for university students in Jinan, Shandong Province, China; (2) reduce stigma against mental illness that impedes help-seeking, targeted prevention, early identification, timely treatment, and optimal recovery; (3) improve interdisciplinary collaboration through collective empowerment and capacity building; and (4) advance implementation of science knowledge in the field of community mental health practices/interventions that can be scaled up in other real-life contexts. The overarching goal of Linking Hearts is to evaluate and document the process of intervention implementation and the resultant knowledge uptake by stakeholders and decision makers to transform existing professional capital in health and social care into expanded capacity in mental health care for university students. The processes of adaptation and implementation utilize an integrated, evidence-informed mental health intervention model, namely, acceptance and commitment to empowerment (ACE), which combines concepts and processes from ACT and GEP, and were found to be effective in reducing mental illness stigma and promoting mental health among Asians and other racialized groups in Canada [11]. Specifically, the team will adapt the ACE model into the *Acceptance and Commitment to Empowerment-Linking Youth N' Xin* (ACE-LYNX) for use with university students.

Three Components of the Linking Hearts Project

The Linking Hearts project consists of 3 components: (1) *contextual assessment and analysis* with service providers and students to inform the adaptation of the ACE intervention; (2)

implementation of the refined ACE intervention with service providers and university students; and (3) *integrated knowledge translation* to engage diverse groups of knowledge users throughout all stages of this study. The Linking Hearts project activities are informed by the implementation science RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework of project planning that seeks to improve the sustainability of interventions by examining the reach, effectiveness, acceptability, implementation, and maintenance [22]. This paper describes the protocol of the first component of Linking Hearts, that is, the *contextual assessment and analysis* of mental health needs of Chinese students. In this component, we will engage service providers and university students to explore and identify the common mental health issues faced by students, their mental health literacy, and the contextual factors relevant to their mental health and resilience.

Contextual Assessment of Mental Health Needs

As Linking Hearts is an international multi-interdisciplinary collaborative implementation research and the ACE intervention was developed and tested with Asian and racialized people in Canada, it is critical for the team to first conduct a contextual assessment and analysis of the needs of the students in Jinan. To effectively adapt ACE into the ACE-LYNX intervention for use with university students in Jinan, we will engage service providers and university students from 6 universities to identify the contexts and socio-environmental factors that determine the acceptability, feasibility, and effectiveness of ACE-LYNX. We will assess the psychological, cultural, social, and environmental contexts of university students in Jinan to gain a better understanding of their mental health needs in terms of not only challenges but also the resilience and protective factors of their mental health [23,24]. Knowledge generated from the contextual analysis will inform the adaptation of ACE into ACE-LYNX, a culturally relevant intervention.

Methods

Study Design

The conceptualization of the Linking Hearts Project was developed during a field visit by Canadian team members to Jinan. During this field visit, Canadian team members met with student groups, researchers, service providers at a community health center, and clinicians at the provincial mental health center. When the Linking Hearts Project was funded, the Jinan team also did a field visit to Toronto to meet with clinicians, on-campus counsellors, and community-based service providers to learn about community mental health. After these 2 field visits, the 2 teams held many teleconferences to develop the contextual assessment questions and data collection tools. The Linking Hearts Project was developed collaboratively between academic researchers and knowledge user researchers from Jinan, including counsellors on university campus and clinicians working in the mental health field. This study engages 2 participant populations—service providers and students. The researchers, professors, and service providers who are collaborators will be involved in the outreach and promotion to participants but not in direct recruitment.

Data Collection Tools

The Linking Hearts project and study protocols have been approved by the research ethics boards of all participating institutions in China and Canada. Canadian institutions include Ryerson University (REB 2018-455), University of Toronto (RIS 37724), University of Alberta (Pro00089364), and York University (e2019-162). Informed consent will be obtained from all participants prior to data collection. The team will employ both qualitative and quantitative tools for data collection, including self-reported questionnaires, general response surveys, and focus groups conducted with students and service providers (Table 1).

Table 1. Design of the contextual assessment for each participating university site in Shandong, Jinan, China.

Participants	University 1	University 2	University 3	University 4	University 5	University 6
Students for quantitative survey (n=600)	100	100	100	100	100	100
Sample for qualitative data and focus groups (n=288)						
Students	12	12	12	12	12	12
Service providers	12	12	12	12	12	12

The survey and questionnaire instruments will include the following:

1. Student demographics: To better understand the social, economic, and cultural contexts of the university students whom we will engage in ACE-LYNX training, we will collect information on their background characteristics, program of study and year in program, living arrangement, family history, and family socioeconomic background.
2. Self-reported psychological symptoms: We will use the depression, anxiety, and stress scale (DASS-21), a widely used measure of self-reported mental health symptoms [25]. This measure contains 21 items, with 7 items in each of the 3 subscales intended to evaluate the depression, anxiety, and stress across student populations. Cronbach alpha coefficients of subscales with Chinese university student samples were acceptable, ranging from .72 to .81 in previous research [26]. The DASS-21 subscale totals will be interpreted along with the recommended cut-off scores for the interpretation of mild, moderate, and severe categorical distinctions of mental health symptoms.
3. Mental health literacy: Mental health knowledge and literacy will be evaluated using the mental health knowledge questionnaire (MHKQ) [27]. This measure consists of 20 true and false questions and 5 vignettes designed to evaluate mental health–related knowledge across general mental well-being issues [28]. The response rate of MHKQ in past research with Chinese samples ranged from 19% to 94%, with Cronbach alpha coefficients ranging from .57 to .73 [29]. The overall response rates, as well as individual question response rates, will be assessed in this study.
4. Mental illness stigma: The community attitudes toward mental illness (CAMI) scale is a 40-item questionnaire that measures externalized stigmatizing attitudes toward those with mental illness [30]. These include authoritarianism (viewing those with mental illness as inferior), benevolence (caring for the well-being of those mentally ill), social restrictiveness (seeing those with mental illness as a threat to society), and community ideology (accepting the therapeutic value and inclusion of mentally ill in society). The Cronbach alpha coefficients for subscales of the CAMI were reported to be acceptable, ranging from .60 to .81 in a sample of Asian men [16]. Subscale totals will be used as indicators of mental illness stigma in this study.

In addition to surveys and quantitative measures, participants will also be asked to identify their top mental health concerns, perceptions of the causes of mental illness, and areas of prioritization for service provision and training of health care professionals. We will list mental health resources based on information from the regional research team and advisory committees and ask participants to indicate whether they are aware of or have utilized them personally. In addition, participants will also be asked to list who they would turn to for advice regarding mental health issues. A small number of participants (144 university students and 144 service providers) will be recruited equitably from participating institutions by using stratified random sampling to participate in focus groups to explore (1) participants' perspectives on mental health and mental illness, (2) common mental health needs of university students and the influencing factors, (3) how university students understand and respond to their mental health needs, (4) facilitators and barriers to accessing mental health care, (5) strategies to engage university students in mental health promotion and to improve access to care, and (6) participants' perceived acceptability of the ACE-LYNX intervention to promote mental health among university students.

Participant Populations and Inclusion Criteria

The target populations are health and social care providers and university students at 6 universities in Jinan, Shandong, China. The 6 universities were chosen based on (1) the diversity of the student population, that is, students from local and rural areas, (2) the diversity of disciplines and programs, and (3) their locations in each of the 3 regions within Shandong, China.

University Students

We will recruit 600 participants (100 per university site) to take part in a survey of general mental health-related symptoms, including depression, anxiety, and stress (DASS-21), stigma of mental illness (CAMI), mental health literacy (MHKQ), and mental health resources. Other measures evaluating clinical mental health symptomology were not included, as the purpose of the contextual analysis is to observe trends in mental health and resources supporting mental well-being. Inclusion criteria for participation include students, self-identified as 18 years of age or older, and attending 1 of the 6 partnering universities in Jinan (Table 1). They will also be asked complete the qualitative data collection tool to identify concerns and needs in mental

health care. Survey participants interested in taking part in the follow-up focus group will be entered into a database. We will select 144 participants (24 per university site) to take part in focus groups to gain a deeper understanding of the complex contexts and factors of mental health issues among university students, including social structures and networks of access.

Psychiatric and Nonpsychiatric Health and Social Service Providers

At each university, we will host 2 focus groups (12 people each) with a total of 144 service providers to take part in a needs assessment. Inclusion criteria are service providers who self-identified as 18 years of age or older and provide health care, social care, or supportive services to university students in Jinan. Participants will first complete basic demographics information and information to identify concerns and needs in mental health care. Service providers participating will include psychiatrists, primary care physicians, nurses, social workers, university counsellors, and youth league leaders. Similar to above, focus groups will explore the complex contexts and factors of mental health issues among university students as well as identify training needs.

Participating and Collaborating Organizations

Partner organizations will keep track of and establish a 6-month baseline on quantities and types of services used by students. These organizations will include university counselling centers, individual school/faculty/departments at the 6 partner universities, community hospitals and clinics, and other regional organizations with stakes in the promotion of mental health and well-being of university students. These data will be used to measure reach and effectiveness.

Data Analyses Plan

Quantitative data, including demographic information and descriptive statistics of the psychometric measures, will be tabulated from the student surveys by using SPSS (IBM Corp). Quantitative data will provide descriptive and inferential details regarding mental health trends and identify important resources for students and areas of needs regarding mental health support and service utilization. In addition, these mental health resources, including use of institutional programs and trusted advisors/consultants, will be collected, analyzed, and visualized with social network analysis methods using EgoNet (University of Florida). Qualitative data from focus groups will be transcribed verbatim, and NVivo (QSR International) will be used to aid in data management. We will use both inductive and deductive approaches to analyze the data. We will start with repeated readings of the transcripts to gain a broad understanding of the data. We will then perform line-by-line coding of key themes specific to the ideas articulated by the participants, followed by coding concepts/ideas posed in our research questions and derived from our theoretical understanding [31].

Results

Linking Hearts was funded in January 2018 for 5 years. The protocol of Linking Hearts and its 3 components was approved by the research ethics boards of all participating institutions in China in November 2018. Canadian institutions that gave approval were Ryerson University (REB2018-455) in January 2019, University of Alberta (Pro00089364), York University (e2019-162) in May 2019, and University of Toronto (RIS37724) in August 2019. Data collection took place upon ethics approval and was completed in January 2020. A total of 600 students were surveyed. An additional 147 students and 138 service providers took part in focus groups. Data analysis is ongoing. Results will be published in 2021.

Discussion

The results of the 3 types of data, that is, quantitative, qualitative, and social network, will form the basis of the contextual framework to guide the adaptation of the intervention to best suit the unique contexts and needs of Chinese university students in Jinan. Specifically, they will inform the adaptation of the psychoeducational component of the intervention (Mental Health 101). For example, aggregated survey results and relevant local statistics will be used to highlight the current trends of the mental health status and needs of university students. In addition, thematic analyses from the focus groups will inform the development of case examples used in the mental health education. Findings from the contextual assessment will be made available on the Linking Hearts project website.

Authors' Contributions

JPW and CXJ are the nominated principal investigators of the collaborative grant. MV, ATL, XC, JG, SC, and KPF are the coprincipal investigators of this project. JJWL, MKL, JY, GS, and XW are the coinvestigators of this project. The nominated principal investigators and coprincipal investigators developed the initial protocols funded by the National Science Foundation of China and the Canadian Institutes for Health Research. All team members contributed to the refinement and implementation of the protocols. JPW, JJWL, and XN contributed to the initial draft while all authors reviewed, revised, and approved the final submission.

Conflicts of Interest

None declared.

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Abbreviations

ACE: acceptance and commitment to empowerment
ACE-LYNX: Acceptance and Commitment to Empowerment-Linking Youth N' Xin
ACT: acceptance and commitment therapy
CAMI: community attitudes toward mental illness
DASS-21: depression, anxiety, and stress scale-21 item
GEP: group-based empowerment psychoeducation
MHKQ: mental health knowledge questionnaire

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Protocol

Virtual Overdose Response for People Who Use Opioids Alone: Protocol for a Feasibility and Clinical Trial Study

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Abstract

Background: A recent quarterly report released by Alberta Health reports that on average 2.5 Albertans die every day from accidental overdose deaths, and that between April 1, 2020, and June 30, 2020, the province lost a total of 301 people. In Canada, between January 2016 and March 2020, a total of 16,364 people died due to opioid-related overdose. The World Health Organization reports that 70% of the 0.5 million deaths worldwide caused by drugs are related to opioid overdose. Although supervised consumption sites or safe injection sites have been shown to be effective in reducing the harms associated with the use of illicit substances and increasing uptake of addiction treatment and other health services, there is still significant stigma associated with them, and it is unlikely that all of the people who would benefit from supervised consumption service will ever access a site.

Objective: To help prevent deaths in populations that cannot or will not access physical safer consumption services in Alberta, we propose to provide virtual (telephone-based) overdose response services, staffed by people with lived experience.The primary outcome for this study is uptake of the service as measured by the number of calls to the service. Secondary outcomes will include patterns of use of the phone line (days of the week and time of calls) and outcomes from the calls (number of emergency medical services dispatches for overdoses from the service and the results of those dispatches).

Methods: This phase 1 clinical study is set to officially launch in early May 2020. The service will be available to up to 15 participants who self-disclose as using opioids unobserved and have given informed consent for both data collection and interviews. This group will have access to a toll-free telephone number and be invited to call when they plan to use opioids alone.

Results: The analysis will include mixed methods. To improve the design of the service and ensure safety of all involved, quantitative data will be collected on phone calls and participant health care usage, while qualitative data will be collected from both participants and virtual overdose response operators

Conclusions: This clinical trial aims to test the feasibility of a service that provides virtual overdose response in order to help prevent deaths in populations that cannot or will not access physical supervised consumption services in Alberta.

Trial Registration: ClinicalTrials.gov NCT04391192; https://www.clinicaltrials.gov/ct2/show/NCT04391192

International Registered Report Identifier (IRRID): DERR1-10.2196/20183

KEYWORDS

XSL·FO
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Introduction

Background

Between January 2016 and March 2020, a total of 16,364 individuals across Canada lost their lives to accidental opioid-related poisonings [1]. In 2016, Alberta recorded the third highest number of opioid-related deaths in Canada [2]. A recent report from Alberta Health states that the province totals since the beginning of the opioid crisis have reached upwards of 3139 [3]. The World Health Organization (WHO) reports that 70% of the 0.5 million deaths worldwide caused by drugs are related to opioid overdose [4]. Opioid misuse is one of the most pressing public health problems of our time. Why this has happened is unclear but appears to have come from a number of factors, with prescribing practices being of primary concern.

Alberta had the highest number of defined daily doses of opioids prescribed in 2016, with 7955 per 1000 population. This was over twice as high as that in Quebec (the province with the lowest number per 1000 population) [5]. This represents a small decrease in prescriptions from 2015; however, the high level of prescriptions might have led to an increase in both dependence and addiction in the population with a resulting increase in the related harms. The rate of emergency department visits in Alberta related to opioid use and substance misuse has increased by 41% from 2016 to 2019 [6].

It has been postulated that as opioid prescriptions have become more regulated and more restricted, there has been an increase in demand for black market opioids, and that demand has shifted towards stronger formulations [7,8]. The increase in fentanyl and analogues has a direct impact on overdose rates, as they have come to contaminate a majority of illicit substances. Recent testing demonstrated that 88% of all opioids sold on the street contained fentanyl and only 19% contained the expected substance in any detectable amount, creating a toxic drug supply [9].

In Alberta, to face this mounting overdose crisis, concerted efforts have been made. The Alberta government has increased funding for prevention, treatment, and harm reduction, while also creating new educational tools and convening the Minister's Opioid Emergency Response Committee [10]. There is also work ongoing to educate physicians on safer prescribing practices. The Alberta government, along with Alberta Health Services and the community harm reduction organization, Alberta Community Council on HIV (ACCH), have all actively supported and run a provincewide community-based naloxone program that now dispenses between 8000 and 9000 kits to individuals at risk of overdose each month (internal report, May 2020). These same partners have worked together to successfully apply for federal approval to open multiple supervised consumption service sites in the province. This has included conducting needs assessments in multiple communities in Alberta and applying for and receiving federal exemptions from the federal government.

Supervised consumption service (SCS) locations (sometimes referred to as safe injection sites or safe consumption sites) have been an effective harm reduction technique available since the late 1980s [11]. They have been shown to reduce some of the harms associated with illicit substance use, lowering disease transmission rates and mortality from overdoses [12]. In 7 studies that evaluated overdose harms in people who use supervised consumption services, no death by overdose was reported, and in Vancouver specifically, a 35% reduction in lethal overdoses in the vicinity was reported (this report was prior to 2014, and the current overdose crisis was not a factor during the evaluation) [12]. Despite these interventions, presentations to the emergency departments for overdoses due to opioid poisonings have not declined, demonstrating that more tools are needed.

Unfortunately, even though SCSs have been shown to be very effective in reducing the harms associated with the use of illicit substances and increasing uptake of addiction treatment and other health services [12], there is still significant stigma associated with them. This is demonstrated by the call for a review of the evidence by the Ontario government that was based on vocal objections by the public and claims that SCSs increase drug use [13]. This stigma can make it difficult to establish new sites in neighbourhoods that are experiencing increased harms from illicit substance use. Moreover, it may also make people who use illicit substances reluctant to visit the sites for fear of being seen and identified as someone who uses illicit substances [11], which in turn can potentially impact their personal and professional lives. Stigma impacts visible minorities and women disproportionately and also deters people who are employed and housed from accessing SCSs [11,14].

Further, due to the fact that people are bringing illicit substances into the SCS, an SCS must have a federal exemption in order to legally operate. This approval process can take a significant amount of time and is a further barrier to the establishment of more locations. Due to these factors, it is unlikely that all of the people who would benefit from SCS will ever access a site. Our project addresses this health care gap.

Another barrier to accessing SCSs is the impact of geographic location. Physical SCSs are only statistically effective in reducing mortality within 500 meters of their location [15]. This is of particular significance as the most recent (fourth quarter of 2019) provincial data show that the majority of the opioid-related deaths in the province occur outside of an SCS service areas with suburban and rural communities in Alberta accounting for 81% of overdose-related deaths [3]. SCSs cannot be established in every neighbourhood, and, while multiple analyses demonstrate that SCS are cost effective [16], at an average operation cost of $2.9 million per year, it is cost prohibitive to create SCSs for many of our communities [17]. In Alberta, the gap in care is exacerbated by geographical realities, as there are many people in rural and remote communities for whom SCSs are not supportable. Other barriers to access SCS treatment include the following: access to inhalational supervised consumption services for those who smoke or inhale substances, limited hours of access to some SCSs [18], and management of clients who need to use a substance expeditiously due to substance withdrawal symptoms [19].

The current COVID-19 pandemic guidance suggesting all capable individuals self-isolate and practice social distancing has exacerbated the opioid crises [18]. With more individuals who use substances isolating alone and with the reduction in client capacity for existing SCSs, further innovative interventions are required to support clients.

Evidence for a Technology-Based Approach

Although there is limited information on technology-based harm reduction services, recent literature has demonstrated that clients who are dependent on opioids may be more likely to be retained in opioid agonist treatment [20] when their treatment is offered primarily through telehealth services. According to regulations around opioid agonist treatment, these services are generally video calls through secure technology in a clinic. This demonstrates that clients who use illicit substances will use technology for treatment and suggests that they may also use it for harm reduction. Further, a review from 2015 [21] reported that all illicit drug or alcohol helplines in the published literature have started with moderate call rates but have experienced increases in the call rates, high satisfaction with the call lines, and no negative effects.

Additionally, there are new technologies and services within Canada that have recently launched, including the Lifeguard app and the Brave Be Safe app in the province of British Columbia and a grassroots volunteer run overdose prevention line in Hamilton, Ontario [22-24]. The Lifeguard App requires that people who use drugs push a button once they have used their substances, after which the app will sound an alarm after about a minute has elapsed. Clients using this app are required to push the button once the alarm has sounded; otherwise, emergency services will be contacted. Both the Brave Be Safe app and overdose prevention line require the client to stay on the phone with a volunteer.

Study Plan

To help prevent deaths in populations that cannot or will not access physical SCSs in Alberta, which may disproportionately include women and those who are not able to self-inject [11], we propose providing virtual (telephone-based) overdose response services staffed by people with lived experience (PWLE). Due to COVID-19 and the recent changes in protocols for research, study staff will engage potential participants with the necessary physical distancing precautions and with the highest personal protective equipment standards.

Study Objectives

The primary objective of the study is to establish the feasibility of a virtual overdose response service with PWLE operators.

The secondary objectives of the study will include understanding how the service is used (demographics, timing, number of emergency medical services [EMS] responses); determining the outcomes of calls to the service; and using feedback from clients, peer operators, 911 dispatch, and EMS services to determine improvements to service provision.

Methods

General Design

We designed a small open-label clinical study to demonstrate proof of concept that will follow Consolidated Standards of Reporting Trials (CONSORT) guidelines. We aim to recruit approximately 15 people who are currently using illicit substances, specifically opioids, and those who sometimes use these substances alone. The sample size of 15 balances pragmatic issues (difficulty in recruiting people who are actively using illicit substances) and the need to have a good sample of the population. These participants will be interviewed by the research coordinator (SB) prior to intervention initiation to determine baseline use, history of overdose, and current harm reduction activities. They will then be asked to call the intervention number if they are going to be using alone and the PWLE operator will follow the call (the call flow is documented in Multimedia Appendix 1). Additionally, PWLE will be asked to participate in weekly interviews where the research coordinator will ask about their experience on the phones and to disclose any perceived issues or suggestions for improving the service.

Each time a participant calls the number, the operator will gather (as part of the intervention) the address where the participant is located, their name or pseudonym, and a phone number that can be used as a call back number in case the call is disconnected. The phone line operator will then ask what they planned on using, the method of use, if the participant is using sterile supplies (and provide information on where they can get new supplies in their community), and if they have a naloxone kit (overdose reversal kit) available. They will then inform the participant that they will be checking in on them every 5-10 minutes and if they do not respond, they will call emergency medical services for them.

If the participant responds to each verbal prompt (calling their name) over a minimum of 30 minutes, the operator will let them know that they are disconnecting the call. The operator will offer to connect the participant to other health services, such as the location of new supplies, social services, addiction treatment, and opioid agonist therapy. If the participant fails to respond to a prompt (or the call is disconnected and is not able to be reconnected), the operator will contact 911 and the process for emergency services dispatch will be initiated.

If a participant calls the phone line and a virtual overdose response (VOR) operator is not available to answer their call, the call will go to voicemail where the participant will be prompted to leave their phone number and ID so they can be contacted as soon as possible by the next available operator. The phone line infrastructure will operate such that there will be a total of 4 lines open at all times, meaning the VOR service can accommodate 4 calls simultaneously. Given the nature of the supervision, operators should be able to place participants on hold to either answer a new incoming call or to toggle between calls during the 30-minute supervision period. Each operator will be responsible for tracking by hand which participants are on which line so as to ensure they provide support to the right individuals. All papers or documents created

for the purpose of tracking multiple calls will be destroyed immediately prior to the end of an operator's shift; this does not include the call logs which will be entered into the database on a regular basis.

Because the investigators are building a phone line with the ability to accommodate 4 active lines simultaneously, they will not leave participants unanswered or on hold for any length of time. Instead, if they cannot immediately reach an operator, the call will go to voice mail. This protocol and subsequent software were co-designed with our PWLE advisory group, TELUS (providing in-kind technology support) and the research team.

Recruitment

The site of the study and location of recruitment will be Calgary, Alberta. Study personnel will share details of the study with the following organizations and representatives who make up the advisory team: chapter of Alberta Addicts Who Educate and Advocate Responsibly (AAWEAR), Safeworks (who provide some of the harm reduction in Calgary), the SORCe (community resource center in Calgary), HIV Community Link (a local harm reduction nonprofit organization), and the Calgary Canadian Mental Health Association.

The organizations will be asked if they are willing to share information about the study with clients. Interested participants will be able to contact the study team directly or have the organization's representative contact the study team on their behalf (to simplify the process for the potential participant).

Recruitment commenced in June 2020 and was paused at government request in June 2020. Recruitment is designed to be paused at 4 participants until there have been 15 calls to the phone line. This will allow for changes to the phone line if necessary (due to high volumes at certain times, etc).

The eligibility criteria for clients are the following: able to give informed consent (ie, able to speak and understand English and be over 18 years of age); admission of using opioids nonmedically, including using illicit opioids, using prescription opioids without a current prescription, using doses greater than those prescribed, or using opioids recreationally; access to a phone line in the location they primarily use opioids (this can be a landline or a cell phone); and a resident of Calgary. Meanwhile, the client exclusion criteria are as follows: unable to give informed consent (ie, unable to understand English, under 18 years of age, or otherwise legally unable to give consent), exclusive medical use of opioids, no access to a phone, or not a resident of Calgary.

For peer operators, the eligibility criteria are the following: able to give informed consent (ie, able to speak and understand English and be over 18 years of age) and currently employed as a peer operator for the VOR study. Meanwhile, the exclusion criteria for peer operators are the following: unable to give informed consent (ie, unable to understand English, under 18 years of age, or otherwise legally unable to give consent) or not employed as a peer operator for the VOR study.

Peer operators were hired with a job posting that prioritized individuals with lived experience of substance use and a working knowledge of harm reduction and peer support practice. In all,

10 interviews were conducted, and 7 individuals were hired in late March 2020 so as to ensure sufficient coverage of the phone lines.

Each peer operator participated in over 20 hours of training that included a combination of online (zoom) and in person sessions throughout April, May, and June of 2020. Two local Calgary, Alberta agencies partnered to provide virtual training that covered a range of topics necessary for the project's success, including theory and practice of peer support, recovery-oriented treatment, harm reduction, and phone-based crisis intervention. The research coordinator (SB) and primary investigator (KR) led training on the clinical trial's standard operating procedures and how to use the phone technology.

Further to the training detailed above that we believe helps mitigate harms to individuals working as peer operators, SB, KR, and physician coleads (MT and SG) were available to peer operators for additional support and counsel after difficult calls or shifts. In case a peer operator could not reach supervising staff immediately, they would fill in a post-shift survey that would notify the research team that follow-up with a peer operator was needed. Finally, as an added precaution, it was arranged that peer operators could reach out to Calgary's Distress Centre supervisors for immediate support in case of serious emotional distress.

Enrolment Visit

Client

Normally, the enrolment visit would take place where the potential participants are most comfortable, with preference to the organization that they normally access. However, due to COVID-19 safety precautions, study staff will engage with potential participants only once a screening has taken place and an agreed upon outdoor public space is chosen.

During the enrolment visit, the study personnel will review the information sheet and consent form with the potential participant and screen for eligibility. If the person is eligible and consents to participate, the study personnel will complete the baseline data collection survey.

After the survey is complete, the study personnel will review the information about the phone line and service with the participant and provide the information sheet with the number and reinforce that they should call the line if they are using opiates alone.

Peer Operator

Prior to the first shift on the phone lines, each peer operator will be contacted by KR to discuss participation in the research trial (registered with ClinicalTrials.gov; NCT04391192). The information sheet will be discussed, and consent offered. They will be told they can revoke consent at any time and that participation will not affect their employment.

Service Usage

Client

Participants will dial in to the service number (toll free) when they are using opiates alone. The PWLE operator will follow

the call flow (Multimedia Appendix 1). The PWLE operator will record caller information during the call (Multimedia Appendix 2). There is no limit to the number of times a participant can use the service during their enrolment, each call will be identified by date and time.

PWLE Operator

After each shift, there will be a short survey for each PWLE operator to complete regarding the operator's experience during that shift. The survey will be part of the job to ensure operators are supported appropriately; however, those PWLE operators who have given consent will have these surveys included in the analysis of the study.

Although an overdose during a call is not considered an adverse event and is rather the purpose of the intervention, there will be ongoing monitoring of the resultant 911 dispatch and continual work to ensure appropriate follow-up. The weekly interviews of clients and monitoring of the administrative database to identify opioid overdose emergency visits that occur without use of the intervention may result in information that could be considered adverse events and will be investigated by the research team to understand the context and implications for the project.

Interviews

Client

The participants will all be interviewed weekly by study personnel to gather information on the service (Multimedia Appendix 3).

If administrative data show that a participant attended an emergency department in Alberta or EMS was dispatched to them for an opioid poisoning, the participant will be contacted within a week and interviewed regarding why they did not call the service. The participants will explicitly consent to the study team monitoring administrative data for this purpose.

PWLE Operators

The PWLE operators will be interviewed weekly (Multimedia Appendix 4) during the study. These interviews will focus on the impact on the PWLE operator and process impact.

Ethical Considerations

This study is to be conducted according to International standards of Good Clinical Practice (International Conference on Harmonization guidelines), the Declaration of Helsinki (2008 amendment, Seoul, Korea), applicable government regulations, and institutional research policies and procedures.

This protocol and any amendments have been submitted to a properly constituted independent ethics committees at the University of Alberta, known as the Health Research Ethics Board – Health Panel (HREB), and the University of Calgary, known as the Conjoint Health Research Ethics Board (CHREB), and are in agreement with local legal prescriptions for formal approval of the study conduct. The HREB has given approval under the study ID, Pro00088754, and the CHREB has given approval under the study ID, REB20-1043.

All participants for this study will be provided a consent form describing this study that contains sufficient information for participants to make an informed decision about their participation in this study. This consent form, along with all study materials, has been approved by the HREB. The formal consent of a participant, using the HREB-approved (Pro00088754) and CHREB-approved (REB20-1043) consent form, must be obtained before that participant undergoes any study procedure, and the consent form must be completed by the participant.

Data Collection and Analysis Plan

Collection of all data will be compliant with the Health Information Act of Alberta [25]. Identifiers collected will include the Alberta Health Care number, birth year, and address for the location of each call to the service. All data will be collected originally on paper, transferred into electronic form by the study personnel, and then kept on an encrypted, password-protected laptop. The paper forms will be held in a locked filing cabinet in an office in a secured building.

Analysis Plan

This is a phase 1 study designed to show the feasibility of a peer operator staffed virtual overdose response service, and thus there are no hypotheses being statistically tested.

Interview responses from both recruited participants and peer operators will be analyzed for common themes and any responses that demonstrate a safety concern. Safety concerns will be addressed as soon as they are identified. The interviews will be transcribed and entered into NVivo (QSR International) for coding and theme identification. Analysis will highlight barriers and facilitators to use of the intervention.

Process information will be collected and analyzed for trends in time of call, length of call, location of the participant (consistency), outcome of call EMS call outs, results of EMS call outs, and number of overdoses responded to.

Study Withdrawal and Completion Rates

Any participant can withdraw at any time for any reason, and no further data will be gathered; however, data gathered to that point will not be removed from analysis. Peer operators can withdraw from the study without resigning from the position at any time; however it will be a qualified withdrawal where the previous data are included in the study.

Statistical Plan

All statistics will be descriptive. The investigators will report on how many times each participant calls the line, the time of the calls, and the outcome of the calls.

Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Health Information Act of Alberta. These regulations require a signed consent informing the participant of the following: What protected health information will be collected from participants in this study? Who will have access to that information and why? Who will use or disclose that information? What rights

does the participant have to revoke authorization for use of protected health information?

In the event that a participant revokes authorization to collect or use protected health information, the investigator, KR, by regulation, will retain the ability to use all information collected prior to the revocation of participant authorization.

This study is investigating a novel intervention in a group that can be highly marginalized; therefore, we have formed an advisory council of people with lived experience to provide direction and interpretation of results.

Results

The study was funded in 2019, enrolment opened in June of 2020 and paused in June of 2020. The intervention and study received significant community support, suggesting that it is an acceptable intervention; however, there are no study results available at this time.

Discussion

Due to the physical distancing requirements currently in place due to COVID-19, many organizations are considering novel, virtual health care services. The timing of this study, which will provide vital information about providing overdose response to people who use substances alone, could not be better. This model of care does not replace the care and services provided in physical supervised consumption services, where clients can receive sterile supplies, overdose response kits, and some health care. However, this type of service is low barrier and innovative and may reach people who will not or cannot use physical supervised consumption services due to a myriad of reasons.

Authors' Contributions

SB drafted and edited the publication. SG designed the protocol, and reviewed and edited the manuscript. MT designed the protocol, and reviewed and edited the publication. CW reviewed and edited the manuscript. The Canadian Mental Health Association-Calgary Region reviewed the protocol. KR designed the protocol, is the principal investigator, and reviewed and edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Call flow for VOR participant and nonparticipant calls.
[PDF File (Adobe PDF File), 60 KB - resprot_v10i5e20183_app1.pdf]

Multimedia Appendix 2
Call logs for participant calls, completed by VOR operators.
[PDF File (Adobe PDF File), 177 KB - resprot_v10i5e20183_app2.pdf]

Multimedia Appendix 3
Participant interview guide.
[PDF File (Adobe PDF File), 128 KB - resprot_v10i5e20183_app3.pdf]

Multimedia Appendix 4
Operator interview guide.
[PDF File (Adobe PDF File), 93 KB - resprot_v10i5e20183_app4.pdf]

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Abbreviations

AAWEAR: Alberta Addicts Who Educate and Advocate Responsibly
ACCH: Alberta Community Council on HIV
CHREB: Conjoint Health Ethics Research Board
CONSORT: Consolidated Standards of Reporting Trials
EMS: emergency medical services
HREB: Health Research Ethics Board
PWLE: people with lived experience
SCS: supervised consumption services
WHO: World Health Organization
VOR: virtual overdose response

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<u>Protocol</u>

A National Comparative Investigation of Twins With Congenital Heart Defects for Neurodevelopmental Outcomes and Quality of Life (Same Same, but Different?): Protocol for a Prospective Observational Study

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Abstract

Background: Due to the increased survival rates of patients with congenital heart defects (CHD), associated disorders are an increasing focus of research. Existing studies figured out an association between CHD and its treatment, and neurodevelopmental outcomes including motor competence impairments. All these studies, however, compared their test results with reference values or results of healthy control groups. This comparison is influenced by socioeconomic and genetic aspects, which do have a known impact on neurodevelopmental outcomes.

Objective: This study protocol describes a setting that aims to find out the role of CHD and its treatments on neurodevelopmental outcomes, excluding socioeconomic and genetic aspects. Only a twin comparison provides the possibility to exclude these confounding factors.

Methods: In a German-wide prospective cohort study, 129 twin siblings registered in the National Register for Congenital Heart Defects will undergo testing on cognitive function (Wechsler Intelligence Tests age-dependent: Wechsler Adult Intelligence Scale, fourth edition; Wechsler Intelligence Scale for Children, fifth edition; and Wechsler Preschool and Primary Scale of Intelligence, fourth edition) and motor competence (Movement Assessment Battery for Children, second edition). Additionally, the self-reported health-related quality of life (KINDL-R for children, Short Form 36 for adults) and the parent-reported strength and difficulties of the children (Strength and Difficulties Questionnaire, German version) will be assessed by standardized questionnaires. CHD data on the specific diagnosis, surgeries, transcatheter procedures, and additional medical information will be received from patient records.

Results: The approval of the Medical Ethics Committee Charité Mitte was obtained in June 2018. After getting funded in April 2019, the first enrollment was in August 2019. The study is still ongoing until June 2022. Final results are expected in 2022.

Conclusions: This study protocol provides an overview of the study design's technical details, offering an option to exclude confounding factors on neurodevelopmental outcomes in patients with CHD. This will enable a specific analysis focusing on CHD and clinical treatments to differentiate in terms of neurodevelopmental outcomes of patients with CHD compared to twin siblings with healthy hearts. Finally, we aim to clearly define what is important to prevent patients with CHD in terms of neurodevelopmental impairments to be able to develop targeted prevention strategies for patients with CHD.

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Introduction

Congenital heart defects (CHD) are the most common congenital malformation and are associated with increased morbidity and mortality [1,2]. Based on the medical progress made in recent decades in the fields of prenatal diagnostics, pediatric cardiology, and heart surgery, mortality has been substantially reduced, and life expectancy has increased significantly [1,3,4]. Therefore, currently, more than 90% of children with CHD reach adulthood [1,5-7]. Thus, a major scientific focus lies on the clinical outcome and especially on neurologic concomitant diseases or sequela. Newborns with a CHD are already considered to be at risk of often starting with acidosis and low Apgar levels after delivery. After birth, acute initial oxygen deficiency, low cardiac output, and cyanosis are risk factors as are medical interventions such as surgery, transcatheter interventions, or other invasive medical procedures that may influence the developing brain [8-10].

Several studies on patients with CHD after surgery have shown that neurodevelopment, including motor competence, is significantly impaired compared to healthy controls [9,11-14]. Although it seems obvious to consider the heart defect and its treatment consequences as the main cause of this difference, the patient's genetic predisposition, individual support, and socioeconomic factors play a central role in cognitive development as well [15,16]; it is, however, not known to what extent. How would the same child have developed without the CHD? Theoretically, these influences could be differentiated, comparing patients with CHD with healthy volunteers who have the same genetic predisposition and the same socioeconomic environment. In a practical approximation, our study on twins of whom only one sibling has CHD tries to differentiate the influence of heart defects and medical treatment on one hand from genetic predisposition and environmental factors on the other hand, focusing on neurodevelopmental outcome.

Methods

Study

This study is a national, German-wide prospective cohort study investigating twin siblings with at least one having a CHD. They are registered in the National Register for Congenital Heart Defects (NRCHD), the largest register for patients with CHD in Europe [17]. The inclusion takes place by written information sheets and an invitation to participate (see Figure 1). Participation in the study is voluntary and only takes place after the participants or, in the case of minors, their parents have given their written consent.

Figure 1. Flowchart of recruitment and implementation. IPAQ: International Physical Activity Questionnaire; M-ABC: Movement Assessment Battery for Children; SDQ: Strength and Difficulties Questionnaire, German version; SF-36: Short Form 36; WAIS-IV: Wechsler Adult Intelligence Scale, fourth edition; WISC V: Wechsler Intelligence Scale for Children, fifth edition; WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence, fourth edition.
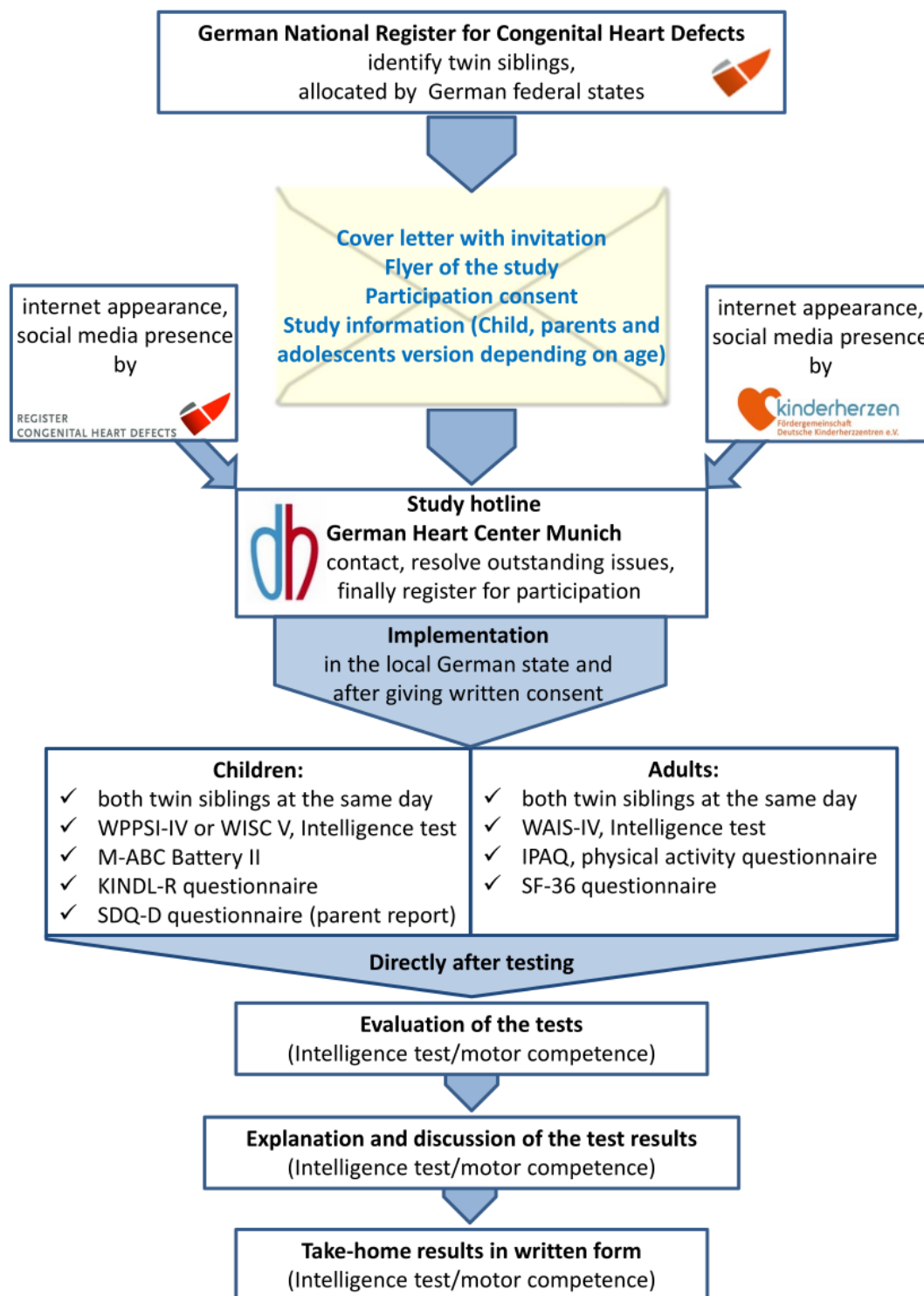
Participants

The study population consists of patients with CHD and their twin siblings as well as both twins having CHD. To enable the participation of as many twins as possible, to keep the effort for the participants as low as possible, and to offer optimal test conditions with short travel distances and the same test settings,

the tests are carried out at regional test facilities performed by one single investigator for all the tests throughout Germany.

Inclusion Criteria

The inclusion criteria were the following: all kinds of CHD (this includes all cardiac diagnoses defined by the International Paediatric and Congenital Cardiac Code [18]), age between

3-99 years, and both twins or their parents agreeing to participate.

Exclusion Criteria

The exclusion criteria were the following: surgery or interventional treatments within the last 6 month, massive mental retardation (to avoid a selection bias, all patients who wish to participate are admitted; if testing is not possible due to massive mental retardation, the twin siblings are excluded from the analysis but recorded as "drop-outs"), other medical examinations on the test day, or insufficient language skills (German).

Procedure

Primary Outcome

Wechsler Intelligence Test

The Wechsler Intelligence Test is designed for three age groups to assess cognitive function. The current version of the Wechsler Preschool and Primary Scale of Intelligence, fourth edition [19] is used for children aged 3-7 years, and the Wechsler Intelligence Scale for Children, fifth edition [20] is intended for children and young people aged 6-16 years. Finally, the Wechsler Adult Intelligence Scale, fourth edition [21] is an intelligence test for adolescents and adults within an age range of 16-99 years.

These tests consist of 10 subtest groups, which results in IQs for the four competence areas (working memory IQ, verbal comprehension IQ, processing speed IQ, and perceptual logical thinking IQ) and a full-scale IQ calculated using the results of all subtest groups.

Motor Competence

For the evaluation of motor competence, the Movement Assessment Battery for Children, second edition (M-ABC 2) [22] is used. It is a standardized test for assessing the motor competence of children aged 3-16.9 years. The M-ABC 2 is divided into three competence groups according to age (first: 3-6 years; second: 7-10 years; third: 11-16 years) and thus adequately records the three competence categories: manual dexterity (consisting of 3 tests), ball skill (consisting of 2 tests), and balance (consisting of 3 tests).

The total test value, consisting of all three areas, represents motor competence [23].

International Physical Activity Questionnaire

To measure adult participants' physical activities in everyday life, the International Physical Activity Questionnaire (IPAQ) [24] for adult patients will be used, due to there being no international standardized motor assessment battery for adults. The test results are categorized into three activity levels:

1. Health-promoting active (vigorous intensity activity on at least 3 days achieving a minimum of at least 1500 metabolic equivalent task [MET] minutes per week or 7 days of any combination of walking, moderate intensity, or vigorous intensity activities achieving a minimum of at least 3000 MET minutes per week)

2. Minimally active (3 or more days of vigorous activity of at least 20 minutes per day; 5 or more days of moderate intensity activity or walking of at least 30 minutes per day; or 5 or more days of any combination of walking, moderate intensity, or vigorous intensity activities achieving a minimum of at least 600 MET minutes per week)

3. Inactive (no activity reported or some activity reported but not enough to meet *health-enhancing physical active* or *minimally active*) [25]

The IPAQ is closely correlated with the results of spiroergometry [25].

Secondary Outcome

KINDL-R Questionnaire to Assess the Health-Related Quality of Life

To assess the health-related quality of life, parents (for preschool age children) and children receive the KINDL-R questionnaire [26], which they fill in independently. This is a multidimensional generic instrument for recording health-related quality of life. There are three versions for the corresponding age groups (first: 3-6 years; second: 7-12 years; third: 13-17 years); these comprise 24 questions, and validation has already been carried out [26].

Short Form 36 Questionnaire for Measuring Health-Related Quality of Life in Adults

The Short Form 36 (SF-36) consists of 36 questions and is a general health questionnaire that allows statements about the patient's health status using means of 8 different dimensions [27]. It makes statements about general health perception (5 questions), physical health (10 questions), limited physical role function (4 questions), physical pain (2 questions), vitality (4 questions), mental health (5 questions), limited emotional role function (3 questions), and social functioning (2 questions).

The possible score ranges from 0 to 100 points. Zero points represent the worst quality of life value in terms of health, while 100 points describe the best possible state of health. Bullinger and Kirchberger [27] validated the German version, and the SF-36 is used to evaluate individual patients' health status and monitor and compare disease burden with an acceptable internal consistency [28]. Therefore, it is used worldwide and is a well-established questionnaire, which is used in various fields of medicine, with great clinical relevance and is available in over 170 languages.

Strength and Difficulties Questionnaire

The Strength and Difficulties Questionnaire, German version (SDQ-D) [29] assesses behavioral problems and strengths in children and young people aged 4-17 years, and it is available in over 75 languages. The two-page parent-reported questionnaire contains a total of 25 characteristics, 10 of which are positive, 14 negative, and 1 neutral, and asks about problematic experiences of the child.

The SDQ-D measures the scales emotional problems, conduct problems, hyperactivity, behavioral problems with peers, and prosocial behavior.

From these scale scores, a total problem score is calculated, ranging in value from 0 to 40. Validation and updating of age-specific German reference values by Robert-Koch Institute published in 2020 [30].

Data Handling

Since the study participants come from the NRCHD and the data processing takes place under the umbrella of the NRCHD, the study is subject to the data protection concept established in the NRCHD. All study participants already have a pseudonym and a randomly generated number as a result of their participation in the NRCHD. The latter is used to identify the questionnaires. The data obtained are stored separately from the personal identifying data under the aforementioned pseudonym. All information and data remain within the jurisdiction of the NRCHD. People outside this area, except for the study directors, have no access to the data. The study director conducts the tests personally.

The collection and storage of all data are carried out following the NRCHD's data protection concept, which is registered with the Berlin Commissioner for Data Protection and Freedom of Information (No. 531.390). The study directors receive the data for statistical evaluation for a limited time and without direct reference to the participating persons. In addition, only NRCHD employees who are bound to secrecy have access to the data. The data collected via German Heart Center Munich are stored on hospital servers and only the research team has access. Data transfer between NRCHD and German Heart Center Munich takes place in person or a password-protected version. The written consent and collected data will be stored separately for 10 years after the end of the study. At the end of the study, both the participants and the funding agency will be informed about the results.

Statistical Analysis

Power Analysis and Sample Size

Due to the explorative character of the study and the, so far, unknown prevalence of CHD in twin siblings in Germany or in any other country, this makes adequate case number planning difficult. Using G*Power analysis for "a priori required sample size" for student t test with paired samples with a medium effect size (0.5), a power set to 0.95, and an alpha error probability set to .05, we ended up with a total number of 54 twins. However, this study aims for a total survey of twins with CHD living in Germany. Based on previous experience, a conservative estimate of at least 50% inclusion can be expected, that is, 129 pairs of twins from 259 twins recorded in the NRCHD throughout Germany (as of February 2018).

Primary and Secondary Analysis

The planned primary and secondary analysis are displayed in Figure 2.

Figure 2. Planned statistical analysis. CHD: congenital heart defects; SDQ-D: Strength and Difficulties Questionnaire, German version.
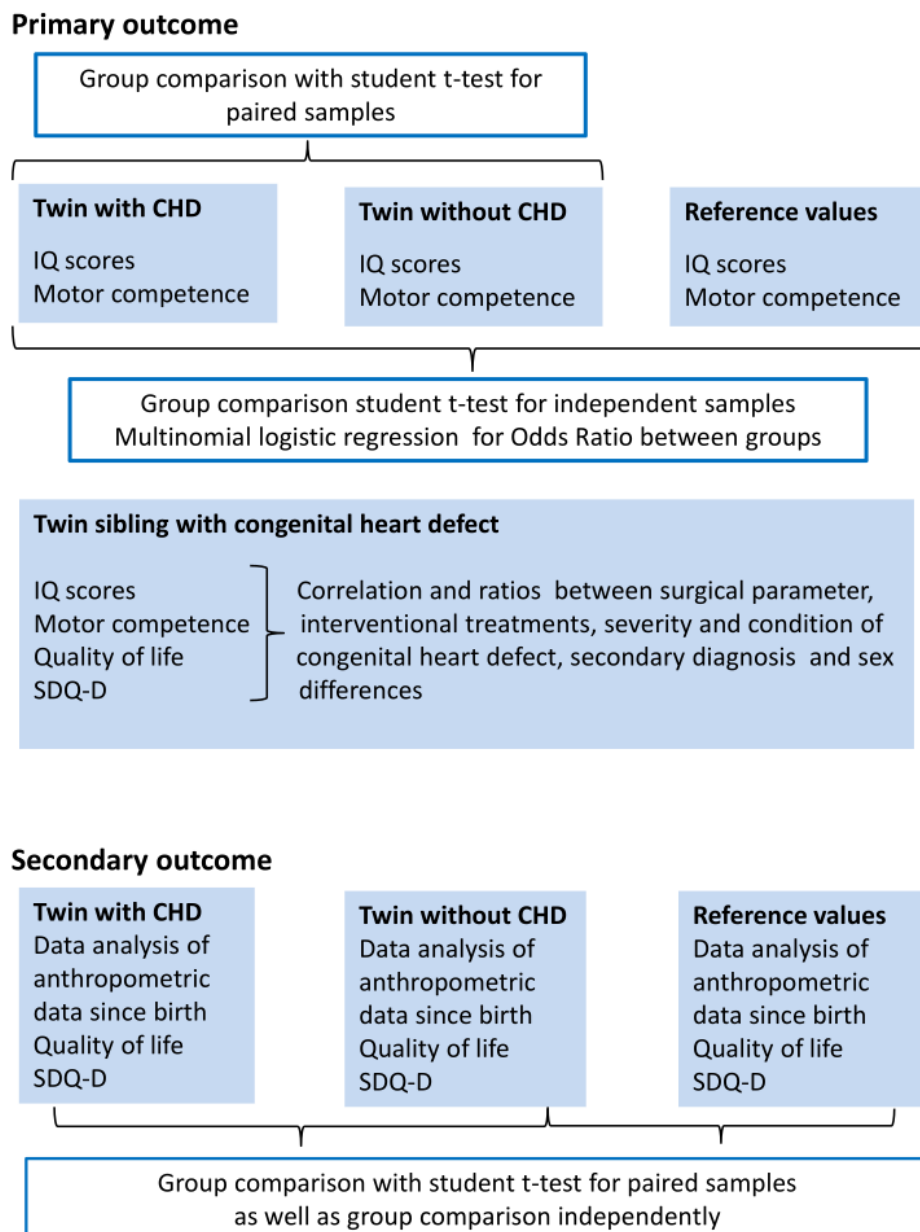
Results

The approval of the Medical Ethics Committee Charité Mitte was obtained on June 26, 2018 (EA2/086/18). After getting funded in April 2019, first enrollment began in August 2019. The study is still ongoing until June 2022. Final results are expected in 2022.

Discussion

This study protocol provides an overview of technical details of the study design, offering an option to exclude confounding factors on neurodevelopmental outcomes in patients with CHD. This will enable a specific analysis focusing on CHD and clinical treatments to differentiate in terms of neurodevelopmental outcomes of patients with CHD compared to twin siblings with healthy hearts. In the end, we aim to clearly define what is important to prevent patients with CHD in terms of neurodevelopmental impairments and to define targeted prevention strategies for patients with CHD.

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Authors' Contributions

JR and OT came up with the study; PE supported and supervised it. UMMB and TP supported bringing it to the national level. JR and PCH contributed toward statistical analyses and the first draft with PE. PE, ROF, UMMB, and TP critically reviewed the protocol and made amendments. All authors critically reviewed and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

CHD: congenital heart defects
IPAQ: International Physical Activity Questionnaire
MET: metabolic equivalent task
M-ABC 2: Movement Assessment Battery for Children, second edition
NRCHD: National Register for Congenital Heart Defects
SDQ-D: Strength and Difficulties Questionnaire, German version
SF-36: Short Form 36

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Protocol

Allostatic Stress and Inflammatory Biomarkers in Transgender and Gender Expansive Youth: Protocol for a Pilot Cohort Study

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Abstract

Background: A growing number of adolescents are coming out as transgender and gender expansive (TGE). These teenagers have been shown to have significantly worse health outcomes than their cisgender peers. Hypotheses to explain this discrepancy are based on increased stress levels surrounding the societal acceptance of gender identity. In this context, elevated allostatic load (AL), which describes the wear and tear sustained by the body in response to repeated exposure to stress, has been associated with adverse long-term health outcomes.

Objective: This protocol aims to measure AL among TGE adolescents compared with their cisgender peers and assess how AL varies depending on psychological stress and perceived societal acceptance.

Methods: This is an observational proof-of-concept pilot study in which AL will be measured by assaying an array of inflammatory cytokines and cortisol in urine, saliva, and hair samples of TGE youth, and these parameters will be compared with those of age-matched control participants. A questionnaire will assess 4 aspects of psychosocial well-being: presence and management of depression and anxiety, gender identity support by family members, gender minority stress, and degree of perceived safety in the surrounding community. Samples and surveys will be collected at 3 visits (baseline, 6 months, and 12 months). This study will incorporate TGE coinvestigators to inform all aspects of design, data collection, and analysis and ensure that practices are carried out in a respectful and sensitive manner.

Results: As of May 2021, the start of data collection for this project has continued to be postponed as a result of the COVID-19 pandemic, which has both impacted the functioning of the clinic and funding requests. We hope to begin participant recruitment and interviews with coinvestigators soon.

Conclusions: We hypothesize that AL will be primarily influenced by psychological well-being and perceived support and that it will be similar in TGE adolescents and in age-matched cisgender control participants when acceptance and perceived support are high. The results of this study have the potential to increase our understanding of the health challenges faced by TGE individuals during adolescence as well as to show that low levels of acceptance may have detrimental health outcomes secondary to elevated ALs; this may lead to the development of a biomarker profile to assess allostatic stress in TGE patients that can be used to guide management.

International Registered Report Identifier (IRRID): PRR1-10.2196/24100

KEYWORDS

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Introduction

Health Disparities in Transgender Youth

On the basis of recent research, it is estimated that between 0.7% and 1.8% of children and adolescents identify as transgender and gender expansive (TGE), the highest percentage of any age group in the United States [1,2]. A TGE individual is a person who is assigned a sex at birth that does not match their current gender identity. Sex refers to someone's genetic and hormonal makeup (male, female, or intersex), whereas gender is the societally informed expression of assigned sex, and gender identity is someone's internal sense of gender [3]. Research has shown that TGE adolescents tend to have significantly worse perceived health, higher rates of depression and suicidal ideation, higher rates of HIV, higher rates of experienced violence (childhood sexual abuse and trauma), and fewer preventive health checkups than their cisgender peers [4-9]. Many hypotheses have been proposed to account for these adverse health outcomes, including an increased incidence of bullying and other forms of social rejection [10-13]. The minority stress model is most relevant to this proposal (Meyer [14]), which explains health disparities among sexual minorities and proposes that chronic stress arises from the marginalization, discrimination, rejection, and violence that may be encountered, feared, or internalized. This leads to mental health issues such as depression, anxiety, suicidal ideation and/or attempts, and/or substance abuse [14]. The minority stress model was recently extended to encompass transgender people by including gender-related stressors and transphobia [15,16].

Allostatic Load

Allostasis is the process to remain stable during change. However, in contrast to homeostasis, in which the internal environment remains steady, allostasis refers to the body's active fluctuation in response to stressful changing conditions [17]. In response to this stress, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenomedullary axis are both activated and in turn incite many physiologic changes to allow the body to adapt to stress, with primary mediators including neuroendocrine chemical messengers such as cortisol, epinephrine, and norepinephrine, and immune and inflammatory chemical messengers such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [18]. These primary mediators in turn exact a secondary physiologic response ranging from metabolic (dyslipidemia, elevated glucose levels, and waist-hip ratio) to cardiovascular (increased blood pressure and heart rate variability) and inflammatory (C-reactive protein [CRP] and fibrinogen) [18,19]. In addition, nutrition and medication use can influence primary and secondary responses [20]. The allostatic load (AL) model is the end product, the cumulative toll of this stress to a certain point in time on physical and mental health to create a comprehensive picture of the body's response to stress and trauma. This model has been used successfully in children, with recommendations on measuring both primary and secondary end points to best capture both axes [17,21]. IL-6 and CRP were the most frequently measured inflammatory biomarkers based on a systematic review published in 2020 [22]. An elevated AL in the absence of a current stressor represents the *wear and tear* put on the body's ability to adapt

due to repeated exposure to stressful events, whether these events pose a real or interpreted threat [23]. These real or perceived threats trigger the activation of both the sympathetic nervous system adrenal medullary axis and the HPA axis, releasing catecholamines and glucocorticoids, respectively [24]. Although beneficial in the short term, chronic overactivation of these axes can have a detrimental effect on biological systems, leading to overcompensation and eventual collapse as well as decreased ability to respond to future stressors due to changes in the nervous system [17]. One's resilience to stress and ability to perceive threats and properly mobilize allostatic mechanisms is determined by a combination of many factors, including individual (eg, genetics), behavioral (eg, coping abilities), and historical differences (eg, prior episodes of trauma, abuse, or stressful environments) [17].

Elevated cortisol, in addition to other inflammatory cytokines such as interleukins and TNF-α, is associated with deleterious health consequences [25], such as cardiovascular compromise [26], increased susceptibility to asthma exacerbations [27], and impaired wound healing [28]. An increase in overall AL has also been associated with negative health outcomes later in life. The large-scale American National Health and Nutrition Examination Survey found that AL can serve as a predictor of ischemic heart disease in conjunction with income gradient and education [29]. Seeman et al [30] documented that among older adults, higher baseline AL was associated with increased 7-year mortality and decreased physical and cognitive function. They also found that AL was a better predictor of mortality and physical ability than either looking at specific syndromes or individual stress markers [30]. Furthermore, there is evidence that the effects of increased AL may be particularly significant during key developmental periods, such as adolescence [18].

AL and the Lesbian, Gay, Bisexual, and Transgender Community

Chronic stress affects the physical well-being of lesbian, gay, and bisexual (LGB) adults, which has been demonstrated in studies showing different baseline cortisol levels and altered cortisol reactivity to stress in LGB adults compared with heterosexual adults [31,32]. However, very few studies have examined the stress biomarkers of TGE people [33]. A study by Colizzi et al [34] of 70 adult transmen and transwomen who had cortisol levels measured before and 12 months after initiating gender-affirming hormones found that the participants had lower cortisol levels after gender-affirming hormone therapy [34]. In addition, DuBois et al [35] explored cortisol levels in transitioning adult transgender men; transmen who reported higher levels of transition-related stressors had higher morning cortisol levels than men who did not report feeling transition-related stressors.

Despite the dearth of studies on stress biomarkers, multiple studies have demonstrated that psychological distress is not inevitable for TGE persons but rather mediated through the degree of social and community acceptance and, in particular, parental affirmation of TGE identity [36]. When TGE children were raised in supportive environments, levels of depression, as determined by parent-filled surveys, did not differ from age-matched cisgender control participants [34,35]. Furthermore,

having parents who were interested in a gender-affirming program was a protective factor against depression in TGE youth [37,38]. The positive effects of parental support appear to persist through adulthood based on a study of LGB adults who had improved responses to acute stress compared with LGB adults with less parental support during childhood [39]. Other protective factors include pride in one's gender identity and strong connections to TGE communities [36].

In addition to the support children receive in their homes, multiple other areas could lead to elevated stress around gender identity, such as the safety of a neighborhood and possible comorbid depression and anxiety [40]. Furthermore, these extrafamilial environments, which also include school, religious, and work environments, had an immense influence over intrafamilial experiences [41], demonstrating the interconnectedness of all environments on the experience of TGE youth. These results highlight the importance of affirmative care in all situations, a stance echoed in a recent policy statement issued by the American Academy of Pediatrics [42].

Filling in the Gaps

To further explore the importance of affirmative care and social acceptance in TGE youth, we propose using AL measurements in addition to psychosocial surveys to monitor physiological stress. The addition of an array of inflammatory biomarkers is important because it not only provides greater insight into overall stress levels but also underscores the physical consequences of an unsupportive environment that may arise from familial disapproval, unsafe geosocial environments, societal stress or marginalization, and/or comorbid psychiatric disorders. These include anxiety and depression, which most likely arise secondary to gender-related discrimination. To the best of our knowledge, no previous studies have explored the interaction of these factors in TGE youth.

Methods

Study Aims

This study aims to (1) determine the AL of TGE youth compared with appropriately matched cis-gender control participants based on assays of inflammatory cytokines and cortisol levels and (2) explore the relationship between supportive environments and communities, supportive families, safe geosocial environments, and well-controlled psychiatric comorbidities on the AL of TGE youth.

Ethics Approval

This study was approved by the New York University (NYU) Langone Health Center Office of Science and Research Institutional Review Board (IRB).

Study Participants and Sites

We plan to recruit a total of 80 participants, 40 TGE adolescents and 40 cisgender control participants. TGE participants will include children and adolescents aged between 12 and 18 years who attend the gender clinic at Fink Children's Ambulatory Care Center at NYU Langone for evaluation of gender dysphoria. This age range was chosen as it reflects the ages of the patients seen at the gender clinic and ensures that participants

are at a similar life stage. Although the clinic does see patients aged up to 24 years, young adults aged 18 years and older have more autonomy over their bodies and lives, which may influence their perceived stressors. As this was a pilot study, the only required baseline characteristic for all participants was that they identified as either TGE for the study population or cisgender for the control population. However, patients with preexisting chronic conditions, including obesity (BMI>95%), chronic kidney disease stage 3 or higher, liver disease, chronic infections such as hepatitis B, hepatitis C, HIV, tuberculosis, or autoimmune disorders such as systemic lupus erythematosus or primary immunodeficiency, receiving treatment with steroids, or current smokers will be excluded from the study because these conditions and medications or habits may alter levels of stress and inflammatory biomarkers [43-45]. We will also focus recruitment efforts on patients who have not initiated hormone therapy, although this will not be a requirement. In addition, nongender affirming care medication use will not influence participant selection.

A total of 40 cisgender control participants will be recruited from the adolescent clinic where adolescents are seen for a variety of issues, including adolescent consultative care such as gynecological concerns and sexual health. Patients with chronic diseases or diagnosed infections will be excluded as outlined above for TGE participants. Recruitment of control participants in this subspecialty clinic will minimize biases that might occur when recruiting in other clinics, such as different socioeconomic backgrounds or home locations. Control participants will be matched by age and sex assigned at birth in a 1:1 ratio with TGE participants. These variables were chosen to ensure the correlation between neurologic development and the activity of stress hormone pathways.

TGE participants must be able to return for all 3 visits and fill out all surveys in English, whereas control participants will only be required to attend 1 visit.

Participant Recruitment

TGE adolescents and control participants will be asked if they are interested in participating in this study before or after their usually scheduled appointment. The full details of the study will be discussed, including details of the questionnaire and the need for hair, urine, and saliva samples. Potential participants will be told that not wanting to partake in the study will not affect current or future medical care. Treating physicians will not be included in the consent process to ensure that patients will be comfortable saying no to study inclusion. As the participants will all be under 18 years of age, they will give assent and their parents and guardians will provide consent. If they wish to withdraw from the study at any point, any sample will be immediately retrieved and destroyed. To maintain the study's statistical power, we will adopt a recruit to replace the enrollment strategy.

TGE Coinvestigators

A unique aspect of our study, which will hopefully be commonplace in biomedical research, is the active inclusion of members from the study community, in this case TGE individuals, in the implementation and analysis of the study.

There are multiple reasons for this. First, the TGE community has often been misrepresented and mistreated by medicine, especially TGE people from racially minoritized backgrounds; consequently, many TGE people feel uncomfortable and unsafe with health care providers [46]. Including community members on the research team to give insight into respectful research practice will hopefully demonstrate the research team's willingness to learn and help instill trust between the medical professionals involved and community members. Furthermore, TGE coinvestigators will help identify areas of the study that may be easily misinterpreted or difficult to understand for members of the study population. This insight will be invaluable in ensuring the feasibility of the study and the validity of the findings. Finally, TGE coinvestigators will be able to provide invaluable insight into data interpretation and help guide how the findings can be best implemented to help the community.

TGE coinvestigators, who have not yet been recruited, will include 1 transfeminine and 1 transmasculine person between the ages of 18 and 24 years, which should help prevent any overlap with the study population. The sole requirement is the ability to read and write in English and physically come to the clinic in a COVID-19–safe manner. We will try to involve individuals who have an interest in research and/or medicine and have had limited opportunities to become immersed in the field, therefore recruiting from multiple groups. We will recruit patients at the gender clinic seen by an alternative physician not involved in this study. A community institute that provides gender-affirming services, including mental health and support groups, was also chosen as a recruitment site because of the connection the study team has with the institute and to avoid overlap between the study population and coinvestigators. Finally, we will also recruit from a local shelter for TGE youth who are unhoused. Recruiting from these places will ensure that we are providing all TGE youth who may want to participate in the opportunity to apply. After filling out an initial interest form on Research Enterprise Data Capture (REDCap), accessible with a quick response (QR) code and link on the pamphlet, applicants will be contacted for a phone interview and asked about their availability, goals, and interest in the project. Prior experience with research will not be a requirement because we are particularly seeking individuals with limited previous opportunities. We acknowledge that using a web-based survey for application will limit the opportunity to those who have the technology. However, we believe this will have a minimal effect because most young adults have telephones with the capacity to use QR codes [47].

Although we acknowledge that the TGE coinvestigators were not involved in the research question formation or the original design, and therefore this project cannot be labeled participatory action research, they will be involved in the setup and implementation of the project going forward. TGE coinvestigators will have the opportunity to review the study design and surveys to ensure that they agree that the design will be effective and that there are no overlooked assumptions, leading or poorly worded questions, or other issues with the protocol. If TGE coinvestigators suggest that it may alter previously agreed-upon end points, there will be a research team meeting to discuss the proposal and decide if that end point is needed or discuss an alternative way to reach that end point. During this time, they will undergo the Collaborative Institutional Training Initiative program training, as required by all researchers at the hospital. This training will include Health Insurance Portability and Accountability Act training to help protect research participants' identities. TGE coinvestigators will be involved in data analysis, helping to provide a community perspective when interpreting the results, and will be involved in writing up and presenting the study results in academic journals and conferences, respectively. The research team has committed to teaching data analysis methods to help TGE coinvestigators with this section, as we feel that imparting specialized knowledge is an important aspect of this project.

We anticipate that being a part of this research team will help these youth personally and professionally in multiple ways, from gaining research experience to mentorship opportunities. TGE people are underrepresented in medicine and research teams, so including them as coinvestigators will help close this gap [48]. Although TGE coinvestigators will receive many different intangible opportunities, we will also compensate them monetarily for their time and effort. This demonstrates that the research team values the commitment from the community, which helps decrease important economic disparities in minority communities and acts as an equalizer to show commitment to inclusion [49]. In addition to monetary compensation, we place a strong emphasis on mentorship. All of the study investigators will make time for TGE coinvestigators to review the project in smaller groups and discuss other aspects of medicine and research in general, as TGE coinvestigators would like.

This novel aspect of the study design has several limitations. Although we would prefer to include more than 2 coinvestigators to obtain a broader range of perspectives, there are limited resources to adequately compensate more individuals who might want to take on this role. As the clinic at which the study will take place is not insular but rather part of a larger institution, steps will be taken to limit exposure to possible institutional transphobia that TGE coinvestigators may face in the workplace. These will include informing staff and security about TGE coinvestigators and their role in the project ahead of time and providing support during onboarding procedures, which may have limited gender options.

Study Design or Data Collection and Measures

There will be 3 visits in total for the TGE participants, 6 months apart (baseline, 6 months, and 12 months). The total duration of participation will be 1 year. Figure 1 shows a schematic representation of the TGE arm study design. Control participants will only require a single baseline visit for bio-sample collection and will not be required to take any surveys.

Figure 1. Schematic of the study design. This schematic demonstrates the tasks completed at enrollment and at each subsequent visit for transgender and gender expansive TGE participants.
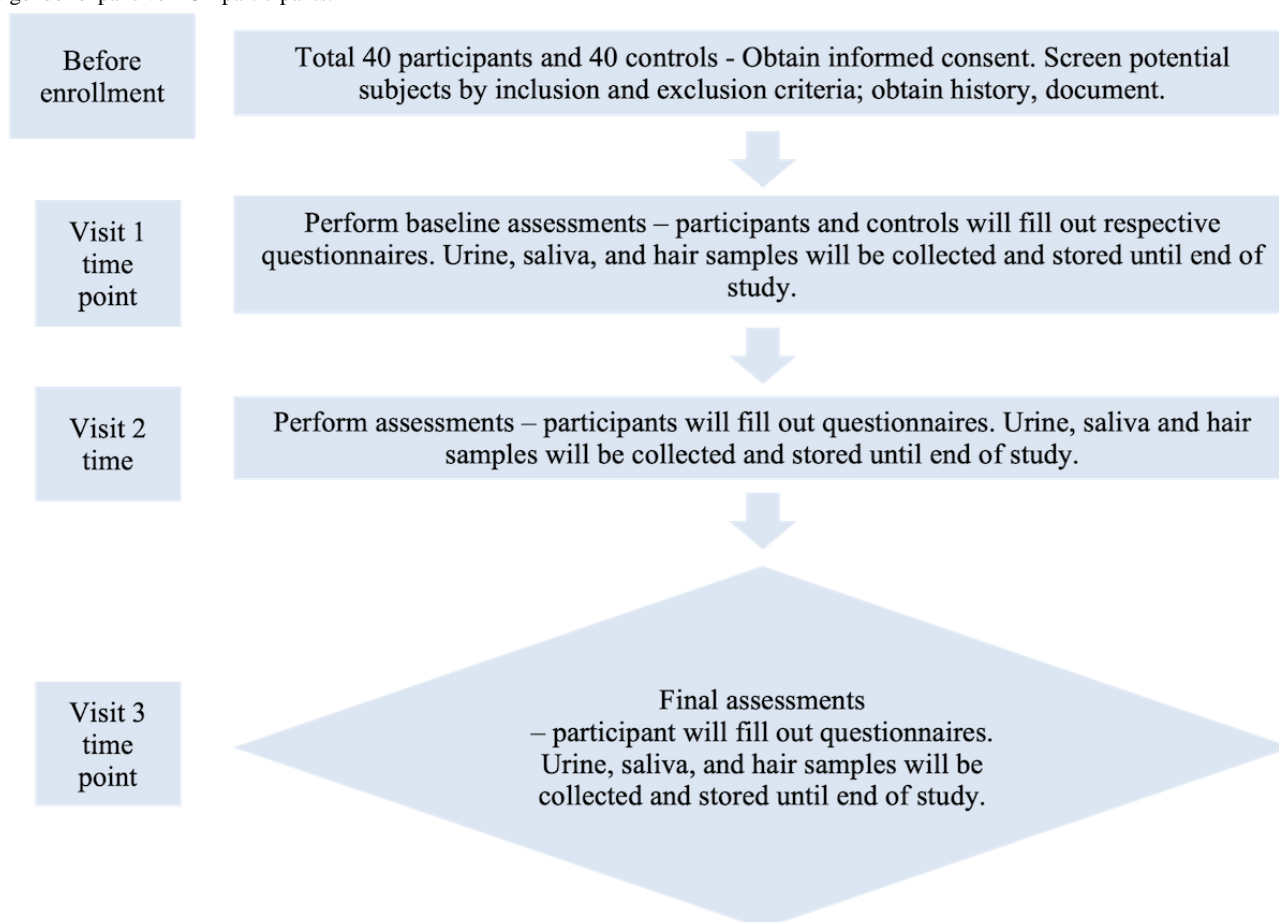
During all visits, the child's gender identity and 4 main variables—familial support, geosocial safety perception, comorbid depression and anxiety, and gender identity minority stress—will be determined via a survey questionnaire administered on REDCap, which will also store participant data. Participants will be given the Parental Attitudes of Gender Expansiveness Scale for Youth and the Adverse Childhood Experience Questionnaire to determine familial support [50,51]. To determine geosocial safety perception, a previously used questionnaire to inquire about a child's perception of neighborhood safety will be given [52,53]. Participants will be given the modified Patient Health Questionnaire-9A (adolescent) and Self-Report for Childhood Anxiety Related Emotional Disorders survey [54] to assess depression and anxiety. Finally, gender-related discrimination, rejection, and victimization experienced internally and externally will be surveyed with the gender minority stress and resilience (GMSR) measure modified to be suitable for adolescents [55]. The GMSR also addresses intersectionality and how gender identity may be perceived with other identities, such as religious, race or ethnicity, or occupational identities, as well as addresses community support by exploring how welcomed individuals feel by their communities. All surveys used have strong reliability and validity, and each participant has approximately 150 questions to complete. These surveys are expected to take approximately 1 hour to complete. A study investigator will be nearby to help participants in the survey if needed. All surveys used except for the GMSR have been validated in children aged 12 years and

older. Although the GMSR has not been validated in people younger than 18 years old, it is the only measure of gender minority stress of which the authors are aware. The question responses were modified to be appropriate for participants aged between 12 years and 18 years. The research team recognizes that answering 150 questions can be demanding, especially for young people, and the risk of decreased attentiveness as the questions continue can affect the results. To help prevent this, snacks and beverages will be provided. In addition, every approximately 20 minutes until completion, participants will be asked to stand up, walk, and/or stretch. Participants will have the option of asking for the accompaniment of a research team member should they desire. Insurance information will be collected from the electronic health record, which will indicate the family's access to medical care.

Stress and inflammatory biomarkers will be measured at the initial visit and the 2 follow-up visits. To capture the primary mediators of AL, the biomarkers measured were cortisol, IL-6, and TNF-α. The secondary mediators measured included CRP, BMI, and waist-to-hip ratio. Measuring both primary and secondary mediators is recommended in pediatric patients to best capture the AL [21]. Efforts will be made to schedule all appointments during the afternoon to minimize diurnal variation and enable a more uniform assessment of cortisol and urine inflammatory markers levels [43,56-58]. At each session, participants will have stress and inflammatory biomarkers measured before the survey and after listening to a 10-minute

relaxation tape to account for possible transient increases in stress on route to the appointment. Researchers will be blinded to the sample source to reduce possible bias.

Urine samples will be collected and assayed using the Luminex Panel (model number HSTCMAG28PMX21BK), which has been used successfully to determine inflammatory and stress biomarkers in infants and toddlers enrolled in an obesity prevention trial [59]. This panel can measure an array of cytokines, including IL-1ß, IL-6, IL-10, and TNF-α. Salivary and hair cortisol levels will also be measured. Salivary cortisol has been used previously in adolescent populations to explore the effects of parental support on stress response [60]. Hair cortisol content is an integrated index of stress over an extended period. A small sample of hair from the head will be collected with child-safe scissors as a measure of chronic stress levels [61,62]. Saliva will be collected into a polypropylene vial with a straw using the *passive-drool technique* [63]. All samples, marked with the participant ID number, will be stored at –70 °C within 1 hour of collection until the batch assay of the analyte panels. If agreed upon by participants, the residual samples on will be stored in the NYU Biorepository for potential use in future studies. Otherwise, all samples will be destroyed after the completion of the study.

Sample Size

Recruitment will end when approximately 40 TGE participants and 40 control participants are enrolled for a total of 80 participants, as determined by a total of approximately 200 patients in the gender clinic with an expected enrollment of 20% to 30%. On the basis of a total population of approximately 21,000 transgender youth in New York State from the Williams Institute and a total of 200 patients in our clinic, a sample population of 13 participants and 13 control participants would be adequate to generate a study with 80% power with a 95% CI of 17 [34]. Therefore, by aiming for 40 participants in each arm, we will exceed this value.

COVID-19 Precautions

This pilot study was conceptualized before the COVID-19 pandemic. Most of this study will not be affected. Participants will be able to complete the survey on a computer either by themselves or with a single research team member in the room, which will allow COVID-19 safety precautions. Sample collection will also be done with a single research team member in compliance with COVID-19 precautions. The recruitment of TGE coinvestigators will be done using fliers and pamphlets, as previously discussed, and interviewing TGE coinvestigators will be performed over Zoom, Skype, or FaceTime. Although originally the TGE coinvestigators were to be a part of data collection, because of COVID-19 restrictions, this will not be possible. However, the research team will keep TGE coinvestigators abreast of implementation and be available to discuss data collection.

COVID-19 has added numerous stressors to everyday life, and as such, has most likely caused changes to individual ALs. However, no studies have explored COVID-19 and ALs in pediatric patients to the research team's knowledge. The control group will correct for any universal increases. If another major shift in the pandemic should occur during the study period, then the control group will have an additional measurement session added to adjust for how this shift may affect ALs.

Statistical Analysis

Primary Objective

Our general approach of comparing TGE youth biomarkers with cisgender control participants will include paired two-tailed *t* test analysis and analysis of variance (ANOVA) to determine whether there is a significant difference in the cytokine profile between the 2 groups' levels, as defined by a *P* value of less than .05.

Secondary Objective

Within the TGE youth samples, we will use paired *t* test analysis and ANOVA to determine if there is a difference in biomarker levels between different age brackets (12-14 years and 15-18 years) and ethnicity (White vs Black or Hispanic), with significance being determined by a *P* value less than .05. If we do not have enough participants in a certain age bracket, we will not perform this analysis.

Linear regression analysis will be conducted to determine if there is a relationship between questionnaires and biomarker levels for each participant. We will also include a regression analysis to ascertain correlation, with an R-squared value greater than 50% needed to determine the relationship.

Statistical Execution

All statistical calculations will be performed using GraphPad Prism version 8.0.0 for Mac (GraphPad Software).

Results

As of September 2020, the study received IRB approval but had not yet begun data collection. Although we planned to begin active recruitment in the summer of 2020, we have had to postpone owing to the COVID-19 pandemic. This health emergency has significantly affected the frequency of in-person visits and clinical research. In addition, we are still waiting to hear from multiple grants that were delayed as a result of the pandemic. We hope to receive funding support and begin participant recruitment and interviews with coinvestigators shortly.

Discussion

Summary

As described above, adolescents have the highest percentage of TGE identifying members of any age group in the United States, yet this population has minimal published research [1,2]. This study seeks to fill some of the gaps in the literature regarding the physical consequences of acceptance. We propose that AL of TGE individuals may be used as an integrated biomarker for the risk of long-term adverse health consequences based on the level of acceptance in different environments. To reiterate, we hypothesize that TGE status is not a cause of increased AL, but rather that an increase is the consequence of social and environmental experiences. To this end, we therefore

sought to measure the presence of 4 variables—depression and anxiety, gender identity familial support, gender identity community support, and gender-related minority stress—which may influence the AL in TGE youth. The effects of psychiatric, familial, and community support on AL may help target areas of effective intervention going forward and provide a better understanding of the stress sources among TGE youth.

Strengths and Limitations

This study has some limitations that must be acknowledged. The confounding variable of socioeconomic status, which can increase stress, is outside the scope of this study. By recruiting all patients from the same site, there were some limitations to the range of backgrounds represented. However, given the diversity of the area surrounding the hospital and the limited number of sites providing adolescent gender care in the New York metropolitan area, we expect to be able to recruit a diverse range of participants. Furthermore, the fact that participants are already seeking care at an adolescent gender clinic can bias the sample toward more accepting situations. We hope that we can still identify subtle variations in levels of support and validation by using a number of surveys. Although the results of this study are limited by sample size, they will provide the first data set that can hopefully be expanded over time as more research is conducted with the TGE youth population.

Another area of potential concern is the direct effect of gender-affirming therapy on the results. However, we believe that this effect, even longitudinally, should be minimal. There are no consistent data indicating that exogenous hormones influence the HPA axis [34,64-66]. Colizzi et al [34] reported that estrogen might alter hormone-binding globulin levels, thereby skewing stress hormone levels. In addition, brain plasticity, synapse formation, and signaling pathways differ between male and female rodents based on sex hormone levels,

with some indication that a similar process could occur in the human brain [64]. However, in a study of 20 postmenopausal cisgender women, exogenous estrogen was associated with only slightly elevated levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate and not significantly elevated levels of cortisol [65]. In a separate study of 12 cisgender women, exogenous testosterone was found not to influence endogenous cortisol levels [66]. Although commencement of gender-affirming therapy at any point during the study should not significantly alter our data, we will document gender-affirming hormone use to enable later adjustment for any effect. Furthermore, the effects of gender-affirming therapy on self-perceived stressors will be captured during our surveys.

Conclusions

The results of this study will be useful in guiding larger-scale studies to assess allostatic stress in TGE youth. These results also have the potential to shape practical interventions to benefit TGE youth by providing scientific evidence in favor of affirming programs, including support groups for both parents and teenagers, parental consultations with gender experts with a range of backgrounds to increase familial acceptance, encouragement of Gay-Straight Alliance and LGB club involvement, and encouragement of community centers with a TGE focus. In addition, the results of this study have the potential to enhance the argument for policies that would increase TGE safety and acceptance in the community, such as antibullying measures. The implications of physical harm caused by a lack of acceptance will hopefully increase the trend toward broader acceptance of the TGE population. Finally, the findings may enable the development of a biomarker profile that can be used as an objective measure of allostatic stress in TGE patients and to monitor the effectiveness of therapeutic interventions on their well-being.

Conflicts of Interest

None declared.

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Abbreviations

AL: allostatic load
ANOVA: analysis of variance
CRP: C-reactive protein
GMSR: gender minority stress and resilience
HPA: hypothalamic-pituitary-adrenal
IL-6: interleukin-6
IRB: Institutional Review Board
LGB: lesbian, gay, and bisexual
NYU: New York University
QR: quick response

REDCap: Research Enterprise Data Capture
TGE: transgender and gender expansive
TNF-α: tumor necrosis factor α

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Protocol

Using Assisted Partner Services for HIV Testing and the Treatment of Males and Their Female Sexual Partners: Protocol for an Implementation Science Study

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Abstract

Background: Despite the effective scale-up of HIV testing and treatment programs, only 75% of people living with HIV (PLWH) globally know their status, and this rate is lower among men. This highlights the importance of implementing HIV testing and linkage interventions with a high uptake in this population. In a cluster randomized controlled trial conducted in Kenya between 2013 and 2015, we found that assisted partner services (APS) for HIV-exposed partners of newly diagnosed PLWH safely reached more HIV-exposed individuals with HIV testing compared with client referral alone. However, more data are needed to evaluate APS implementation in a real-world setting.

Objective: This study aims to evaluate the effectiveness, acceptability, fidelity, and cost of APS when integrated into existing HIV testing services (HTS) in Western Kenya.

Methods: Our study team from the University of Washington and PATH is integrating APS into 31 health facilities in Western Kenya. We are enrolling females newly diagnosed with HIV (index clients) who consent to receiving APS, their male sexual partners, and female sexual partners of male sexual partners who tested HIV positive. Female index clients and sexual partners testing HIV positive will be followed up at 6 weeks, 6 months, and 12 months postenrollment to assess linkage to care, antiretroviral therapy initiation, and HIV viral load suppression. We will evaluate the acceptability, fidelity, and cost of real-world implementation of APS via in-depth interviews conducted with national, county, and subcounty-level policy makers responsible for HTS. Facility health staff providing HTS and APS, in addition to staff working with the study project team, will also be interviewed. We will also conduct direct observations of facility infrastructure and clinical procedures and extract data from the facilities and county and national databases.

Results: As of March 2020, we have recruited 1724 female index clients, 3201 male partners, and 1585 female partners. We have completed study recruitment as well as 6-week (2936/2973, 98.75%), 6-month (1596/1641, 97.25%), and 12-month (725/797, 90.9%) follow-up visits. Preliminary analyses show that facilities scaling up APS identify approximately 12-18 new HIV-positive

males for every 100 men contacted and tested. We are currently completing the remaining follow-up interviews and incorporating an HIV self-testing component into the study in response to the COVID-19 pandemic.

Conclusions: The results will help bridge the gap between clinical research findings and real-world practice and provide guidance regarding optimal strategies for APS integration into routine HIV service delivery.

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Introduction

The HIV epidemic continues to cause significant morbidity and mortality, disproportionately affecting sub-Saharan Africa (SSA), where most HIV infections occur [1]. Approximately 65% of people living with HIV (PLWH) globally know their status, suggesting that expanding targeted testing strategies are needed to achieve the first 95 of the Joint United Nations Programme on HIV/AIDS ambitious testing, treatment, and viral suppression targets [2]. PLWH in SSA are largely diagnosed through facility-based HIV testing; however, testing coverage is lacking and insufficient to curb the HIV epidemic, particularly in men and vulnerable populations [3]. Barriers to facility testing include distance, costs, and confidentiality concerns, which result in many PLWH presenting late for care when they are already symptomatic or at advanced stages of the disease [4,5].

Assisted HIV partner services—providers contacting and testing sexual and injecting partners of people diagnosed with HIV—can be an efficient strategy for diagnosing people with HIV, linking them to HIV care and prevention [6,7]. In 2016, the World Health Organization recommended offering assisted partner services (APS) to all PLWH to close the gap in HIV testing coverage [8], and these services are now rapidly scaling up globally. Partner contacting and testing can be conducted through (1) client referral—newly diagnosed individuals (index clients) are asked to notify their partners of exposure and encourage HIV testing; (2) provider referral—providers contact partners and offer testing while ensuring the clients' confidentiality; and (3) contract referral—index clients and providers agree on a set amount of time for clients to notify partners, after which providers contact partners and offer testing [9]. In practice, APS are implemented as a combination of these options.

Clinical trials and demonstration projects of APS in SSA have found high HIV positivity (30%-63%) among sexual partners of index clients and high median CD4 counts at diagnosis, indicating that individuals are identified earlier in their disease course compared with those identified by facility-based testing [3,10-13]. Early case detection and linkage to care can improve clinical outcomes [11,14,15]. Mathematical modeling analyses indicate that APS are a cost-effective strategy for reducing HIV burden in SSA [16]. In addition, APS are an effective method to reach men through their HIV-positive female partners, as women are tested for HIV at higher rates than men [17]. Men in SSA are more likely to start antiretroviral therapy (ART) at

advanced disease stages and consequently have poorer clinical outcomes compared with women [18,19]. Low male testing and treatment rates also serve to increase HIV transmission to their female partners.

Despite its demonstrated efficacy, scaling up APS presents challenges. The translation of findings from randomized controlled trials into real-world settings can be a challenge because of weaknesses in health system structures and differences in intervention delivery, monitoring, and available resources [20]. The implementation of science evaluations of APS offers a real-world approach using existing systems to scale up interventions. As a critical next step in bringing APS to scale in Kenya and across SSA, this study uses implementation science methods to assess the effectiveness and feasibility of APS and generates evidence to inform rapid and sustainable implementation across the region.

Our objective is to evaluate the effectiveness, feasibility, and cost of implementing APS integrated within routine HIV testing services (HTS) in Western Kenya, a region with high HIV prevalence (>15%) [21]. Specifically, we aim to (1) evaluate the effectiveness of integrated APS and (2) determine the integration, implementation fidelity, acceptability, demand, and costs of implementing APS. By identifying health facility and individual-level factors that influence the uptake of HIV testing, linkage to care, and fidelity to APS, we will evaluate how these factors inform the successful scale-up of APS in Kenya.

Methods

Study Design

This hybrid type 2 implementation science study [22] has two aims: (1) to determine the effectiveness of APS when integrated within routine HTS and (2) to evaluate the implementation of APS in these settings, including the integration, implementation fidelity, acceptability, demand, and costs of the intervention. The study leveraged existing integrated HIV prevention, care, and treatment platforms from the Afya Ziwani project, the existing President's Emergency Plan for AIDS Relief–funded and PATH. PATH is a local nongovernmental organization in Western Kenya. HTSs are provided in facility and community settings, including *safe spaces* where DREAMS (Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe) interventions are provided to vulnerable adolescent girls and young women.

The DREAMS program aims to reduce new HIV cases by providing girls and young women at the highest risk of HIV

infection and their partners, families, and communities with a tailored, comprehensive, and evidence-informed HIV service package, including HTS. Afya Ziwani provides technical implementation support to health facilities that serve as sites for study enrollment. Nine safe spaces have been created within the catchment areas of health facilities that provide a variety of services, including HTS, by staff for adolescent girls and young women. Excluding the antenatal care clinics, around 50-80 persons test HIV positive each month in larger facilities and 10-20 in smaller facilities, with more than 50% of newly diagnosed individuals being female. In 2018, HIV prevalence in Homa Bay and Kisumu counties was estimated at 19.6% and 17.5%, respectively, in the general population [23]. Therefore, this is a high number of girls and women with HIV who are enrolled in health facilities and linked safe spaces. This study integrated APS into the existing infrastructure of Afya Ziwani in collaboration with county and subcounty health management teams in Homa Bay and Kisumu counties.

The study was approved by the ethics and research committee of Kenyatta National Hospital (P465/052017) and the University of Washington institutional review board (STUDY00002420).

No payment was provided to the participants for their participation. Breaches in confidentiality, study protocol, or adverse events attributable to this study were reported to both ethics and research committees and institutional review boards. The findings of this study will be disseminated to the Kenya Ministry of Health (MOH) and Kenya National AIDS and Sexually Transmitted Infection Control Programme (NASCOP) through direct communication and technical working group meetings and to the greater scientific and public health community through national and international conferences and peer-reviewed manuscripts in academic journals.

Aim 1: To Evaluate the Effectiveness of Integrated APS

Study Sites

Table 1 shows the distribution of study sites where HTS was provided and study activities were conducted. These facilities were in four Homa Bay County and five Kisumu County wards, encompassing a total of 31 study sites, some of which were connected to DREAMS safe spaces and nine additional safe spaces supported by the Afya Ziwani project.

Table 1. Distribution of 31 study sites in Western Kenya.

Facility name	Private or public	Subcounty	County
Kabondo Sub-County Hospital	Public	Kabondo	Homa Bay
Kauma Health Centre	Public	Kabondo	Homa Bay
Nyangiela Sub-County Hospital	Public	Kasipul	Homa Bay
Othoro Sub-County Hospital	Public	Kabondo	Homa Bay
Rachuonyo County Hospital	Public	Kasipul	Homa Bay
Tala Dispensary	Public	Kabondo	Homa Bay
Atela Dispensary	Public	Kabondo	Homa Bay
Kasewe Dispensary	Public	Kabondo	Homa Bay
Kokwanyo Health Centre	Public	Kabondo	Homa Bay
Matata Hospital	Private	Kasipul	Homa Bay
Nyalgosi Dispensary	Public	Kasipul	Homa Bay
Ober Sub-County Hospital	Public	Kabondo	Homa Bay
Ombek Dispensary	Public	Kasipul	Homa Bay
Nyawango Health Centre	Public	Kasipul	Homa Bay
Kimonge Dispensary	Public	Kabondo	Homa Bay
Airport Health Centre	Public	Kisumu West	Kisumu
Kowino Dispensary	Public	Kisumu East	Kisumu
Ojola Health Centre	Public	Kisumu West	Kisumu
Port Florence Hospital	Private	Kisumu West	Kisumu
Simba Opepo Dispensary	Public	Kisumu East	Kisumu
St. Elizabeth Chiga Hospital	Private	Kisumu West	Kisumu
Chiga Dispensary	Public	Kisumu West	Kisumu
Gita Sub-County	Public	Kisumu West	Kisumu
Migosi Sub-County Hospital	Public	Kisumu Central	Kisumu
Nyalenda Health Centre	Public	Kisumu Central	Kisumu
Ober Kamoth Sub-County Hospital	Public	Kisumu West	Kisumu
St. Mark's Lela Sub-County Hospital	Public	Kisumu West	Kisumu
Ring Road Dispensary	Private	Kisumu East	Kisumu
Disciples of Mercy	Mission	Kisumu East	Kisumu
Usoma Dispensary	Public	Kisumu West	Kisumu
Nightingale Hospital	Private	Kisumu Central	Kisumu

Study Participants

We planned to enroll up to 8000 female index participants (girls and women who tested positive for HIV at the facilities) and 10,000 sexual partners across study sites. The target enrollment was 2000 in year 1 of the study and 3000 per year in years 2 and 3. The inclusion criteria for the index participants were (1) female, (2) testing HIV positive and not in care or on treatment, (3) aged ≥18 years or emancipated minor (girls aged ≥15 years who are married; pregnant; or have had a sexually transmitted infection, including HIV), (4) willing to participate in the study, and (5) willing to provide contact information of ≥1 sex partner. Pregnant women, those younger than 15 years, and individuals who reported intimate partner violence (IPV) within the past

month of enrollment were excluded. History of IPV was determined using an IPV screening questionnaire that included questions about emotional, physical, and sexual violence (Multimedia Appendix 1). Male sexual partners of index clients who tested HIV positive also received APS and their other female partners were notified of their potential HIV exposure and offered HTS.

Study Procedures

Index Participant Recruitment and Enrollment

Recruitment of index participants occurred at the study sites. Females testing HIV positive at the participating sites were provided information on the study, including an overview of

APS and study procedures in English or local languages (Swahili and Luo) by HTS providers. The HTS staff screened the interested participants for eligibility and were asked to provide written informed consent if eligible. Enrolled participants were interviewed using structured forms regarding their demographic characteristics, sexual behavior, substance use, HIV testing history, and the number of male sex partners in the past 3 years. HTS providers collected contact information for all male sex partners in the past 3 years and emphasized that all information would be kept confidential and that the index cases' identities would not be revealed when contacting their partners.

APS Procedures

HTS providers called all elicited male sexual partners to inform them of their HIV exposure and offer HIV testing at the facility or a convenient location in the community. Initially, up to three attempts were made to notify the partners by phone; if unsuccessful, or if the female index client did not provide a phone number for the partner, HTS providers physically traced the partners in the community. If unsuccessful, two further attempts were made to notify the partners, either by phone or in-person. Partners were classified as lost to follow-up after six unsuccessful attempts or if a partner refused to meet with an HTS provider.

When implementing APS, HTS providers informed the partners of their potential HIV exposure without identifying the index participant. They asked the partners about their HIV testing history, provided HIV counseling, and offered HIV testing. Partners with a prior HIV diagnosis were asked about their current HIV care, and those who were out of care were counseled about the benefits and locations to access care. If a notification occurred over the phone, partners were encouraged to seek HTS at a study site or offered the opportunity for study staff to conduct a home-based HIV test. For partners who chose to seek HTS at a facility or safe space, the HTS provider who conducted the initial outreach generally contacted the partners via telephone to remind them of their testing appointment, rescheduled appointments as needed, conducted HTS, and documented test results, even if HTS was conducted at nonstudy sites. If HTS was completed at a nonstudy site by the partner, results were obtained via self-report. If a notification occurred as part of a home visit, partners were offered HTS after verbal consent per Kenya national guidelines [24]. When possible, HTS providers accompanied HIV-positive partners to the nearest HIV comprehensive care center for linkage to care.

Partner Participant Recruitment and Enrollment

Partners were aged ≥18 years. Recruitment and enrollment of partner participants took place during the tracing visit. Before testing for HIV, partners were invited to enroll in the study; however, they did not need to enroll to get tested. When possible, male partners who tested HIV positive were offered APS for their other female sexual partners.

Participant Follow-Up

HTS providers made phone calls to assess linkage to and engagement in care and ART initiation for index clients and partners with HIV at 6 weeks and 6 months postenrollment. At 12 months postenrollment, participants were asked to make a physical visit to the comprehensive care center for clinical care consultation and to conduct an HIV viral load test. For all follow-up timepoints, participants who were not reached after three attempts by phone were physically traced.

IPV Monitoring

Adolescent girls and women reporting IPV within the past month were excluded from participation and instead referred to IPV counseling and other support services, as needed. Those reporting that they had not experienced recent IPV but feared IPV and abuse from a partner were eligible for study participation but had the option to refuse both APS and study participation. They received instructions regarding confidential reporting to clinical providers and study staff, and case report forms documenting any IPV were completed by phone or in person, depending on their preference. We provided additional training on IPV counseling for study staff and ensured that resources had been identified at all sites to safely refer females who reported abuse or concern for their safety. Individuals experiencing IPV were excluded at enrollment to avoid any harm as a result of notifying their partners. However, if they reported IPV at a follow-up visit (after enrollment), they were followed to ensure that they were safe and referred to IPV services as needed. In addition, these data will be helpful in studying the safety of APS.

Outcomes

The effectiveness outcomes included (1) number of persons testing for HIV for the first time among all tested, (2) male partners who are newly diagnosed with HIV versus known to be living with HIV among all tested, (3) linkage to care and initiation of ART by 6 weeks and follow-up at 6 months for male partners with HIV and female index clients, and (4) suppression of plasma HIV RNA levels to <400 copies/μL at 12 months among male partners living with HIV and female index clients. We also monitor adverse events, including IPV and relationship dissolution.

Data Collection

Study data were collected using the open-source Open Data Kit platform using questionnaires administered on Android smartphones or tablets [25]. Data were encrypted for storage on the devices and transferred immediately over an encrypted connection to a secure server at NASCOP. The study database was backed up nightly to a secure server at the University of Washington.

Data Analysis

We will use log-binomial regression with robust standard errors to assess the proportion of participants with the main outcomes of interest and use multivariate log-binomial and logistic regression to examine the potential predictors of outcomes of interest, including participant demographics, HIV testing history, sexual behavior, and location. We will conduct time trend analyses to examine the changes in proportions with outcomes of interest over time as the APS are scaled up.

Aim 2: To Determine the Fidelity, Integration, Acceptability, Demand, Technical Efficiency, and Cost of Implementing APS

Study Sites

The aim 2 implementation evaluation occurred in (1) Homa Bay and Kisumu HTS facilities and DREAMS sites; (2) selected subcounty and county administrative offices linked to health facilities; and (3) NASCOP's national administrative offices in Nairobi, Kenya. We included both high-performing and low-performing facilities and covered the range of facility levels from small rural outposts to high-volume urban clinics.

Study Participants

HTS providers involved in tracing and HIV testing of partners underwent in-depth interviews (IDIs) with a qualified qualitative interviewer for the evaluation of acceptability of APS, perceived community demand for APS, and implementation fidelity to the APS protocol. The enrolled index participants and male partners who had received APS also underwent IDIs to evaluate the acceptability and perceived demand for APS. Key APS stakeholders, including facility in-charges, county or subcounty AIDS/sexually transmitted infection coordinators, and administrators at NASCOP, were interviewed to evaluate the integration and perceived demand for APS.

Study Procedures

HTS providers, index and partner participants, and key APS stakeholders were informed of and invited to participate in the study. Those interested were screened for eligibility and provided consent for an IDI. IDIs were conducted in the language preferred by an experienced qualitative researcher who spoke English, Swahili, and the local languages in a quiet place at a study facility or another location chosen by the participant.

Outcomes

Key outcomes for aim 2 included the determination of (1) health facility and individual-level factors that influence fidelity to APS; (2) acceptability, demand, and health system requirements influencing the feasibility of APS; and (3) costs of APS when integrated into existing HTS. Cost metrics included total incremental economic costs of APS, cost per person traced, cost per person HIV tested, and cost per person linked to ART.

Data Collection

Implementation Fidelity

Although we anticipated some variation in APS implementation across sites, it was difficult to know how contextual differences in the execution of APS procedures would affect outcomes unless we examined how well the implemented intervention matched the intended implementation. We used a conceptual framework for implementation fidelity to identify and describe the key implementation fidelity elements [26].

A convergent mixed methods approach was used to concurrently collect qualitative and quantitative data. A total of two data sources, facility data and staff, were used to triangulate the implementation fidelity to the APS. Facility-level data were collected daily by HTS providers to ascertain the frequency, type, and success of each tracing attempt using structured questionnaires. Measurement of fidelity started at least 12 months after site activation to provide enough time for HTS providers to familiarize themselves with the APS intervention. In addition, as a staggered study started in the 2 counties, with Homa Bay sites initiating 6 months after Kisumu sites, the 12-month period ensured that HTS providers had significant exposure to APS in both counties before assessment.

Acceptability of and Demand for APS

We examined APS acceptability among HTS providers, index clients, and male partner participants. We conducted 14 IDIs with HTS providers (same population in the implementation fidelity aim) and 32 IDIs with clients (16 index clients and 16 partners) to address questions related to APS acceptability from 8 purposively selected facilities that vary in patient volume and APS performance. We selected 1 female index who elicited ≤2 male partners and another female index who elicited >2 male partners at each facility in both Homa Bay and Kisumu. Interview guides addressed APS satisfaction, perceived benefits of the intervention, and challenges that may affect delivery or uptake.

To assess demand, we conducted IDIs with 14 HTS providers, 32 clients, and 20 key stakeholders (same population in the integration aim) to assess experiences with provision, administrative oversight, and use of APS intervention activities. Guiding questions were "To what extent is APS likely to be used or supported, and how much demand for APS is perceived to be there in people (general and specific groups) in the community?" In addition, APS delivery statistics provided information on the actual usage of the services.

All IDIs were conducted by a qualified qualitative interviewer using a semistructured interview guide and audio recorded and transcribed for analysis.

Integration

We adapted the analytic framework by Grepin and Reich to develop and assess a strategy for integrating APS into existing HIV programs, [27] measure the extent of integration. Integration was measured by the extent of coordination, collaboration, and consolidation, occurring at various levels (policy, organizational, national or regional, and local). We conducted 20 IDIs with purposively selected key NASCOP policy makers, subcounty and county health management team members, facility staff, and community representatives at study initiation and 1 year into APS scale-up to identify opportunities and challenges for both integration within Kenya's current HIV cascade of care and extent of integration over time. The findings were used to develop metrics to monitor the extent to which integration occurs at each level during APS implementation, along with specific scoring criteria.

Cost

We conducted a microcosting and time-in-motion observation of APS activities. Start-up and recurrent cost data were obtained from financial records, including budgets and expense reports from the MOH, PATH-Kenya, and study sites. We collected information on the quantities of inputs and prices of each input

used to implement enhanced APS services, including personnel, commodities, and capital goods (such as vehicles, computers, phones, and other equipment). We also obtained budget expense report data on program design, adaptation, and installation related to awareness raising, materials development, training, and the costs of other start-up activities that are essential for expanding the program. The team sought to obtain information directly from the study sites whenever possible. However, if this information was not available, estimates were used from the MOH records of facilities with similar characteristics. Cost data were synthesized using Microsoft Excel spreadsheets.

Technical Efficiency of Health System Requirements

Technical efficiency is a relative measure that compares the inputs used (human, technological, and financial) with the outputs attained (number and level of services) [28]. It is designed to assess whether an organization is deploying the right mix of personnel, equipment, supplies, and facilities to produce outputs at the lowest cost. Using data collected from the cost aim, we examined the necessary health system requirements needed to operate APS provision, identify environmental constraints, and determine their technical efficiency. The domains examined were (1) facility-level characteristics (organizational structure, management, governance, decision-making processes, funding sources, training, supervision, incentives, and accountability) and (2) environmental contextual constraints (size of target population and population actually using the services). Determinants of efficiency are those that affect the cost of delivery, which depends on a facility's performance.

Data Analysis

Implementation Fidelity

Using a convergent mixed methods approach, we will examine the health facility characteristics (eg, location or staffing) associated with high fidelity to protocol elements and positive implementation outcomes by triangulating facility-level data with qualitative findings from the HTS provider IDIs. IDI audio recordings will be transcribed and analyzed by 2 independent coders using thematic content analysis to determine the key implementation fidelity themes using both deductive and inductive coding [29].

Descriptive statistics will be used to describe the characteristics of participants by county, type, and success of tracing attempts. Categorical variables will be described using counts and proportions, and continuous variables will be described using medians and IQRs. The time needed to conduct tracing attempts will be described using median and IQR and compared with the standard APS protocol to determine the fidelity to the protocol. Pareto charts based on the Pareto principle that 80% of the effects originate from 20% of the causes will be used to determine the tracing attempts through which most clients are successfully traced [30]. Data collected from HTS providers will be used to describe contextual factors.

In the multivariate analysis, successful tracing attempts (coded as either yes or no) will be the outcome of interest. We will consider two levels of data: individual level with clustering at the facility level. Log-binomial generalized estimating equations

with exchangeable correlation structure and robust SEs will be used to estimate the relative risks and 95% CIs of successful attempts by the type of tracing attempt (phone vs physical). Variables associated with linking to care in these univariate analyses ($P<.10$) will be included simultaneously in the multivariate model. Moderators will not be included in this multivariate model; however, they will be used to provide context to the results of the quantitative analysis.

Acceptability and Demand of APS

Recordings of the interviews will be transcribed verbatim and translated into English. Codebooks will be developed and tested using the first five to six interview transcripts and applied to all transcripts for coding, once finalized. Transcripts will be independently coded by two analysts who will reach consensus through discussion. Disagreements will be adjudicated by a third qualitative researcher. Qualitative data will be analyzed thematically using an inductive coding approach [29]. Analysis will be conducted first for all interviews and then we will perform a comparative analysis among different participant groups and different types of facilities varying in patient volume and APS performance.

Cost

Microcosting data will be used to estimate total incremental costs by facility and all-sample-weighted average incremental cost per partner traced, cost per partner tested, and cost per partner newly diagnosed as HIV positive. We will estimate the total incremental and unit costs for each facility and estimate the average and weighted cost metrics for the facilities in our sample. We will generate cost profiles based on activity and input. Using a government payer perspective, we will construct an Excel-based static deterministic model to simulate the budget impact analysis of APS on an annual basis over a 5-year time horizon using HIV prevalence estimates from Kisumu and Homa Bay counties. We will assume that 70% of this population will test for HIV and that 50% of these will receive APS.

Cost estimates for budget impact analysis, will include incremental costs for APS, ART, clinic visits, and hospitalization. We will compare two scenarios, assuming 50% and 100% APS implementation within the health facilities. We will assume that HTS providers working a 5-day work week will have a case load of no more than 10 clients per day per counselor based on national Kenyan HTS standards and previous studies.

Study Registration

The study was registered on clinicaltrials.gov on June 22, 2017. Enrollment started in May 2018 in Kisumu County and in November 2018 in Homa Bay County. The study is expected to be completed in May 2022.

Results

As of March 2020, we recruited 1724 index clients, 3201 male partners, and 1585 female partners. We completed recruitment for this study and 6-week (2936/2973, 98.75%), 6-month (1596/1641, 97.25%), and 12-month (725/797, 90.9%) follow-up visits. We are now completing the remaining 12-month

follow-up visits. Preliminary analyses demonstrate that by scaling up APS, facilities can identify 12-18 new HIV-positive males for every 100 men contacted and tested. This is considerably higher than the average HTS yield in Kenya of <2%. During this period, 21 individuals were ineligible for the APS study because of IPV concerns. Despite this, there have been 35 IPV events related to HTS and APS, which were not due to procedures. Overall, 32 relationships were dissolved during this period.

Discussion

The Kenya MOH and NASCOP guidelines for HIV testing recommends voluntary APS implementation as part of routine HTS. This study is designed to assess how best to implement and scale up APS within public health settings in low-income countries such as Kenya. We have integrated study activities and follow-up visits into existing routine HIV testing, prevention, and care programs at participating sites to assess how APS functions at scale in a real-world setting.

With the current global goal of reaching 95-95-95 in HIV epidemic control, the pool of undiagnosed PLWH continues to decline, and APS are an effective modality for reaching those who are undiagnosed. This is especially true for certain subgroups, such as men, who are more likely to be missed by standard HTS. In addition, the study documents other aspects of APS implementation, such as cost, fidelity, and acceptability, which will inform a costed national scale-up of this modality. We sought to identify the most critical factors for successful APS implementation by rigorously documenting process outcomes such as provider elicitation rates and phone versus physical tracing outcomes. The study results will inform national and county-level approaches for scaling up APS to prioritize the critical factors for success. The elicitation and documentation of IPV in the study also provides insights into the safety of APS. In addition, those identified as probable or confirmed IPV cases through the study are referred to gender-based violence centers of excellence for appropriate care, following best practices.

The limitations of this study include that some key outcomes, including linkage to care and ART, are self-reported by participants. Furthermore, the proportion of index clients who were adolescents was low (11%). To overcome these challenges, we are assessing viral loads that are at 12-months post APS to objectively assess ART linkage and adherence. In addition, our study did not enroll clients who were men who have sex with men, who are a key population that should be targeted via APS; future work is warranted in this area. Finally, some of the findings regarding implementation fidelity, integration, acceptability, demand, and cost may not be generalizable to other settings outside Kenya.

Scaling up APS is an important step in providing HTS in sub-Saharan countries as it facilitates testing of undiagnosed individuals in populations such as men who have been challenging to reach with the existing HTS. We are conducting this APS scale-up study using implementation science methodologies and existing HTS infrastructure in Homa Bay and Kisumu counties. We expect to complete a 12-month follow-up for participants by May 2021 and will share results with NASCOP as well as in local and international practice-oriented and scientific meetings.

In response to the COVID-19 pandemic and accompanying challenges in conducting standard APS [31], we are shifting to investigate the effectiveness of self-testing for testing partners identified through APS. HIV self-testing is an essential adaptation to the current COVID-19 pandemic to limit the effect of physical distancing measures and lockdowns, particularly on facility- and community-based partner tracing and testing. In addition, the World Health Organization recommends self-testing as an approach to increase access to HTS [32], and it has the potential to both reach partners who would not otherwise participate in standard APS and reduce the costs associated with provider-delivered HIV testing in standard APS. The results of our studies will be used to bridge the gap between clinical research findings and everyday practice and provide guidance on optimal strategies for APS integration into HIV service delivery.

Authors' Contributions

E Kariithi, MS, and E Kemunto wrote the first draft of the manuscript. HL, BMW, GO, RB, MM, PM, and WL wrote specific sections of the manuscript. DAK, MS, URP, SM, BJW, CEL, and CF provided technical input, revisions, and edits on multiple drafts of the manuscript. All authors critically revised the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Intimate partner violence screening questionnaire.

[DOCX File , 22 KB - resprot_v10i5e27262_app1.docx]

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Abbreviations

APS: assisted partner services
ART: antiretroviral therapy
DREAMS: Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe
HTS: HIV testing services
IDI: in-depth interview
IPV: intimate partner violence
MOH: Ministry of Health
NASCOP: National AIDS and Sexually Transmitted Infection Control Programme
PLWH: people living with HIV
SSA: sub-Saharan Africa

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Protocol

Phototherapy Using a Light-Emitting Fabric (BUBOLight) Device in the Treatment of Newborn Jaundice: Protocol for an Interventional Feasibility and Safety Study

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Abstract

Background: Neonatal jaundice is a common condition occurring in 60%-80% of all healthy-term and late-preterm neonates. In the majority of cases, neonatal jaundice resolves spontaneously and causes no harm; however, in some neonates, significant hyperbilirubinemia can develop and lead to kernicterus jaundice, a serious neurological disease. Phototherapy (PT) is the preferred treatment for jaundice; however, to be effective, PT devices need to have a broad light emission surface to generate no or little heat and to provide an optimal wavelength and light intensity (420-490 nm and ≥30 μW/cm²/nm, respectively).

Objective: This study aimed to investigate the feasibility, safety, and level of satisfaction of parents and health care teams with the BUBOlight device, an innovative alternative to conventional hospital PT, in which luminous textiles have been incorporated in a sleeping bag.

Methods: This interventional, exploratory, simple group, nonrandomized, single-center trial will be conducted at Lille Hospital. In total, 10-15 neonates and their parents will be included to obtain evaluable data from 10 parent-neonate pairs. Neonates weighing more than 2500 g at birth and born with ≥37 weeks of amenorrhea that required PT in accordance with the guidelines of the National Institute For Health and Clinical Excellence will receive one 4-hour session of illumination. Total serum bilirubin and transcutaneous bilirubin levels were obtained at the start and 2 hours after the end of PT. Cutaneous and rectal temperatures, heart rate, and oxygen saturation will be measured at the beginning and during PT. The number of subjects is therefore not calculated on the basis of statistical assumptions. We aim to obtain a minimum proportion of 90% (ie, 9 of 10) of the neonates included, who have been able to undergo 4-hour PT without unacceptable and unexpected toxicities. We will calculate the mean, median, quartiles, minimum and maximum values of the quantitative parameters, and the frequency of the qualitative parameters. The rate of patients with no unacceptable and unexpected toxicities (ie, the primary endpoint) will be calculated.

Results: The first patient is expected to be enrolled at the end of 2020, and clinical investigations are intended for up to June 2021. The final results of this study are expected to be available at the end of 2021.

Conclusions: Our findings will provide insights into the safety and feasibility of a new PT device based on light-emitting fabrics for the treatment of newborn jaundice. This new system, if proven effective, will improve the humanization of neonatal care and help avoid mother-child separation.

Trial Registration: ClinicalTrials.gov NCT04365998; https://clinicaltrials.gov/ct2/show/NCT04365998

International Registered Report Identifier (IRRID): PRR1-10.2196/24808

Introduction

Neonatal jaundice or hyperbilirubinemia is very common in neonatology. Neonatal livers are generally immature, and this condition leads to poor metabolism of bilirubin. Bilirubin is not sufficiently degraded and accumulates excessively in the blood. This clinically manifests as yellowing of the skin and mucous membranes. Based on etiology, jaundice can be divided into physiological and pathological jaundice [1,2].

The evolution of pathological jaundice is often favorable, but it can lead to complications such as acute or even chronic encephalopathy known as kernicterus [3].

Hyperbilirubinemia from any cause among healthy infants is considered to be of concern if the bilirubin level is >18 mg/dL (>308 μmol/L) in infants who are 49-72 hours old [4] and requires prompt management. Furthermore, jaundice is the primary cause of rehospitalization in the first 15 days of life, which makes it an important issue for health professionals.

Screening and diagnosis of jaundice is routinely performed for all neonates. It is based on a daily visual clinical assessment, which must be combined with a transcutaneous bilirubin measurement or total serum bilirubin measurement as only 50% of neonates with a total serum bilirubin concentration of >128 μmol/L visually appear to have jaundice, especially dark-skinned neonates [5].

Bilirubin is a yellow pigment that preferentially absorbs blue, violet, or green light (400-490 nm) [6]. Phototherapy (PT) is used as first-line treatment for hyperbilirubinemia. The aim of PT is to decrease or prevent an increase in the concentration of circulating bilirubin by using blue light.

Light absorption by bilirubin induces the formation of photoisomers that can be excreted in the urine or bile, thus bypassing hepatic conjugation [7,8].

The indication for PT depends on the total bilirubin levels in blood and the presence or absence of conditions that increase the risk of bilirubin neurotoxicity.

Intensive PT, defined by an irradiance of ≥30 μW/cm^2/nm, is more effective than conventional PT [9], but there is no standardized method for delivering efficient PT. Nonetheless, PT for a short duration (ie, 4 hours) by illuminating the largest body surface bas been recommended [10].

There are several PT devices that contain light-emitting diode–based lights, conventional fluorescent blue lights, or conventional halogen lights with an emission spectrum of 420-490 nm, which can provide effective irradiance to reduce serum bilirubin levels [11], but characteristics such as the distance of the light source from the neonate, the area illuminated, and the irradiance affect the effectiveness of phototherapy [12].

The BUBOLight PT device is composed of a light source and light-emitting fabrics (LEFs) in a sleeping bag. LEFs incorporate optical fibers inside a textile structure. By controlling the density of the fibers and the bending angles, this structure makes it possible to obtain a homogeneous light distribution on a very flexible textile surface.

BUBOLight emits light with a wavelength of 445 nm, an irradiance equal to 3.5 mW/cm², and a useful surface of 756 cm². It thus has the characteristics of an effective PT; that is, a sufficiently exposed surface, a wavelength similar to the maximum absorption peak of bilirubin, a sufficiently high irradiance, bilateral illumination to increase the total treatment surface, and a homogeneous and stable light distribution.

In addition, BUBOLight has been designed not to heat up, thus avoiding the risk of hyperthermia in neonates. When used in the infant's bed, it helps preserve parent-child interactions and does not require the wearing of protective glasses because the light cannot pass through the sleeping bag. Finally, the infant is installed with a special diaper that includes protection for the genitals. The aim of the present protocol is to evaluate the feasibility and the safety of the BUBOLight device as a new PT method.

Methods

Trial Design

This interventional, exploratory, simple group, nonrandomized, single-center study will include 10-15 neonates in order to obtain evaluable data from 10 parent-child pairs.

Setting

The study will be conducted at the department of obstetrics at Lille University Hospital (Lille, France), over a period of 6 months until June 2021. Parent-neonate couples will be included and followed-up in the study until neonatal serum bilirubin levels are measured 2 hours after the end of PT. The participation of parent-child pairs in this study will then be limited to a 6-hour session.

Device

The complete BUBOLight device consists of an electrically powered light source that emits blue radiation with a predefined wavelength of 445 nm connected to an active textile part (Figure 1). The active textile part of the device consists of sleeping bag system in which are integrated 2 removable LEFS (Figure 2) to diffuse a blue light from a light source. The light source was designed by the ONCO-THAI U1189 (Lille, France) and is composed of 2 light sources with an output power of 4 W. The active textile part (MDB Texinov) has a usable surface area of 756 cm² and can deliver an irradiance of 3.5 mW/cm² (with a variation of 20%) in blue light.

Figure 1. Complete device and light source.

Figure 2. Light-emitting fabrics in the sleeping bag.

Participants

To be eligible for the study, neonates must meet all the inclusion criteria described in Textbox 1. Neonates must not meet any of the exclusion criteria.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Infants born at the Lille University Hospital and not out of this hospital

- Gestational age of ≥37 weeks with amenorrhea

- Presence of jaundice confirmed through transcutaneous bilirubin measurement with a bilirubinometer (model JM-105, Dräger) (Reference graphs related to gestational age–specific thresholds for initiating PT treatment [13])

- Rate of total serum bilirubinemia requiring phototherapy (Reference graphs related to gestational age–specific thresholds for initiating PT treatment [13])

- Absence of rhesus or Kell fetal-maternal incompatibility

- Weight at birth of ≥2.5 kg

- Discerned to be in good health by the investigator after clinical examination and on the basis of medical data (absence of perinatal asphyxia, antibiotic treatment, and respiratory disorders)

Exclusion criteria

- Neonate who has already been treated with PT

- Febrile state with a body temperature of >37.5°C

- Total bilirubinemia rate or excess of 100 μmol/L as an indication for PT

- Neonates with jaundice due to hemolysis or functional or anatomical obstruction

- Weight loss of >10% of the birth weight

- Neonates requiring treatment other than PT

- Neonates with congenital erythropoietic porphyria or a family history of porphyria.

- Presence of ≥2 of the following risk factors:

  - Gestational age of <38 weeks of amenorrhea

  - Icterus of the first 24 hours

  - ABO incompatibility

  - Positive irregular agglutinin test status of the mother

  - History of jaundice treated in siblings

  - History of familial hemolysis

  - Serosanguineous bump, bruise, cephalohematoma

  - Ineffective breastfeeding

  - Weight loss of ≥8%

- Parents who are noncompliant with the study design

Study Objectives and Outcomes

The primary objective of the study is to evaluate the safety of the BUBOLight PT device as an alternative to conventional tunnel PT under the usual conditions for the management of jaundice in neonates.

Safety will be based on the proportion of neonates who received complete and effective 4-hour PT with the BUBOlight device and did not experience unacceptable and unexpected toxicities (target set at least 90% of neonates).

The key secondary objectives are the individually frequency of each adverse effect, monitoring of serum bilirubin and transcutaneous levels under phototherapy, and the perceptions of parents and health team with the use of the device (comfort, heat, humidity, ease of breastfeeding, proximity, and possibility of contact with the baby) and causes of PT discontinuation. Table 1 summarizes the study objectives and outcomes.

Table 1. Study objectives and outcomes.

Outcomes	Inclusion: initiation of phototherapy (hour 0)	1 hour after the beginning of phototherapy	2 hours after the beginning of phototherapy	4-hour effective phototherapy	2 hours after the end of phototherapy
Primary outcomes: safety					
Monitoring of hyperthermia (body temperature of ≥38°C) or hypothermia (body temperature of ≤36°C)	✓	✓	✓	✓	
Oxygen saturation of <90% for >15 seconds	✓	✓	✓	✓	
Heart rate of >160 beats/minute during inactivity or <80 beats/minute for >15 seconds	✓	✓	✓	✓	
Allergic contact reaction of grade ≥3 (Ring and Messmer classification [14])	✓	✓	✓	✓	
Secondary outcomes					
Description of the number of neonates presenting each adverse event individually (skin lesion, dehydration, diarrhea, etc)	✓	✓	✓	✓	
Monitoring of serum bilirubin levels	✓				✓
Monitoring of transcutaneous bilirubin levels	✓				✓
Evolution of the EDIN[a] score: neonatal pain and discomfort scale	✓			✓	
Number of feedings, number of diaper changes and the causes of cessation of phototherapy			✓	✓	
Perceptions of the parents with the use of the device and interaction with their child					✓

[a]EDIN: Échelle de Douleur et d'Inconfort du Nouveau-né.

Sample Size

This is a pilot feasibility study. The number of subjects is therefore not calculated on the basis of statistical assumptions. We propose to include 10-15 neonates and their parents in order to obtain evaluable data from 10 parent-neonate pairs. The feasibility objective is to obtain a minimum proportion of 90% (ie, 9 of 10) of the neonates included in this study, having undergone PT without unacceptable and unexpected toxicities.

Allocation and Randomization

There will be no randomization in this study; all neonates will receive PT with the BUBOLight device.

Implementation and Blinding

The study will not involve blinding as it is an uncontrolled clinical trial with a single group of patients receiving the same treatment. Data will also be analyzed without blinding.

Intervention

Neonates who have not been discharged from the hospital and who require PT for jaundice will be included in the study after verification of the inclusion and exclusion criteria.

As shown in Figure 3, parent-neonate pairs who meet all of the inclusion criteria and none of the exclusion criteria are invited to participate in the study, which will involve a single visit.

The study will include an effective 4-hour PT session (which may be discontinued for a few minutes to change diapers if necessary) followed by a 2-hour rest period in accordance with the recommendations of the French National Reference Center for Perinatal Hemobiology. Serum bilirubin levels will be determined upon initiation of PT (H0) and 2 hours after the effective end of PT; that is, at approximately H0+6 hours, in order to check for a reduction in bilirubin levels. Transcutaneous measurement with a bilirubinometer (Dräger Jaundice Meter JM-105) will be also performed upon initiation of PT and 2 hours after the effective end of PT.

Heart rate and oxygen saturation will be continuously recorded using a monitor, which is usually used during PT. Alarms will be set to detect desaturation and bradycardia episodes lasting >15 seconds. The investigator will check the scope at the end of the monitoring period for false episodes related to an artefact.

In addition, axillary and cutaneous temperatures will be regularly monitored in order to prevent any risk of dehydration and hyperthermia. Room temperature will also be measured.

The neonatal pain and discomfort scale (Échelle de Douleur et d'Inconfort du Nouveau-né [EDIN] score) and the opinion of parents and health professionals on the use of the device will also be sought.

Figure 3. Study design and data collection.
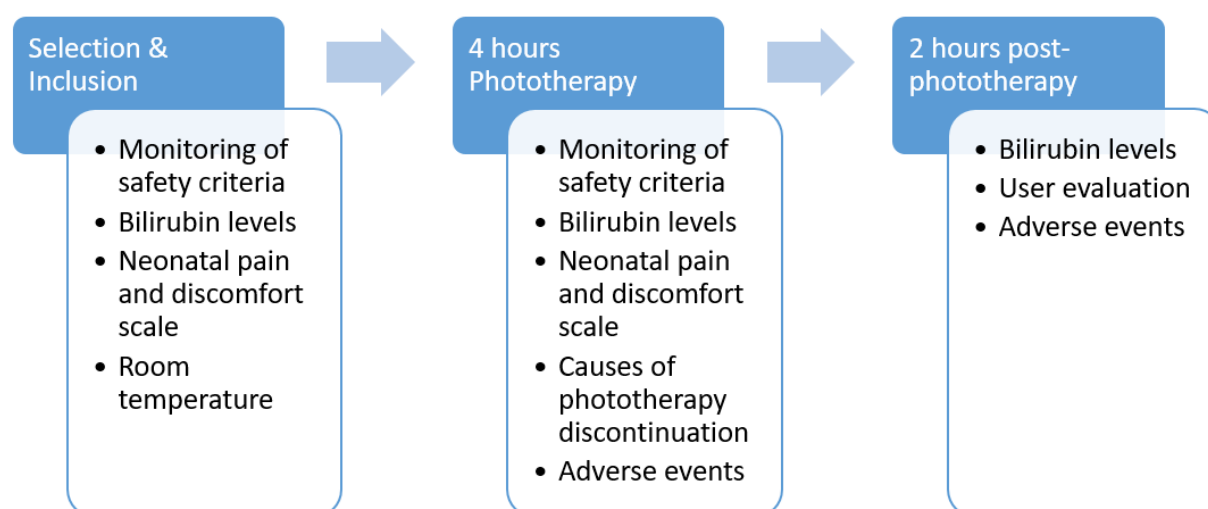
Variables and Data Collection

The collected medical data will consist of demographic and medical data (sex, weight, height, day of birth, and gestational age), risk factors for severe hyperbilirubinemia, and the blood type of the mother and the child.

To achieve the primary and secondary endpoints, we will measure serum and transcutaneous bilirubin levels.

Temperature, oxygen saturation, and heart rate data will be monitored throughout the PT session. EDIN scores of 0-15 will be considered for monitoring neonatal pain and discomfort, and data regarding PT discontinuation will be collected (including the number of changes, feedings, and cares).

Parents and medical staff will be asked to complete feedback questionnaires at the end of the observation period. Data will be collected on device usability, assessment of noise, and the design of the device.

Data Management

This study complies with methodology MR-001 of the Commission nationale de l'informatique et des libertés for the treatment of personal data, which is a simplified declaration of data from medical research to the French National Data Protection Authority. The only persons authorized to access

data and modify the files generated in this study are those who are directly involved in the study. These participants will have access to data and be able to modify them at any moment in consultation with one of the referring investigators of the study. The sponsor affirms the patient's right to protection against invasion of privacy.

The data will be collected through a case report form and be saved in an electronic file (database). All participants will receive a trial identifier, and only the investigator knows the personal details. The sponsor's monitor will plan several monitoring visits, after initial enrollment at the study site and periodically to assess data quality and study integrity. The sponsor's monitor will review the study records and directly compare them with the source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. The trial will be monitored in accordance with the monitoring plan. A planning meeting with the principal investigator will hence be held before the start of the trial. During the trial, several checkpoints are defined, including the presence of signed informed consent forms obtained by the investigator, adherence to the inclusion and exclusion criteria, reporting of any adverse events, and the monitoring of all steps of patient follow-up. At the end of the trial and once the final analysis is completed and validated, all the files are sealed and

archived in accordance with specific procedures at a secure location at the clinical research department of the sponsor.

The trial support unit will coordinate the data management. The database is stored and secured on the network of Lille University Hospital. Before the closeout of the database, data monitoring will be performed using XLSTAT software (Addinsoft Inc) in accordance with consistency guidelines set with the project manager (eg, missing data, outliers, and inconsistency among several variables). The data will be analyzed at the OncoTHAI Laser Assisted Therapies and Immunotherapies for Oncology unit (U1189, Inserm, CHU Lille). Only the investigator participating in the study or a collaborator designated by the physician and participating in the study may modify the data. The study data will be archived for a minimum period of 15 years from the end of the study or its early termination without bias toward the laws and regulations in force.

Statistical Analysis

Security and acceptability will be assessed using descriptive data. All data will be described individually and summarized using the following statistical parameters:

Primary objective: the mean, median, quartiles, minimum and maximum values of the quantitative parameters, and the frequency of the qualitative parameters will be calculated. The rate of patients with no unacceptable and unexpected toxicities (primary endpoint) will be calculated.

Secondary objectives: bilirubin levels and EDIN score data for neonatal pain and discomfort will be expressed as means, medians, quartiles, and minimum and maximum values at each measurement time.

Changes in serum and transcutaneous bilirubin levels among PT initiation (H0), H0+4 hours (only transcutaneous), and 2 hours after the end of PT, and changes in the EDIN score between PT initiation (H0) and after 4 hours of actual treatment will also be described. Furthermore, we will calculate the mean, median, quartiles, minimum and maximum values of the quantitative parameters (number of feedings, diaper changes, and care), and the frequency of the qualitative parameters (perceptions of the parents and the health team regarding the use of the device and interaction with their infant).

Ethical Consideration

The trial will be conducted in accordance with tenets of the Declaration of Helsinki and the guidelines of the International Council for Harmonization and article L1121-4 of the Public health code. The study protocol has been submitted for review and approval by the French Ethics Committee (protocol# 20/025-1) and the French National Agency for the Safety of Medicines and Health Products (protocol# 2019-A01417-50). The trial was registered at ClinicalTrials.gov (protocol# NCT04365998). The investigator must ensure that the parents of the subjects are informed clearly and thoroughly about the purpose, potential risks, and other critical issues related to the trial in which they volunteer to participate. Written informed consent must be freely obtained from each parent of the subjects prior to their participation in the trial, including informed consent for any screening procedure conducted to establish subject eligibility for the study. The rights, safety, and well-being of the parent-neonate pair are the most important considerations and should prevail over the interests of science and society.

Results

The first parent-neonate pair will be enrolled at the end of 2020. All data collected will provide a basis to analyze the safety and effectiveness of the device. The last subject is expected to be enrolled by June 2021. Analysis of the data and results are expected to be completed at the end of 2021.

Discussion

PT using light emitting diode light tunnels will inevitably lead to a physical and psychological distance, which will interfere with mother-neonate bonding, potentially cause problems with breastfeeding, and increase the exposure to infections. The development of new PT systems that are as effective as conventional PT is therefore necessary.

BUBOLight has been designed to incorporate LEFs to deliver PT directly on the neonate's skin in his/her sleeping bag, thus allowing the mother to change and breastfeed the neonate without interrupting treatment, in the hospital environment. In case we obtain positive results, we hope to initiate a comparative study of BUBOLight versus conventional PT devices in order to use BUBOLight intermittently or exclusively in outpatient follow-up programs.

Conflicts of Interest

None declared.

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Abbreviations

EDIN: Échelle de Douleur et d'Inconfort du Nouveau-né
LEF: light-emitting fabric
PT: phototherapy

Protocol

The United States Chronic Thromboembolic Pulmonary Hypertension Registry: Protocol for a Prospective, Longitudinal Study

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Abstract

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare sequela of acute pulmonary embolism that is treatable when recognized. Awareness of this disease has increased with recent advancements in therapeutic options, but delays in diagnosis remain common, and diagnostic and treatment guidelines are often not followed. Data gathered from international registries have improved our understanding of CTEPH, but these data may not be applicable to the US population owing to differences in demographics and medical practice patterns.

Objective: The US CTEPH Registry (US-CTEPH-R) was developed to provide essential information to better understand the demographics, risk factors, evaluation, and treatment of CTEPH in the United States, as well as the short- and long-term outcomes of surgical and nonsurgical therapies in the modern treatment era.

Methods: Thirty sites throughout the United States enrolled 750 subjects in this prospective, longitudinal, observational registry of patients newly diagnosed with CTEPH. Enrollment criteria included a mean pulmonary artery pressure ≥25 mmHg by right heart catheterization and radiologic confirmation of CTEPH by a multidisciplinary adjudication committee. Following enrollment, subjects were followed biannually until the conclusion of the study. Quality of life surveys were administered at enrollment and biannually, and all other testing was at the discretion of the treating clinician. Details regarding surgical therapy, balloon pulmonary angioplasty, and medical therapy were collected at enrollment and at follow-up, as well as information related to health care utilization and survival.

Results: Data from this registry will improve understanding of the demographics, risk factors, and treatment patterns of patients with CTEPH, and the longitudinal impact of therapies on quality of life, health care utilization, and survival.

Conclusions: This manuscript details the methodology and design of the first large, prospective, longitudinal registry of patients with CTEPH in the United States.

Trial Registration: ClinicalTrials.gov NCT02429284; https://www.clinicaltrials.gov/ct2/show/NCT02429284

International Registered Report Identifier (IRRID): DERR1-10.2196/25397

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a subset of pulmonary hypertension (PH) characterized by obstruction of the pulmonary arteries with fibrotic material and vascular remodeling, which leads to increased pulmonary arterial pressure and right ventricular failure. Although clinical presentation and the pathological changes of the pulmonary vasculature share some characteristics with pulmonary arterial hypertension (PAH), the etiology, diagnosis, and treatment of CTEPH are quite distinct from those of PAH [1]. Registries that focus on PAH have been established [2-6]; however, there has never been an organized collection of multicenter CTEPH data in the United States.

The diagnostic and therapeutic landscape for CTEPH in the United States has changed dramatically in recent years. Digital subtraction pulmonary angiography (DSA) was long considered the gold standard for the diagnosis of CTEPH and determination of operability; however, technological improvements in computerized axial tomography angiography (CTA) have replaced invasive pulmonary angiography in many centers, and magnetic resonance imaging is used at some centers for both angiography (MRA) and assessment of right ventricular function. Nuclear ventilation perfusion scanning remains the recommended screening modality for CTEPH, although dual-energy computed tomography is emerging as a technology that provides the combined imaging required (perfusion mapping and pulmonary angiography) for the evaluation of CTEPH [7,8].

Multiple new treatment options have recently become available to patients with CTEPH, particularly those with inoperable disease or residual PH after surgery. Advances in pulmonary thromboendarterectomy (PTE) techniques have changed the definition of operability, selecting patients with more distal segmental and subsegmental disease who previously were classified to have inoperable disease and are now deemed as surgical candidates. Balloon pulmonary angioplasty (BPA) is now a therapeutic option for those who are not surgical candidates or patients with residual PH following PTE. Riociguat, the first Food and Drug Administration–approved drug for the treatment of CTEPH, is also an option for this subpopulation [9,10].

Despite a growing literature, substantial knowledge gaps remain regarding our understanding of CTEPH. A CTEPH registry involving 26 centers from Europe and one from Canada reported valuable data elucidating the epidemiology, risk factors, and outcomes in this mostly European cohort of patients newly diagnosed with CTEPH [11,12]. However, whether these data are applicable to the US population remains unclear given demographic and cultural differences, as well as the regional disparities in the practice of medicine between Europe and the United States. In addition, this European registry was established prior to the availability of BPA and riociguat for the treatment of CTEPH.

The dramatic changes in the diagnosis and management of CTEPH, and the accompanying knowledge gaps motivated us to organize the first US CTEPH registry. The United States Chronic Thromboembolic Pulmonary Hypertension Registry (US-CTEPH-R) is a contemporary CTEPH registry that will provide data for patients with CTEPH diagnosed between 2014 and 2018. Patient demographics, medical history, symptoms, timeline to diagnosis, risk factors, diagnostic approach, disease management, and long-term outcomes postintervention have been collected. Among the most important issues we sought to address are the longitudinal data on quality of life and health care utilization, and discrepancies between identified subgroups such as gender and race.

Methods

US-CTEPH-R Objectives

The US-CTEPH-R has been established under the guidance of a multidisciplinary Steering Committee consisting of physicians, surgeons, and scientists with expertise in the diagnosis and management of CTEPH and related diseases. The mission of the Registry is to promote a greater understanding of the epidemiology, pathophysiology, evaluation, treatment, and outcomes of patients with CTEPH through shared information, education, and collaborative investigation among PH centers throughout the United States. The Steering Committee defined five overall objectives for the US-CTEPH-R: (1) to characterize the demographics, evaluation, and clinical course of CTEPH; (2) to chronicle short- and long-term outcomes of PTE in patients with operable CTEPH; (3) to evaluate the short- and long-term outcomes of nonsurgically treated CTEPH; (4) to identify pre-, intra-, and postoperative predictors of a successful PTE; and (5) to collect pertinent data that will contribute to the understanding of a successful treatment approach for patients with CTEPH.

The development of the US-CTEPH-R will be an important element in the advancement of understanding CTEPH and

improvement in the care of patients who suffer from this debilitating disease.

Design

The US-CTEPH-R is a multicenter, prospective, longitudinal registry of patients newly diagnosed (within the previous 6 months) with CTEPH. The University of California San Diego (UCSD) is the sponsor and coordinating institution for the study, which was approved by the UCSD Human Research Protection Program (Project #141379). Thirty sites in the United States were selected to participate in the Registry based on a feasibility survey and geographic distribution; all sites obtained permission from their respective institutional review boards. All data were entered into a secure web-based data management system. After providing written informed consent, each patient was assigned a unique numerical patient identifier to maintain confidentiality as required by the Health Insurance Portability and Accountability Act. The first patient was enrolled in April 2015

and the target enrollment of 750 patients was met in March 2018. All subjects were followed biannually until the last subject completed 1-year follow-up in March 2019. Subjects could voluntarily withdraw at any time during the study at which point no additional data were collected.

Subjects

All consecutive patients diagnosed with CTEPH within 6 months of study consent meeting the inclusion criteria outlined in Textbox 1 were offered participation in the study. The time of diagnosis was defined as the date the final of all three hemodynamic and radiologic entry criteria for CTEPH (right heart catheterization, ventilation perfusion scan, and confirmatory angiography) were met. Exclusion criteria are also listed in Textbox 1. Because this is a US CTEPH registry, only patients who were permanent residents of the United States were included. There were no limitations based on age, use of PH targeted therapy, or excessive pulmonary vascular resistance.

Textbox 1. Inclusion and exclusion criteria for enrollment.

Inclusion criteria

- Patient must be a permanent resident of the United States

- Documentation of the following hemodynamic parameters by right heart catheterization

    - Mean pulmonary arterial pressure ≥25 mmHg at rest and

    - Pulmonary artery wedge pressure (PAWP) ≤15 mmHg (or >15 mmHg if justified; ie, if the principal investigator felt the etiology of the pulmonary hypertension was due to chronic thromboembolic disease and not postcapillary pulmonary hypertension).

- Radiologic confirmation that chronic thromboembolic disease is the cause of the pulmonary hypertension by

    - One or more mismatched perfusion defect(s) by lung ventilation/perfusion scan, and

    - Confirmation of chronic thromboembolic disease by evidence of bands/webs, vessel narrowing, or occlusion seen on digital subtraction angiography (DSA), computed tomography pulmonary angiogram (CTA), or magnetic resonance angiography (MRA).

    - All subjects must have the radiologic diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) confirmed by the Adjudication Committee.

- Patients must be diagnosed with chronic thromboembolic pulmonary hypertension within 6 months of being considered for study eligibility (signing of consent to participate). The date of diagnosis will be defined as the time that both hemodynamic criteria have been met and chronic thromboembolic disease is confirmed to be the cause of the pulmonary hypertension by an abnormal ventilation perfusion scan and the presence of chronic thromboembolic disease on CTA, MRA, or DSA. Hemodynamic and radiologic criteria can be met at separate time points; the most recently met criteria time point will be defined as the date of diagnosis.

Exclusion criteria

- Patients unwilling or unable to provide written consent for participation in the study. Appropriate surrogate consent will be obtained for pediatric patients as defined by each investigational site's institutional review board.

- Patients with an underlying medical disorder with an anticipated life expectancy less than 2 years.

- Patients who do not meet inclusion criteria:

    - Have not had documentation of hemodynamic criteria by right heart catheterization as outlined in the inclusion criteria

    - Do not have radiologic confirmation of chronic thromboembolic disease as outlined in the inclusion criteria

- Patients who have undergone a prior pulmonary thromboendarterectomy surgery or balloon pulmonary angioplasty procedure.

- Meet the criteria for inclusion into Pulmonary Hypertension World Health Organization Groups I, II, III, or V.

Adjudication

Radiologic imaging was forwarded to the Adjudication Committee using a web-based platform for review. A ventilation perfusion scan and at least one form of pulmonary angiography

(CTA, MRA, or DSA) were submitted. Six physicians from multiple centers with extensive clinical experience in CTEPH served on the Adjudication Committee. Successful radiologic adjudication of CTEPH required two independent adjudicators to agree that the imaging met the predefined criteria listed in

Textbox 2 [13-16]. In the event the adjudicators did not agree on the diagnosis, a third adjudicator rendered an independent decision as to whether the imaging supported the diagnosis of CTEPH. Two of the three adjudicators had to agree on the diagnosis for the subject to be enrolled in the study and at least one of the adjudicators confirming CTEPH had to come from outside the enrolling institution. When the diagnosis was uncertain based on the submitted imaging, additional clinical history or available imaging could be requested by the Adjudication Committee. Subjects that were deemed to have imaging compatible with acute thromboembolic disease were not entered into the registry unless stability of the findings was documented after 3 months of anticoagulation. Subjects with radiologic imaging supporting the diagnosis of CTEPH were subsequently enrolled and followed longitudinally.

Textbox 2. Chronic thromboembolic pulmonary hypertension (CTEPH) adjudication criteria.

Diagnosis of CTEPH requires both unmatched perfusion defects on ventilation perfusion scan *and* confirmatory evidence of chronic thromboembolic disease on computed tomography (CT), magnetic resonance (MR), or digital subtraction angiography (DSA).

CT and MR findings compatible with chronic thromboembolic disease:

- Eccentric lining material (clot) without distortion of vessels

- Occlusive/recanalized/intraluminal material, associated with vessel distortion and/or narrowing; postobstructive vessel attenuation or "absence" to accompanying occlusive clot

- Intraluminal webs, with or without vessel distortion

- Vessel nonopacification with intimal thickening at vessel origin

CT and MR findings supporting the diagnosis of CTEPH:

- Enlarged central pulmonary arteries

- Systemic collateral vessels

- Enlargement of the right atrium/right ventricle

- Mosaic parenchymal perfusion

- Absence of parenchymal findings that can be associated with vessel destruction/poor perfusion (coexisting "stasis" clot)

- Intact large pulmonary veins

- No significant mediastinal pathology

DSA findings compatible with chronic thromboembolic disease:

- "Pouching" resulting in partial or total occlusion of the vessel

- Pulmonary arterial webs or bands

- Intimal irregularities

- Abrupt narrowing of a major pulmonary artery

- Obstruction of vessels at their point of origin

Patients with radiographic evidence compatible with acute thromboembolic disease will not be included in the registry unless stability of these findings are documented after 3 months of anticoagulation.

CT and MR findings suggesting the diagnosis of acute pulmonary embolism:

- Arterial occlusion with failure to enhance the entire lumen due to a large filling defect

- A partial filling defect surrounded by contrast material

- The "railway track sign," thromboembolic masses seen floating freely in the lumen, allowing the flow of blood between the wall of the vessel and the embolus

- A peripheral intraluminal filling defect that forms acute angles with the arterial wall

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Data Collection

Data collected at enrollment included demographics, medical history, risk factors for venous thromboembolism and CTEPH, duration of symptoms, time from symptom onset to correct diagnosis, alternative diagnoses initially rendered, specialties of physicians involved in the patient's care, World Health Organization (WHO) functional class, Short-Form 36 Questionnaire (SF-36v2) and emPHasis-10 [17] scores, as well as biomarkers, 6 minute walk distance, echocardiography, pulmonary function tests, radiologic imaging, hemodynamics, medical therapies (anticoagulants, PH targeted therapies, diuretics, supplemental oxygen, inferior vena cava filters), and determination of operability status.

Following enrollment, the only requirement for participation in the registry was the administration of the health-related quality of life (HRQoL) SF-36v2 and emPHasis-10 questionnaires. All other evaluations and procedures were at the discretion of the investigator.

For subjects undergoing PTE surgery, the following information was collected: date and location of PTE surgery, surgical classification of thrombus, cardiopulmonary bypass, aortic cross clamp and circulatory arrest times, additional procedures performed at the time of PTE, postoperative hemodynamics, length of mechanical ventilation, inotropic support, intensive care unit and hospital length of stay, postoperative complications, mortality, and cause of death when applicable. Therapy at the time of discharge (anticoagulant, inferior vena cava filter, PH targeted therapies, antiarrhythmic, supplemental oxygen) was also recorded.

Subjects who did not undergo PTE surgery had the reason documented and were followed longitudinally. Patients treated with BPA had each session recorded with identification of segments treated, complications, length of stay, radiation exposure, and hemodynamics.

Longitudinal data were collected biannually (every 6 months) on all patients during patient clinic visits, or by patient phone call and/or chart abstraction. Data collected in follow-up include WHO Functional Class, SF-36v2, emPHasis-10, results of follow-up testing (labs, echocardiography, right heart catheterization, radiologic imaging), performance of PTE surgery, BPA, transplant, changes in medications, hospitalizations/emergency room visits, and death.

Data Analysis

The sample size (750 patients) and duration of follow-up were selected based on estimation of disease incidence from a feasibility survey of US PH centers and budgetary constraints. Aggregate data from all 30 sites will be published, but site-specific data will be confidentially provided to each participating research center. Descriptive statistics will be used to describe demographics, risk factors, time to appropriate testing and diagnosis, PAH targeted medication use, functional status, and hemodynamics at the time of enrollment. Demographic and baseline characteristics will be summarized descriptively. For descriptive comparisons, the Fisher exact test will be used for categorical variables and t tests will be used for continuous variables. Appropriate nonparametric alternatives such as the Wilcoxon rank-sum test will be considered if parametric assumptions fail.

Results will be reported as point estimates (odds or hazard ratios, or mean differences across groups, as appropriate) and interval estimates (95% CIs). All tests of significance will be two-sided. A P value of .05 or less will be considered statistically significant. Statistical analysis will be performed using the statistical software R 3.5.0.

Descriptive statistics of the perioperative data collected will be presented along with any observations of differences in perioperative practice. Comparisons of hemodynamics, functional status, medication and supplemental oxygen use,

HRQoL, and health care utilization will be made between the preoperative data and longitudinal postoperative data.

Descriptive statistics will be used to describe why patients are not operative candidates and the nonsurgical therapies used for treatment. Longitudinal changes in hemodynamics, functional class, HRQoL, medication use, health care utilization, and death will be analyzed using repeated-measures analysis such as mixed models repeated measures. Comparisons of treatment modalities (surgical and nonsurgical) on clinical outcomes will be assessed using regression techniques adjusting for potential confounding variables. Subgroup (such as gender or race) comparisons of risk factors, therapies, and outcomes will be considered, as appropriate. Survival of patients will be analyzed using time-to-event analyses and descriptively summarized using Kaplan-Meier curves.

A separate statistical analysis plan will be developed for each specific investigation prior to statistical analysis.

Results

Data from this registry will help us better understand the demographics, presentation, and risk factors of the disease, as well as the diagnostic approach and treatment patterns in the United States. Impediments to timely diagnosis or effective therapy may also be identified, providing opportunities to improve health care for patients with CTEPH. Longitudinal data will provide insight into the effect of PTE, BPA, and pharmacologic therapies on health care utilization, HRQoL, and survival, and will contribute to our understanding of optimal treatment strategies for these patients. Comparisons between subgroups such as gender and race may identify disparities in risk factors, presentation, evaluation, treatment, and outcome.

Discussion

Overview of Protocol Design

This is the first large, multicenter, observational, longitudinal registry of patients with CTEPH in the United States. A previously published and often quoted European prospective registry that enrolled 679 adults newly diagnosed (≤6 months) with CTEPH found that 36.4% of cases were inoperable in the group of patients who did not undergo PTE surgery experiencing decreased survival [5,6]. However, this study was performed before regulatory approval of riociguat or availability of BPA for the treatment of inoperable CTEPH or residual PH after PTE. Aside from the current availability of these nonsurgical therapies, this US CTEPH registry differs from the previous European registry in several important ways. First, the demographics will be reflective of the US CTEPH patient population with greater racial diversity and differences in comorbidities such as obesity, diabetes, and sleep disordered breathing. Second, pediatric patients are included in this registry. Third, all patients have been adjudicated by a team of CTEPH experts to confirm the diagnosis of CTEPH prior to enrollment. Fourth, outcomes from the patient's perspective (HRQoL and functional status) will be measured. Finally, patients on PH targeted therapy and undergoing BPA are included.

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Limitations

There are several recognized limitations to this registry. Because it is observational, there is no mandated testing except for obtaining the SF-36v2 and emPHasis-10 responses biannually. Hence, timing of follow-up testing will be different between patients and there may be no follow-up testing on others. Although we are attempting to understand the diagnosis and treatment of CTEPH in the United States, the members of the US-CTEPH-R sites are based at academic PH centers, many offering more advanced PAH and CTEPH therapies. Hence, the population enrolled in this registry will not reflect the general population of patients with CTEPH cared for in the community that are never referred to a PH center. This registry was also performed prior to the change in the definition of PH from a mean pulmonary artery pressure ≥25 mmHg to >20 mmHg by the World Symposium on Pulmonary Hypertension in 2018. In addition, the important group of patients with symptomatic chronic thromboembolic disease without resting PH are not included in this registry.

Ethical Concerns

As with all clinical research, there is a potential for loss of privacy. To mitigate this risk, each patient was assigned a unique identifying number upon enrollment in the registry, and only the enrolling centers have access to their own specific patient-identifying data. Data were entered into a secure web-based management system and are password-protected. With approval of the Steering Committee, collaborating researchers requesting to analyze portions of the registry data will be given sets of records stripped of all personally identifiable information. In addition, although the US-CTEPH-R was funded by industry (see Acknowledgments), all registry activities are overseen by the Steering Committee. The sponsor had no role in the design of the study, collection and analysis of data, or preparation of manuscripts.

Conclusion

The US-CTEPH-R with 750 newly diagnosed adult and pediatric patients will provide valuable information on the demographics, risk factors, evaluation, treatment, and outcomes of CTEPH in the United States.

Conflicts of Interest

KK received a research grant paid to the institution from Bayer HealthCare and is a consultant to Actelion. CGE sits on the steering committee for UCSD (via grant from Bayer). KC is a consultant and sits on the steering/adjudication committees of Actelion, UCSD (via a grant from Bayer), United Therapeutics, Altavant, and Gossamer Bio. KC receives research support (paid to the institution) from Actelion, Ironwood, National Institutes of Health, and SoniVie, and receives financial/material support from the American Heart Association. RB is on the advisory board of Bayer. RC receives research support (paid to institution) from Bayer and Actelion; is a consultant for Actelion, Bayer, United Therapeutics, and Gossamer; and is part of the Speakers Bureau for Actelion and Bayer. MM is a consultant for Bayer, Actelion, and Wexler Surgical. VM receives research support (paid to institution) from Acceleron, Actelion, Gilead, Sonovie, Reata, and United Therapeutics, and performs scientific consulting for Acceleron, Actelion, Altavant, Caremark, LLC, CiVi Biopharma Inc, Gossamer Bio, Liquidia, and United Therapeutics. MP is a consultant for Bayer, Actelion, Abbott, and AstraZeneca; is part of the Speakers Bureau for Bayer; and received travel support from Bayer and Actelion. VFT receives research support (paid to institution) by National Institutes of Health, Actelion, Bayer, BMS/Pfizer, United Therapeutics, EKOS/BTG, Inari, Penumbra, and Johnson & Johnson; is on the advisory board/offers consulting to Actelion, BMS/Pfizer, United Therapeutics, EKOS/BTG, National Institutes of Health, Bayer, Johnson & Johnson, and Thrombolex; and has received speaking honoraria from Janssen and EKOS/BTG. WA is a consultant for Bayer, Cereno Scientific, and Actelion. The other authors have no conflicts of interest to declare.

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Abbreviations

BPA: balloon pulmonary angiography
CTA: computerized axial tomography angiography
CTEPH: chronic thromboembolic pulmonary hypertension
DSA: digital subtraction angiography
HRQoL: health related quality of life
MRA: magnetic resonance angiography
PAH: pulmonary arterial hypertension
PH: pulmonary hypertension
PTE: pulmonary thromboendarterectomy
SF-36v2: Short-Form 36 Questionnaire, version 2
UCSD: University of California San Diego
US-CTEPH-R: United States Chronic Thromboembolic Pulmonary Hypertension Registry
WHO: World Health Organization

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Retention of the Aboriginal Health, Ageing, and Disability Workforce: Protocol for a Mixed Methods Study

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Abstract

Background: Despite a plethora of research into Aboriginal employment and recruitment, the extent and nature of the retention of frontline Aboriginal people in health, ageing, and disability workforces are currently unknown. In this application, frontline service delivery is defined as Aboriginal people who are paid employees in the health, ageing, and disability service sectors in roles that involve direct client, participant, or patient contact. There is a need to identify the factors that inhibit (push) and promote (pull) staff retention or departure of this workforce from the sectors. This study will provide additional insight about this topic.

Objective: The objective of this project is to uncover the factors that influence the retention of frontline Aboriginal workers in the health, ageing, and disability workforces in New South Wales (NSW) who do not have university qualifications. The aim of the proposed project aims to discover the push and pull factors for the retention of the frontline Aboriginal workforce in the health, ageing, and disability sectors in NSW in relation to their role, employment, and community and design evidence-based strategies for retaining the Aboriginal frontline workforce in the health, ageing, and disability sectors in NSW.

Methods: The proposed research will use a mixed methods approach, collecting both quantitative and qualitative data via surveys and interviews to capture and represent the voices and perspectives of Aboriginal people in a way that the participants chose.

Results: Indigenous research methodologies are a growing field in Aboriginal health research in Australia. A key strength of this study is that it is led by Aboriginal scholars and Aboriginal controlled organizations that apply an Indigenous methodological framework throughout the research process.

Conclusions: This study uses a mixed methods design. The survey and interview questions and model were developed in partnership with Aboriginal health, ageing, and disability service workers rather than relying only on research publications on the workforce, government policies, and human resources strategies. This design places a strong emphasis on generalizable findings together with an inductive approach that explores employers and workers' lived experience of the Aboriginal health workforce in NSW. Excluding workers who have graduated from university places a strong focus on the workforce who have obtained either school or Technical and Further Education or registered training organizations qualifications. Data collection was conducted during the COVID-19 pandemic, and results will include the unique experiences of Aboriginal workers and employers delivering services in an extremely challenging organizational, community, and personal context.

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KEYWORDS

Introduction

Background

Despite Australia being one of the most developed nations in the world, there is a significant and widening gap in health and welfare between Aboriginal and Torres Strait Islander (Aboriginal) people and non-Aboriginal people. Aboriginal people experience significantly higher rates of chronic health conditions, preventable disease, and disability than non-Aboriginal people because of the effects of colonization and structural barriers to accessing health services. The poor rates of health and well-being are an identified cause of Aboriginal life expectancy being around 10 years lower than that of non-Aboriginal people [1].

During the Aboriginal rights movement, Aboriginal communities built the Aboriginal workforce in health and social services to capitalize on Aboriginal cultures and knowledge to close the gap in life expectancy, health, and well-being between Aboriginal and non-Aboriginal people. An Aboriginal workforce is essential for community self-determination, community governance, and the design and delivery of culturally safe services. A vibrant Aboriginal community-controlled health sector including a substantial Aboriginal workforce has a significant positive influence on Aboriginal families' health and well-being [2,3].

Often, Aboriginal workers known or local to Aboriginal communities who access the health, ageing, and disability supports play a vital role in guiding their non-Aboriginal colleagues in ways to adapt their interactions, advice, and interventions to ensure that they are culturally appropriate and safe for Aboriginal patients and clients. These additional responsibilities that Aboriginal workers in the welfare, health, disability, and aged care systems hold as cultural interpreters and practitioners are typically not included in position descriptions or recognized as an essential part of their role [4,5]. This can create issues in the workplace with respect to roles and challenges for Aboriginal staff trying to have the services sector recognize their cultural obligations as part of their personal and professional roles in the local community. The Aboriginal health workforce can increase access and engagement with service providers and facilitate better health, education, and quality of life outcomes for Aboriginal people [6]. This is supported by

leading groups who suggest that an Aboriginal workforce is effective in promoting access and engagement with health interventions and providing support for people with disabilities through the provision of culturally safe services and practices [7,8].

Both national and international peak health and disability organizations have called for further development and improved retention of Aboriginal workforces to address the existing social, health, and well-being disparities experienced by Aboriginal people worldwide [9,10]. A recent government report on the Aboriginal health workforce stated that "improved opportunities for employment, advancement, and retention also require attention" [11]. It is not sufficient to simply increase the number of Aboriginal staff. Explicit strategies need to be in place so that workplaces are culturally safe and the roles Aboriginal people play as cultural brokers are recognized and valued.

Many scholars have previously highlighted the shortcomings of the current data available on the retention of the health workforce [12-14]. Although there is growing literature, including systematic literature reviews [13,15-17], on the recruitment and retention of the general rural and remote health workforce, there is very minimal research on Aboriginal frontline service at a national level or at state or territory levels [13,16]. Russell et al [14] found that Aboriginal health practitioners working in remote areas of the Northern Territory had a significantly high turnover rate, concluding that the mean annual turnover rates for nurses and Aboriginal health practitioners combined were extremely high, irrespective of whether turnover was defined as no longer working in any remote clinic (66%) or no longer working at a specific remote clinic (128%). Stability rates were low, and only 20% of nurses and Aboriginal health practitioners remained working at a specific remote clinic 12 months after commencing. Half of them left within 4 months.

The report by Russell et al [14] on rural and remote health service providers found that the annual turnover rate for Aboriginal health workers was 20.8% per year compared with 11.5% for doctors and 13.8% for nurses. Russell et al [14] concluded that their evidence suggests that benchmarks for median survival for the different disciplines in rural and remote areas over a 12-month period in 2008 were as given in Table 1.

Table 1. Staff turnover indicator by remoteness and discipline in 2008.

Professional role names	Rural (years)	Remote (years)
Rural remote nurses	5	3.5
Doctors	3	2
Allied health professionals	3	2
Aboriginal health workers	3	3
Managers	5	3.5

A recent national survey of small rural and remote health services by Humphreys et al [12] concluded that the costs for recruiting Aboriginal health workers ranged from Aus $3534 (US $ 2728.87) to Aus $43,600 (US $ 33666.83) during 2008.

Recent systematic literature reviews of Aboriginal health and welfare workforce research found that the experiences of Aboriginal people in the health workforce were affected by their engagement with culturally incompetent staff and managers,

education, training, and employment. These factors also affect the success and longevity of the non-Aboriginal workforce working in Aboriginal health; for example, attitudes and behaviors of the workforce have a direct effect on service delivery and design. These studies [13,15,16] suggested many strategies to improve retention of Aboriginal workers, such as ongoing training and support for non-Aboriginal health workers, culturally appropriate service design, and effective tertiary student placements.

Similar conclusions were shared by Rose and Jackson Pulver [17] in their earlier review of existing literature on parallel work by Aboriginal health workers and the health promotion needs of Aboriginal communities. The existing vocational training provision for Aboriginal health workers and the potential role of university-based programs to further Aboriginal health worker professional qualifications to a level equivalent to allied health professionals was explored. This study advocated that Aboriginal health workers require sophisticated skills and knowledge at a level equivalent to other health professions to succeed in this area with a recommendation that opportunities should be offered to Aboriginal health workers, including opportunities at a university level in parallel with other health professional qualifications [17].

When investigating the extent and nature of the retention of Aboriginal frontline workers, it is important to look at external factors such as education and career development. Tertiary education providers, such as universities and Technical and Further Education (TAFE) institutes, and registered training organizations have policies and initiatives that recruit and support the education of Aboriginal students. However, despite this focus at a policy and practical level across sectors, the Aboriginal health and disability workforce is growing at a very slow rate and will not meet the needs of the future. Currently, there are more employment opportunities in the health and disability sectors than there are Aboriginal people who are appropriately qualified to fill them [18]. In 2013, New South Wales (NSW) TAFE reported that the completion rates for Aboriginal students across all qualifications were less than 30% [19].

A scholarship program for Aboriginal preregistration nursing students used five enablers for success [20] to attempt to address completion rates. This study, using structured interviews with students and staff, examined whether these enablers were associated with academic success. A total of 64.5% of the students (n=20) and 75% of the staff (n=6) participated in the study, and it was found that the five enablers were contributing factors to success. This included individual student characteristics; academics' knowledge, understanding, and awareness; connections, partnerships, and relationships; institutional systems, structures, and processes; and finally, family and community knowledge, understanding, and awareness [20]. Gwynne et al [19] adapted this model for vocational education and identified 2 more enablers: (1) employer support and (2) listening and improving. This program achieved a completion rate of 96.8% using the seven enablers. To further improve completion rates for Aboriginal students, vocational education programs need to be customized to cultural, family, and community contexts. This highlights two points of interest: experiences of success for future Aboriginal health care students and that the environments that customize the student (or worker) experience to a cultural, family, and community context have beneficial results. Ongoing engagement in training may be a key factor in the retention of Aboriginal health care *students* in Aboriginal frontline *health care roles*.

Objectives

There is a need to identify the factors that inhibit (push) and promote (pull) staff retention or departure of this workforce from various sectors. This study aims to identify the barriers and enablers to retaining Aboriginal people who do not have university qualifications in the health, disability, and aged care workforces. In this paper, *frontline service delivery* is defined as Aboriginal staff who are paid employees in the health, ageing, disability, and community service sectors in roles that involve direct client, participant, or patient support.

For further context, this paper adopts the definition of retention as given by Humphreys et al [12] as the length of time between commencement and termination of employment and turnover as the number of terminations in a specified time period.

Historically, research involving Indigenous people around the world was situated on ethnocentric and Eurocentric values and ideals of Indigenous people that served the interests of the Western imperial elite classes [21,22]. This study will apply an Indigenous research methodological framework [23]. Indigenous research methodologies aim to deconstruct the Western research paradigm by prioritizing local Indigenous community social and cultural values of research and knowledge production [23,24]. In the context of this framework, we briefly describe the standpoint of each author of this paper. The authors are all team members on the project, which includes Aboriginal and non-Aboriginal researchers, 3 Aboriginal community-controlled organizations, and 1 disability service peak body. Four of the authors, JG, BR, FT, and MH, are Aboriginal academics with experience in health workforce research. The other authors are non-Indigenous scholars who have long-standing engagement in Aboriginal health workforce research.

Methods

Overview

Through the global Indigenous rights movement, Indigenous advocates have obtained greater control over the research agenda, placing them in a unique position to investigate and decolonize the research processes. This transformation has resulted in a change from a *researcher-directed* approach to *Indigenous community–directed* and *Indigenous persons' research–directed* approach [25,26]. In effect, the responsibility and accountability for Indigenous research has shifted from North-metropole academic institutions to Indigenous scholars, Indigenous community-controlled organizations, and Indigenous representative bodies.

This study is a mixed methods design involving an Indigenous decolonizing methodological framework that drives all phases of the research. Decolonization centers on privileging the needs of Aboriginal people by analyzing and dismantling the power imbalances that exist between Indigenous people and

non-Indigenous people in how research is undertaken to inform government policy, practice, and praxis. This study reflects the decolonizing models developed by Aboriginal scholars Rigney [27] and Gilroy [22,28] for Indigenous research.

1. The research is counterhegemonic to Western ideologies and promotes Indigenous people's self-determination in the production of knowledge.
2. The research privileges Indigenous voices.
3. The research has Indigenous people involved in the research as researchers.

Our model is influenced by other approaches to the conduct of research on Aboriginal communities [29,30]. These approaches privilege Aboriginal community leadership and governance in all phases of research, including development, implementation, data analysis, and interpretation of results [30]. Community governance is ensured through the structures of advisory and reference groups, processes and procedures of the research, and formalized agreements where required. These approaches vary among communities to reflect the diversity of Aboriginal communities.

Ethics and Governance

Ethical approval was received from the Aboriginal Health and Medical Research Council of NSW (1505/19) and the NSW Ministry of Health ethics committee (2019/ETH08775). The study applies the National Health and Medical Research Council (NHMRC) guidelines and principles for Aboriginal research [29,31]. Reflecting the principles of Indigenous research methodologies, the project will be managed using an Aboriginal governance model, as depicted in Figure 1. This model is informed by previous Aboriginal community-led research that involved this project's researchers [31]. However, this representation is not hierarchical and more faithfully aligns with an Indigenous decolonizing methodological approach with a yarning circle at the center and smaller yarning circles surrounding this, involving the various groups and committees who contribute to decision making and idea formation.

The project implementation team primarily consists of Aboriginal research project manager (FT) and the chief investigator A (JG), whose role is to coordinate the project, and an Aboriginal person recruited as a part-time research assistant. This model privileges Indigenous voices in the process of project planning and implementation. The operations committee, consisting of agency partners and researchers on the project, will guide the thinking and delivery of the project. The implementation team consists of project researchers, including the project manager and research assistants, whose roles are the daily tasks for project implementation. The methodology team and the strategic advisory group consist of experts related to research and workforce matters, respectively.

The project manager led the establishment of a workforce reference group, which consisted of 12 Aboriginal people from across NSW undertaking a diploma of nursing scholarship program through the Poche Centre for Indigenous Health and are also working in the health, ageing, or disability sectors. Reflecting the Indigenous research methodology, the purpose of this workforce reference group is to specifically contribute to the co-design and development of the project's survey and interview questions.

Figure 1. Project administration and governance model. AHMRC: Aboriginal Health and Medical Research Council. CIA: chief investigator A. IAHA: Indigenous Allied Health Australia. NDS: National Disability Services. RA: research assistant.
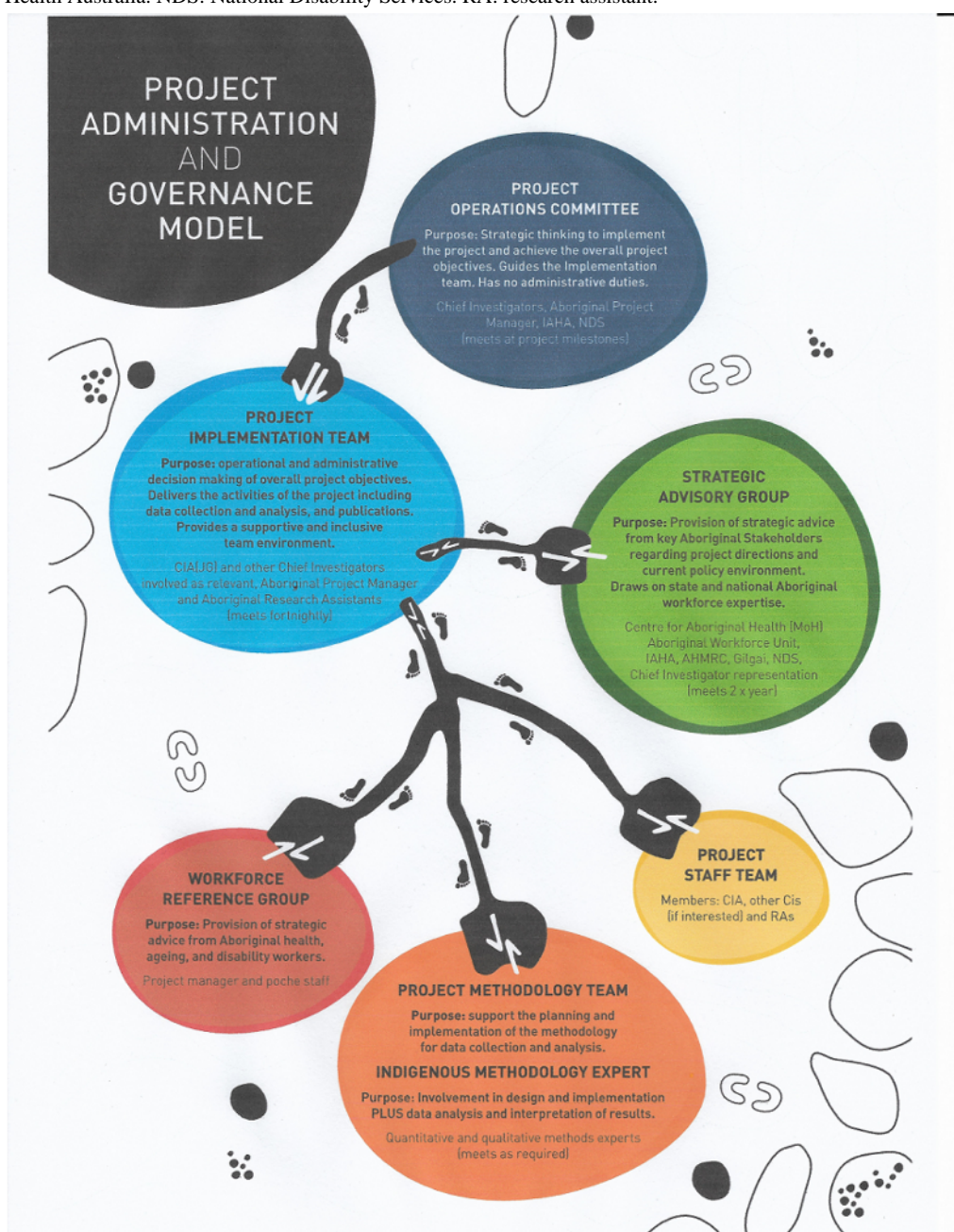
Engagement and Recruitment

Two groups of participants in NSW will be recruited for this study.

Group 1

Group 1 consists of frontline Aboriginal health, ageing, and disability service workers (here on referred to as Aboriginal workers) currently in roles that engage in direct face-to-face client interaction in service delivery in NSW, defined in this study as *frontline service delivery*. The research team aims to recruit a target of 150 frontline workers to complete the survey. This study will exclude those workers who graduated from a registered university to focus on those with vocational qualifications, including diploma certificates or other nonuniversity qualifications. University graduates were excluded

because a considerable body of evidence exists regarding workplace experience factors among this group. Furthermore, a large proportion of the ageing and disability workforce consists of people who do not have university qualifications [32].

Group 2

Group 2 consists of organizational leaders who employ frontline Aboriginal workers. Aboriginal and non-Aboriginal employers of Aboriginal workers (here on referred to as employers of Aboriginal workers), located anywhere in NSW, will be recruited via the networks of the researchers and publicly available information about their organizations. Staff that may be approached with an invitation to this study include chief executive officers and senior staff of health, ageing, disability, community, and personal service organizations. The research

team aims to obtain a target of 50 participants to complete the survey.

The surveys will be sent through the Aboriginal community-controlled organizations, nongovernment industry groups, local health districts, community interagency committees, and nongovernment and for-profit agencies. The alumni of the Poche Centre for Indigenous Health at the University of Sydney and the center's agency networks will be key recruitment targets. In addition, members of the research team aim to attend Aboriginal community events and major conferences to connect with Aboriginal workers and community organizations where COVID restrictions permit.

In-depth interviews or yarns will be conducted with a subset of 20 Aboriginal workers and 20 employers of Aboriginal workers who have completed the survey and consented to be interviewed. These may be conducted via Zoom or phone, depending on the COVID-19 restrictions.

Considerable effort and numerous engagement activities will be required to achieve the desired targets. Targeted and snowball recruitment will be adopted for both surveys. The strategic advisory group and the project steering committee will also support the research team in recruiting participants.

Study Design

Surveys will include both closed and open-ended questions and will be conducted on the internet. The survey and interview questions and format will be co-designed with Aboriginal workers and employers of Aboriginal workers to ensure that the language, topics, and issues reflect the lived experience of the workforce and are culturally respectful for Aboriginal workers. Workshops of Aboriginal workers and employers of Aboriginal workers will be held in metro and nonmetro regions to capture the issues and questions for the survey and interviews.

The methodology team, which consists of relevant research team members and the project staff, will advise on the data collection and analysis software and develop procedures that will support the delivery of both the surveys and interviews. The final web-based draft of the questions and procedures will be sent back to the workshop participants for feedback.

Data Collection

Surveys

The first survey will invite Aboriginal workers to share information about their demographics, qualifications, current work role, length of experience, time in their current organization, career path, intention to leave their position, reasons for remaining in their current position, reasons for considering leaving their current position, their career aspirations, and features of an ideal job.

To obtain organizational-level perspectives on the issues related to retention and departure, the second survey will invite employers of Aboriginal workers to share information about their demographics, nature of their organizations, services provided by Aboriginal people, perceptions of turnover of staff in these positions, and factors they perceive promote retention or departure from roles and strategies they have used

successfully to promote retention. Rather than aiming for a specific number of agencies, this study aims to ensure a state-wide coverage of the agencies and service types.

A matrix of both participant groups will be developed over the course of the study to ensure that the diversity of sex, age, location, and service type of the participants and agencies are captured.

Interviews and Yarning

At the completion of the surveys, participants will be asked if they would be willing to provide further information through participating in a one-to-one telephone interview, Zoom conversation, or in-person yarning session with other local participants if COVID-19 travel and physical distancing restrictions permit. Following Indigenous research methodology, the participants can choose the person on the research team with whom they would like to do the session. Yarning, or yarn ups, is an Indigenous methodology that ensures culturally safe environments for discussing issues that are sensitive and important for Aboriginal people [33]. This method will also be applied to interviews with Aboriginal participants. The direction and contents of the discussions are influenced by the participants. Typically, open-ended questions and *trigger questions* are used to guide discussions, followed by a process of *member checking* as a validation technique [34].

Aboriginal workers will be interviewed separately from employers of Aboriginal workers to ensure that the power relations between these two groups do not inhibit an open discussion. The interviewer will arrange to conduct the interview with the Aboriginal worker at a time requested by the participant to ensure the workers' confidentiality in the workplace. Interviews will be discontinued once saturation is reached for both groups or the target of 20 participants has been reached. Interviews and yarns will be audio-recorded and transcribed with participants' consent. Consent via an audio-recording device will be obtained either orally via telephone or web-based platforms or using the written consent form for face-to-face interviews. A participant information script and form will be used by the researcher to inform the participant about the project.

If the participant does not consent to audio recording, 2 team members will be present during the interview to ensure the fidelity of the handwritten record. One will ask the questions or prompts and take notes when feasible, whereas the other will undertake only note-taking. The handwritten notes will then be provided to the participant for checking before inclusion in the research data set. This qualitative component to the research will provide a rich and nuanced understanding of the retention factors identified in the survey and will promote accurate and culturally sensitive interpretation of the results.

Data Analysis

Descriptive and correlation statistical analyses will be used to examine quantitative data collected via the surveys. Open-ended questions about reasons for staying or leaving their position will be analyzed using the content analysis software NVivo (QSR International), to identify the scope of reasons reported. Similarly, information about career aspirations and ideal jobs

will be subjected to thematic analysis. Employer surveys will be analyzed using the same methods.

Interviews and yarns will be analyzed by Aboriginal and non-Aboriginal team members to ensure that cultural nuances are captured using thematic analysis. All transcripts will be managed using the NVivo software. The transcripts will be segmented into content units that will be coded. The codes will be compared within and across the transcripts. The codes will then be clustered together into potential thematic areas. These themes will be named and described based on a cluster of codes. The researchers will verify preliminary findings with the participants to minimize any possible misinterpretations and perform a member check. The analysis approach and the preliminary findings will be reported to the strategic advisory group and the project steering committee for interpretation and feedback and to design approaches for the knowledge to action (KTA) plan. Providing feedback for research activities and preliminary findings is a key part of Indigenous research methodologies.

The survey data will undergo descriptive statistical analysis to describe the frequency of identified barriers to retention and reasons for staying to better understand the motivators for the non–university-qualified Indigenous workforce in relation to the push and pull factors. The frequency of identified barriers to attention and reasons for staying will be correlated with the participants' intention to leave their current job to explore relationships in the data.

The analysis of the quantitative survey and interview responses will be verified through a second analysis of 20% of the responses by an Aboriginal team member as part of the rigor of the analysis process to minimize potential bias. The thematic analysis of the interviews and yarns will be verified at the code and theme levels. Following this, 20% of the transcripts will be independently coded by a second researcher using the first coder's code book containing a description of each code. Any discrepancies will be noted and resolved via a consensus between the two coders. The themes will be verified by all the research teams on the project. All research teams will familiarize themselves with the codes and clusters and will agree with the content and names of the themes through a consensus process. This is critical to ensuring that the Aboriginal researchers on the team and the Aboriginal people involved in the governance model of the project bring their interpretation and cultural knowledge to the analysis.

Following these analyses, the survey and interview or yarning results will be analyzed using a triangulation model. As there is very little published literature in this area, it will not be possible to triangulate the results with the existing literature. To ensure transparency of the research findings during the data analysis, the preliminary research findings will be discussed with experts in the field, including the committees used for this project.

Communication of Results

Aboriginal communities want research to inform the action in their communities. In this study, we define *community* as the *community of practice,* that is, the target workforce and the connected organizations. Through the implementation of this study, we will develop further understandings about the *community of practice* and this in turn will influence the nature of our communication of results. An effective knowledge translation plan can lead to significant changes in service delivery and health outcomes [35]. The following KTA plan details how this study will engage key stakeholders in the research process and the plan for disseminating findings in an ongoing way over the course of the project. The strategic advisory group and the project operations committee will suggest KTA activities that will occur during each year of the project to facilitate community-wide engagement and discussion. On the basis of previous experiences of research conducted by team members in Central Australia, Queensland, and Central Western NSW, the types of KTA activities will be determined in collaboration with the advisory group, project partners, workforce reference group, and project participants. The diversity of stakeholders will ensure that the research findings inform practice and policy.

As shown in Table 2, the team adapted some KTA strategies from research in Central Australia [36]:

1. Community visits: They provide verbal feedback on project activities during their regular community visits.
2. Project newsletters: A quarterly web-based and hardcopy project newsletter written in plain English for distribution to all stakeholders and available on the internet.
3. Presentation at the institutional partner annual general meetings: The annual general meetings are held at culturally and physically accessible venues. An update on the project activities will be provided, and the newsletter will be distributed.
4. Mass media communications: The research team will engage with mass media over the life of the project. For example, to inform the general Aboriginal and Torres Strait Islander communities, the *National Indigenous Times* and local radio stations will be approached to run stories on the project.
5. Policy papers: The team is involved in a range of government committees and working groups in disability affairs. The findings will be reported in policy papers to provide research partners and community organizations with research evidence to inform their respective government advisory roles.

The materials produced for the KTA will be supported by artwork from an Aboriginal artist from NSW and photos gathered during data collection.

Table 2. Knowledge translation strategies by stakeholders.

Stakeholder types	Community visits, including verbal feedback	Agency AGM[a] presentation	Project newsletter	Mass media	Agency policy papers	Final reports
Research participants	Yes[b]	Yes	Yes	Yes	No[c]	Yes
Communities	Yes	Yes	Yes	Yes	No	Yes
Service provider agencies	Yes	Yes	Yes	Yes	No	Yes
Policy makers	No	No	Yes	Yes	Yes	Yes
Academic circles	No	No	Yes	Yes	No	Yes

[a]AGM: annual general meeting.

[b]Yes, this approach will be used with this stakeholder.

[c]No, this approach will not be used with this stakeholder.

Results

This 3-year (2019-2021) Australian Research Council funded project has fully engaged with Aboriginal workers in the health, ageing, and disability service sectors in NSW. Data collection commenced in 2020, despite the COVID-19 pandemic.

Discussion

An Aboriginal workforce is essential to the delivery of high-quality, culturally safe health and social services and to address structural barriers to service access. Aboriginal people experience higher rates of disability and chronic health conditions than non-Aboriginal people, which heightens the need for responsive support and services.

A key strength of this study is that it is led by Aboriginal scholars and Aboriginal controlled organizations that apply an Indigenous methodological framework throughout the research process.

This study uses a mixed methods design. The survey and interview questions and model were developed in partnership with Aboriginal health, ageing, and disability, service workers rather than relying only on research publications on the workforce, government policies, and human resources strategies. This design places a strong emphasis on generalizable findings together with an inductive approach that explores employers' and workers' lived experience of the Aboriginal health workforce in NSW. Excluding workers who have graduated from university places a strong focus on the workforce who have obtained either school or TAFE or registered training organizations qualifications. Data collection was conducted during the COVID-19 pandemic, and the results will include the unique experiences of Aboriginal workers and employers delivering services in an extremely challenging organizational, community, and personal context.

By identifying the factors that influence the retention of the Aboriginal workforce from yarn ups and surveys completed by Aboriginal workers and their employers, this study will provide a cohesive set of strategies for organizations to apply in improving their retention of Aboriginal workers.

Aboriginal community-controlled organizations and generic mainstream organizations are concerned that research often does not deliver results to their communities. By co-designed research questions, methods, and knowledge dissemination strategies, this project will deliver translatable results to the participating communities. The KTA strategies are designed to share the findings of the research in relevant and accessible ways. This model ensures that the knowledge obtained from this study is returned to the Aboriginal and Torres Strait Islander service sectors.

Conflicts of Interest

None declared.

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Abbreviations

KTA: knowledge to action
NSW: New South Wales
TAFE: Technical and Further Education

Corrigenda and Addenda

Addendum to: Development and Validation of a Scale to Measure Intimate Partner Violence Among Transgender and Gender Diverse Populations: Protocol for a Linear Three-Phase Study (Project Empower)

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Related Article:

Correction of: https://www.researchprotocols.org/2020/11/e23819/

In "Development and Validation of a Scale to Measure Intimate Partner Violence Among Transgender and Gender Diverse Populations: Protocol for a Linear Three-Phase Study (Project Empower)" (JMIR Res Protoc 2020;9(11):e23819), corrections have been made to the authorship list and to the text of the paper to clarify the methods of the protocol.

Author Erin E Bonar has been added to the authorship list of the revised paper. The revised list of authors and affiliations is as follows:

Rob Stephenson[1], MA, MSc, PhD; Kieran Todd[2], MPH; Kristi E Gamarel[3], PhD; Erin E Bonar[2,4,5], PhD; Sarah Peitzmeier[1*], PhD*

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To clarify the age of the participant group, mentions throughout the paper of participants as "aged over 15 years" have been changed to "aged 15 and above."

The section "Protection of Human Subjects" has been edited to clarify the risk management plan for participants.

References 40 and 45 in the original manuscript have been removed. 3 new references have been added to the reference list as References 41-43 and are cited in the "Health Outcomes" section. References have been renumbered accordingly. The full revised reference list appears below [1-86].

In the "Health Outcomes" section, the measure of suicidal ideation has been removed. The measure of substance abuse has been changed to the following:

Substance use measures will assess the use and frequency of use of alcohol and other drugs in the past 3 months and are based on prior work [41-44].

The correction will appear in the online version of the paper on the JMIR Publications website on May 12, 2021, 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.

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Protocol

Person-Generated Health Data in Women's Health: Protocol for a Scoping Review

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Abstract

Background: Due to their ability to collect person-generated health data, digital tools and connected health devices may hold great utility in disease prevention, chronic disease self-monitoring and self-tracking, as well as in tailoring information and educational content to fit individual needs. Facilitators and barriers to the use of digital health technologies vary across demographics, including sex. The "femtech" market is growing rapidly, and women are some of the largest adopters of digital health technologies.

Objective: This paper aims to provide the background and methods for conducting a scoping review on the use of person-generated health data from connected devices in women's health. The objectives of the scoping review are to identify the various contexts of digital technologies in women's health and to consolidate women's views on the usability and acceptability of the devices.

Methods: Searches were conducted in the following databases: Medline, Embase, APA PsycInfo, CINAHL Complete, and Web of Science Core Collection. We included articles from January 2015 to February 2020. Screening of articles was done independently by at least two authors in two stages. Data charting is being conducted in duplicate. Results will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) checklist.

Results: Our search identified 9102 articles after deduplication. As of November 2020, the full-text screening stage is almost complete and data charting is in progress. The scoping review is expected to be completed by Fall 2021.

Conclusions: This scoping review will broadly map the literature regarding the contexts and acceptability of digital health tools for women. The results from this review will be useful in guiding future digital health and women's health research.

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Introduction

Background

Modern-day society is rapidly embracing innovations in connected technologies such as smartphones, text messages, wearables (eg, smartwatches), sensors, the Internet of Things (eg, internet-enabled weight scales) [1], as well as interactive web applications. When used in the context of health care, these technologies enable their users to collect, store, and reflect on their health data. Person-generated health data (PGHD) are defined as clinically relevant data captured outside traditional care settings [2] and describe experiences from the everyday lives of individuals. With information derived from this data,

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users are empowered to take actions toward improving their health [3-7].

The mass adoption of connected technologies and PGHD benefits person-centered care by enabling individuals to play a more active and proactive role in managing their health [8]. Connected health tools provide a platform for information exchange between individuals and their health care providers [9,10] in person and in telemedicine consultations. These tools can also be used asynchronously, at convenient times throughout the day, without requiring health care providers to be online simultaneously with the patient for a real-time conversation. Health outcomes can be measured and monitored weekly, daily, and continuously; these more frequent assessments provide users and health care providers quicker feedback on measures of health status, thus enabling faster medical interventions when necessary [11,12]. Detailed longitudinal PGHD can paint a more complete picture of one's health, minimizing the risk of recall bias [13] at health appointments. Using PGHD to monitor health status over time can help detect health concerns early [14], prevent medical events [15,16], and evaluate patient outcomes during and after medical treatments [17,18].

One of the most promising features of digital health is the ability to personalize and tailor content to address specific health conditions and concerns. With or without consulting their medical team, participants can decide which health metrics are most pertinent to their situation and receive targeted information and feedback based on their personal measurements and symptoms [11,16]. Individualized health plans created from PGHD may encourage personal participation and accountability with respect to health and health-related behaviors [19,20]. The impersonal nature of these platforms, which provide the ability to ask questions and track their conditions anonymously, may be especially appreciated in scenarios where participants have reservations about discussing certain health issues in person with health care providers (eg, sexual health [21,22]); independently monitoring these health issues online allows them to be more forthcoming [23].

Applications specifically targeting women are exploding in what has been coined "femtech." Historically, women were excluded from health research, which meant that very little was known about female-specific health concerns or diseases that impacted mostly women (eg, menstrual health) [24,25]. Considerable advancements have been made in women's health over the past decades [26]. Today, health technology is promising to reverse the tide of research in women's health with women 75% more likely to use digital health tools than men [27]. It is important that research in new areas such as digital health continues to recognize women's needs and address their concerns, as sex and gender can influence adoption and acceptability of connected health technologies.

Despite all the benefits of digital health technologies, many known barriers to successful adoption remain. Users of these technologies still have outstanding concerns around privacy and security of health data collected through these various devices. Data tracked by devices can contain large amounts of personal and sensitive information that users care to keep private [28] and to have more control over who can have access to such

data [29-31]. The lack of perceived direct utility of digital health data [32,33] and the lack of applicable insight have slowed down the adoption of digital tools for clinical decision making [34,35]. Various studies have shown that the accuracy of wearable devices is variable and less reliable during dynamic activity outside of a laboratory [36,37]. The lack of adherence to using the technology over extended periods of time constitutes one of the biggest drawbacks from relying on such data. Users may forget or be unwilling to use the devices on a regular basis, and they may abandon self-tracking after a period of time if the perceived value is not realized [28]. Finally, rates of adoption of digital technologies vary greatly across sociocultural characteristics. Studies have found lower rates of adoption and more negative attitudes among individuals living in rural locations [38,39]. Younger individuals and women are more likely to use health apps and track health information online [40,41]. Women were less willing to share information, in comparison with men who were more confident about protecting their privacy [42,43]. Research has shown that individuals are more accepting of digital health technologies when the health information they deal with is less sensitive [31], and it is possible that women consider their female-specific health data (eg, menstruation, pregnancy) to be more sensitive than other types of general health data. As the femtech industry continues to grow, these concerns are becoming more prominent [44,45].

Scoping reviews on wearable technologies [46] and mobile health apps [47] have not addressed specific areas of women's digital health. While some have looked at areas such as gestational diabetes [48], perinatal depression and anxiety [49], and fertility tracking [50], no study has broadly mapped the use of PGHD from connected devices for women's health.

Objectives

In this scoping review, we aim to explore the different contexts in which digital tools collecting PGHD are being proposed to address women's health issues. We also want to evaluate women's opinions with regards to the acceptability of connected health devices in these different contexts. More specifically, our review aims to answer the following research questions:

1. What are the different areas of women's health or health-related behaviors that are being monitored with PGHD from connected health devices?
2. What personal metrics are being collected by these technologies?
3. What are the facilitators and barriers for women promoting or hindering their use of connected health devices?

The results from this review will allow us to identify gaps and unmet needs in women's health research to help guide future digital and connected women's health innovations.

Methods

Protocol Development

This scoping review protocol has been developed to align with the frameworks developed by Arksey and O'Malley [51] and Peters et al [52]. The completed Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [53] checklist is provided in Multimedia Appendix 1.

Search Strategy

The search strategy, developed in close collaboration with a reference librarian, was first created in Medline and adapted to Embase, APA PsycInfo, CINAHL Complete, and Web of Science Core Collection.

Initial searches were completed between March 2 and 6, 2020. Search alerts were used to include results added to the databases between March 6 and April 1, 2020. Manual searches were done to ensure that the initial search criteria used were comprehensive. On November 13, 2020, and March 10, 2021, we added additional search terms to broadly encompass possible missed articles. We kept a uniform cut-off date of February 29, 2020, for all included articles.

We focused on keywords and subject headings to ensure a broad coverage of the literature at the intersection of the following four topics: women, health, digital devices, and tracking. The topics of women and health were identified by terms such as "women's health," "female," "mhealth," and "digital health." Terms such as "smartphone," "wearable," and "Internet of Things" were used to identify digital devices. Tracking was identified by terms including "tracking," "monitoring," "self-management," "ResearchKit," and "person-generated adj4 data." The full list of search terms is included in Multimedia Appendix 2.

Terms referring to telemedicine (consultations with a health care provider in real time) were not included because we are primarily interested in technologies that allow the user to interact with the device on her own time for the collection of PGHD. Searches were limited to articles published in 2015 or later because publications with the keyword "digital health" started to emerge in the literature around that time [54,55]. We also excluded conference abstracts, conference reviews, editorials, letters, and comments due to limited feasibility and lack of details in such literature.

Eligibility Criteria

Because we wished to broadly map the existing literature on digital data and connected women's health research, we included a variety of studies: randomized and nonrandomized intervention studies, observational and correlative studies, feasibility and acceptability studies, case studies, reviews, descriptions of prototypes, measurement studies, analytical methods, and viewpoints. Study media releases and user reviews of specific applications were excluded. We only included articles written in English, irrespective of the country or the place of research.

We were interested in technologies and interventions targeting women, so papers were eligible if they specifically targeted women-only health topics (eg, pregnancy) or if they only included female participants. Articles including intersex, transgender, or nonbinary participants were not excluded.

We excluded articles that presented digital health tools designed for health care providers, as we are primarily interested in devices and apps that women can engage with independently outside of a clinical setting. Articles discussing the use of real-time consultations, whether through video, phone, or online chat, were excluded; however, some of the included interventions could involve the use of telemedicine services as long as they included asynchronous use. To maintain the focus of the review on tracking or monitoring one's data for health, devices must have allowed users to input personal health data; therefore, publications reporting on apps or websites used solely for educational purposes were excluded. Complete inclusion and exclusion criteria are presented in Textboxes 1 and 2.

Textbox 1. Inclusion criteria.

- Published between January 1, 2015, and February 29, 2020

- Refers to a health issue that pertains only to women or consists of only female participants of any age

- Includes the use of connected health tools for tracking or monitoring some aspect of health. This could include smartphones, wearable devices, the Internet of Things (eg, Bluetooth- or internet-enabled glucometers, blood pressure cuffs, and weight scales), and implantable devices

- Involves data collection from the user of the connected health tool (ie, the user either manually inputs data into the device or it is automatically uploaded)

- The user must be able to interact with the app or device on her own at home (outside of a clinical setting)

- Available in English

Textbox 2. Exclusion criteria.

- Not available in English
- Conference abstracts, conference reviews, editorials, letters, or comments
- Study media releases and user reviews of specific applications
- Research conducted on animals
- Research involving male participants
- Tracking of infants and children, with the exception of tracking breastfeeding (since breastfeeding is directly related to the mother's health and body)
- Devices or apps that are meant for health care provider use, use in a clinical setting only, or cannot be used independently without a health care provider present
- Digital health tools that are only for educational or informational purposes and do not allow the user to enter or track her own data (ie, no information exchange)
- Telemedicine services (eg, live video consultations with health care providers)

Study Selection

Results from the database searches were imported to the Covidence systematic review software [56] and deduplicated. Screening of articles occurred in two stages. First, titles and abstracts were independently screened by at least 2 reviewers according to the eligibility criteria defined above. For articles meeting the inclusion and exclusion criteria at the title and abstract level, the full texts were then reviewed independently, also by 2 different reviewers. Conflicts at either stage were discussed and agreed upon between members of the research team.

If we were unable to locate the full text of the article online or through the library, we made a request to the corresponding authors. Articles that remained inaccessible were excluded at this stage, and the count of such articles will be reported in the PRISMA flow diagram in the completed review.

Data Charting

For each article included, data will be charted by 1 reviewer in a spreadsheet and verified for accuracy by a second reviewer. A preliminary list of data charting elements was proposed and

finalized (Table 1) after charting data from a dozen articles. The research team discussed which elements provided the most useful information and which to discontinue, and added important components of the papers if they were not being adequately captured by our preliminary list.

To investigate the different contexts of women's health that use PGHD from connected health devices, we will record all health area(s) of focus for each article. These areas refer to categories such as maternal health and fetal monitoring, menstruation, gestational diabetes, physical activity, etc. We will also record the year of publication and the country in which the research was conducted. To better understand which health metrics are most collected, we will document the types of connected health technologies discussed in the different studies (eg, wearable), the name of the devices or apps if applicable (eg, Fitbit Charge 2), and the personal metrics collected by the technologies (eg, daily step counts). Finally, to answer the third research question about facilitators and barriers, we will record any comments about the usability and acceptability of the technologies, including features that users liked or disliked. We will not focus on the outcome results of intervention studies, as that would be outside the scope of our review.

Table 1. Data charting elements.

Type of data	Details of charted data
Article information	• Title • Authors • Year of first publication
Study characteristics	• Country in which the research was conducted • Research study design
Contexts for women's connected health	• Health areas of focus (eg, pregnancy, obesity, diabetes, etc)
Digital device details	• Types of digital health (eg, smartphone app, wearable, Internet of Things, implantable device, etc) • Name of device or app • Metrics collected by the devices (eg, heart rate, temperature, daily steps, pain rating, etc)
Usability and acceptability	• Facilitators to use of the technologies • Barriers to use of the technologies

Presentation of Results

A PRISMA flow diagram will be presented to detail the study selection process. Tables and graphs will be used to report findings on the contexts of the applications, including the various health areas of focus and metrics collected. A thematic analysis will be conducted to identify categories of facilitators and barriers in discussions about the acceptability and usability of the digital health technologies. Exact details of the format of the report will be determined as a team after completing data charting.

Results

The searches from March 2020 returned 11,533 results, and the additional searches run in November 2020 and March 2021 returned 3096 results. There were a total of 9102 articles to screen after deduplication in Covidence. We did not encounter any articles in our search that mentioned the inclusion of intersex, transgender, or nonbinary participants. As of November 2020, the full-text screening stage is nearly complete and reviewers have started data charting. Results are expected to be submitted for publication by Fall 2021 and reported in accordance with the PRISMA Extension for Scoping Reviews (PRISMA-ScR) guidelines [57].

Discussion

Reviews have previously been conducted in specific areas of women's health and digital health. However, to the authors' knowledge, no review has been conducted with the broad scope proposed here. This scoping review will provide an extensive report of the literature regarding connected digital health devices for monitoring in all areas of women's health through the collection of PGHD. This information will be useful for women's health and digital health researchers to identify new research questions and design their programs according to the identified facilitators and barriers to use.

One limitation of our scoping review is that it does not include conference abstracts, conference reviews, editorials, letters, comments, or gray literature. Although we are including research conducted worldwide, our review does not include non-English articles. Finally, due to the nature of scoping reviews, quality assessments will not be performed on included articles. However, we are not assessing the outcome results of intervention studies, so this is not pertinent to our review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[PDF File (Adobe PDF File), 160 KB - resprot_v10i5e26110_app1.pdf]

Multimedia Appendix 2
Electronic search strategy.
[PDF File (Adobe PDF File), 198 KB - resprot_v10i5e26110_app2.pdf]

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Abbreviations

PGHD: person-generated health data
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PRISMA-ScR: PRISMA Extension for Scoping Reviews

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