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Protocol

Factors Associated With Trial Completion and Adherence in App-Based N-of-1 Trials: Protocol for a Randomized Trial Evaluating Study Duration, Notification Level, and Meaningful Engagement in the Brain Boost Study

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Abstract

Background: N-of-1 trials promise to help individuals make more informed decisions about treatment selection through structured experiments that compare treatment effectiveness by alternating treatments and measuring their impacts in a single individual. We created a digital platform that automates the design, administration, and analysis of N-of-1 trials. Our first N-of-1 trial, the app-based Brain Boost Study, invited individuals to compare the impacts of two commonly consumed substances (caffeine and L-theanine) on their cognitive performance.

Objective: The purpose of this study is to evaluate critical factors that may impact the completion of N-of-1 trials to inform the design of future app-based N-of-1 trials. We will measure study completion rates for participants that begin the Brain Boost Study and assess their associations with study duration (5, 15, or 27 days) and notification level (light or moderate).

Methods: Participants will be randomized into three study durations and two notification levels. To sufficiently power the study, a minimum of 640 individuals must begin the study, and 97 individuals must complete the study. We will use a multiple logistic regression model to discern whether the study length and notification level are associated with the rate of study completion. For each group, we will also compare participant adherence and the proportion of trials that yield statistically meaningful results.

Results: We completed the beta testing of the N1 app on a convenience sample of users. The Brain Boost Study on the N1 app opened enrollment to the public in October 2019. More than 30 participants enrolled in the first month.

Conclusions: To our knowledge, this will be the first study to rigorously evaluate critical factors associated with study completion in the context of app-based N-of-1 trials.

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International Registered Report Identifier (IRRID): PRR1-10.2196/16362

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KEYWORDS

crossover trials; mobile apps; adherence; nootropics; N-of-1 trials; attrition; study duration; usability; motivation; cognition; mHealth; randomized controlled trial

Introduction

Background

The purpose of this study is to evaluate factors that may impact study completion and adherence in the context of app-based N-of-1 trials. A common challenge for digital research studies is the poor engagement of users [1]. The "law of attrition," as Eysenbach described it in 2005, is of special concern to app-based N-of-1 studies. Unlike a conventional, two-arm, randomized controlled trial (RCT) where a minimum sample size is calculated to detect a treatment effect that also takes into account an expected rate of attrition across the enrolled population, N-of-1 trials operate at the level of the individual, and there is 1 participant per trial. Typically, in an N-of-1 trial, an individual alternates between treatments (ie, "multiple crossover"), and outcomes are measured during each treatment period [2,3]. If there is attrition and the participant fails to complete an N-of-1 trial, there is no result for that individual.

Moreover, if a participant completes an N-of-1 trial, the result may still fail to achieve a level of statistical meaningfulness, especially for shorter trial durations. In this way, any person that aims to design an N-of-1 trial that is capable of informing decision-making for treatment selection for a single individual must strike the right balance between the ease of trial completion and the generation of meaningful results. Therefore, we aim to collect evidence about critical factors that may impact rates of study completion in the context of app-based N-of-1 trials. We hope these findings will inform the design of future app-based N-of-1 trials and improve the adoption of N-of-1 methods and tools.

N-of-1 Trials

N-of-1 trials create an opportunity for individuals to optimize treatment selection more systematically. In contrast, "therapy by trial" is a more common practice in both wellness and clinical medicine and is where individuals begin a therapy and monitor outcomes, often without much formal structure. If a treatment is deemed ineffective or introduces intolerable treatment burdens, a change to the treatment is made. N-of-1 trials are an alternative approach designed to help individuals make more objective, data-driven treatment choices.

Usually, in an N-of-1 trial, an individual alternates between treatments, and outcomes are measured during each period [2,3]. Where feasible, treatments may be blinded or placebo-controlled. Outcomes are measured at baseline and each treatment period. At the end of the trial, outcome measurements for each treatment are compared, and a treatment is selected. N-of-1 trials are particularly relevant in contexts where evidence for treatment efficacy is weak or where treatment response is known to vary across patient populations [2]. N-of-1 trials may also be deployed to answer other common treatment questions, such as optimal dosage or whether a symptom is associated with a treatment's side effects [2]. In what is considered a landmark paper for modern N-of-1 trials, Guyatt and colleagues applied this methodology to compare two treatments in a single patient with uncontrolled asthma and discovered that one treatment made the patient feel worse [4,5].

N-of-1 trials are not useful in every treatment context. Treatments with rapid onset and minimal washout are ideal candidates for N-of-1 trials, whereas curative treatments or treatments with cumulative effectiveness (eg, antidepressants) are not. N-of-1 trials are suitable for individuals with chronic or stable conditions. For example, one might compare melatonin versus herbal tea for chronic insomnia, and another might compare the effectiveness of two topical creams for persistent acne [2].

Hypotheses

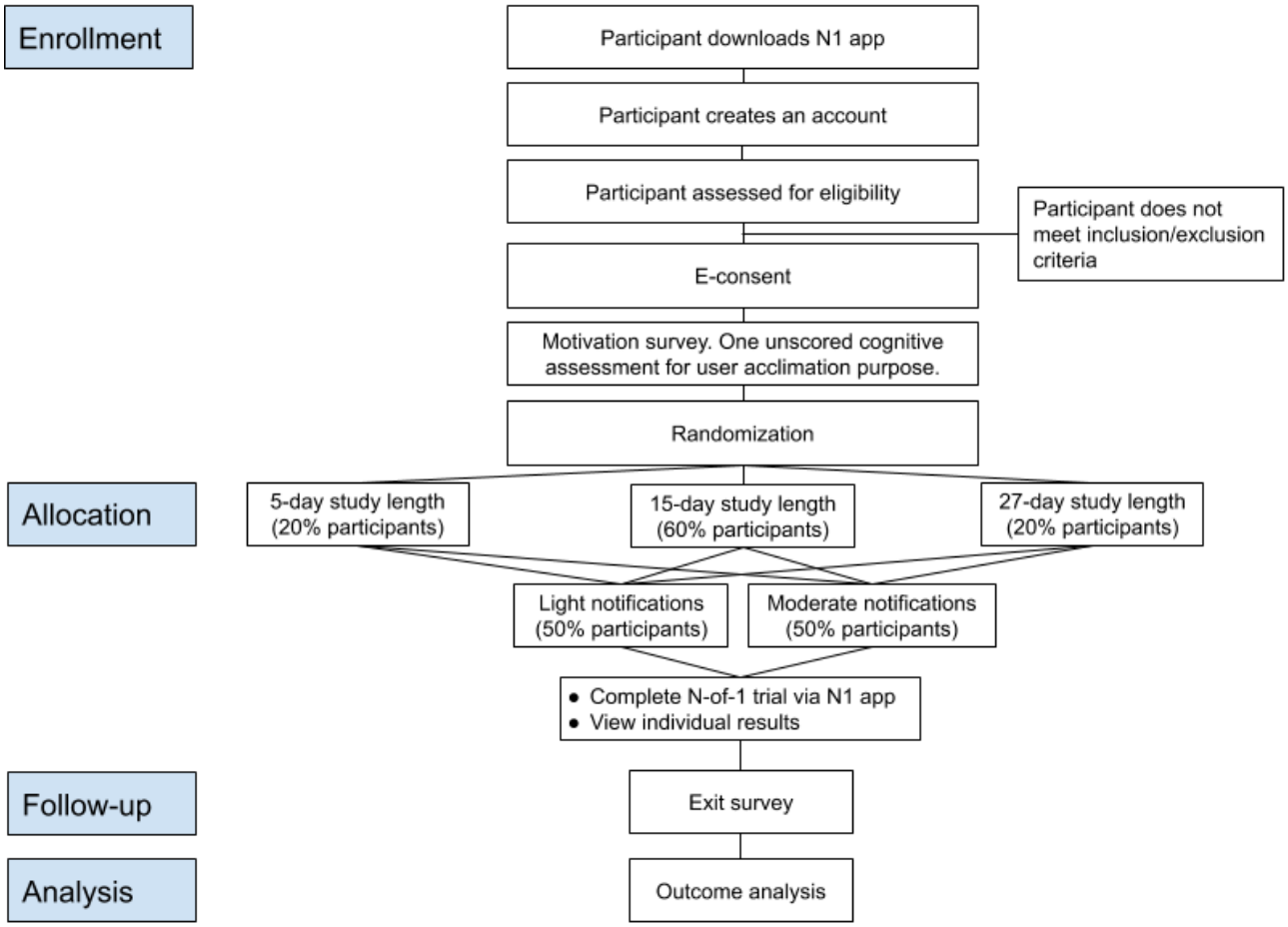
The primary hypothesis is that shorter trials will have higher rates of completion compared to longer trials. The null hypothesis is that no correlation exists between study completion and study duration. We also hypothesize that higher rates of study completion will be achieved with more frequent reminders to complete study tasks, in the form of app-based notifications, especially since the Brain Boost Study requires participants to complete tasks during a specific window of time each day during the trial. The null hypothesis is that no correlation exists between study completion and notification level.

Methods

Study Setting

All study activities are conducted through the N1 app, a smartphone iOS app distributed via the Apple App Store. We will primarily recruit participants via social media and through messages to online communities where there is documented interest in the topics of nootropics, supplements, medical science, or health technology. The informed consent process takes place remotely through the app, as described elsewhere [6]. Participants may contact the study staff at any time via email with questions or concerns. We have a designated health care professional on the study team to follow up on participant-reported, health-related concerns that are related to their participation in the Brain Boost Study. Participant flow through the study is described in Figure 1.

Figure 1. Participant flow through the Brain Boost Study using the N1 app. E-consent: electronic consent.



Eligibility Criteria

Adults aged 18 or older who have an iPhone running iOS 11.0 or later, consume caffeine, and live in the United States are eligible to enroll in the study. Exclusion criteria include anyone with reason to believe that consuming caffeine may be harmful to their health, are pregnant, or are breastfeeding. If a participant is unsure about whether they have a health issue that prevents them from consuming caffeine, they are advised to consult their doctor but are still eligible for the study.

Study Design

This study aims to evaluate a novel platform for conducting single-patient, multiple crossover studies (N-of-1 trials). For purposes of clarity, this protocol describes our methods to assess factors associated with study completion, along with several exploratory measures and analyses. The study design, interventions, cognitive assessment instruments, and methods for evaluating whether there is a detectable treatment effect for an individual participant enrolled in the Brain Boost Study based on their performance on the cognitive assessments are described elsewhere [6]. Participants enrolled in the Brain Boost Study follow a treatment schedule, guided by a mobile app (N1 app), where they alternate between the two treatments: caffeine (treatment A) or caffeine combined with L-theanine (treatment B) during a prespecified window of time. Participants are also asked to complete an app-based cognitive assessment during a prespecified window of time each day. The daily cognitive assessment includes three separate cognitive tests: the Stroop Test, the Remote Associates Test, and the Trailmaking Test [6]. They complete their tasks during one baseline period (where no treatment is assigned), and during four treatment periods where either treatment A or treatment B is assigned according to counterbalanced block design. Participants are not compensated, and the app is free to use. Only after a trial is completed does a participant see their results from the cognitive assessments.

Randomization

The study duration is either 5, 15, or 27 days. Participants will be randomized into study duration according to the allocation of 20%, 60%, and 20%, respectively. The uneven allocation to study duration was chosen out of consideration for the trade-offs between various study lengths. While we hypothesize that 5-day study lengths are more likely to be completed, they are also less likely to generate a meaningful result due to the small number of outcome measures. On the other hand, 27-day studies are more likely to generate a meaningful result with more repeated outcome measures, but we hypothesize that they are more likely to result in early withdrawal. Allocating more people to the 15-day study is a reasonable compromise between these two extremes, which is reflected by our decision to allocate more participants into this group while maintaining a sufficient sample

size for each group to assess our primary outcome measure, as described below.

Notification level is defined as the frequency participants receive reminders to complete study tasks and is either light or moderate. Participants are randomized into the notification level, such that 50% of participants are in each group. Participants randomized into the light notification group receive two notifications per day: one reminder to take their treatment and one reminder to complete the assessment (see Multimedia Appendix 1). Participants randomized into the moderate notification level receive 4-5 notifications per day: 2 reminders to take their treatments and 2-3 reminders to complete their assessment (see Table 1).

Table 1. Notification levels for the Brain Boost Study.

Notification level	Treatment reminders	Assessment reminders
Light	• At treatment time	• At assessment time
Moderate	• 15 minutes before • At treatment time	• 15 minutes before • At assessment time • 15 minutes before the end of assessment window, only if the assessment is incomplete at this time

Measures

The Proportion of Studies Completed

The primary outcome of interest is the proportion of studies completed. A study is considered complete if a participant reaches the end of a trial without a study failure (involuntary withdrawal) or voluntary withdrawal. A study failure occurs when there is insufficient data generated during baseline or any treatment period due to missed treatments (self-reported) or incomplete assessments. Participants must complete all assigned treatment and assessment tasks for 1/3 of the days in each period to avoid study failure and involuntary withdrawal, except for the 5-day study where all tasks must be completed each day because there is only one day per period. For the 15-day and 27-day trials, we inevitably expect participants to miss some tasks during these periods, so we wanted to allow for some nonadherence. While the requirement of task completion for 1/3 of the days in each treatment period is somewhat arbitrary, the choice of 1/3 of the days means that, at a minimum, completed 15-day trials will at least have the same amount of data as completed 5-day trials and are also likely to have more. We applied the same criteria to the 27-day trial so that the criteria for study failure are uniform across all three study durations. It is also worth noting that the 3 study lengths are primarily dictated by our randomized, counterbalanced, crossover design that defines N-of-1 trials: NABBA or NBAAB, where N is baseline, A is treatment period A, B is treatment period B, and AB or BA is a block. The minimum N-of-1 trial for a counterbalanced design with two blocks is five days if you have only one day per treatment period and one day of baseline.

We anticipate that a 27-day trial approaches what is likely to be the maximum number of days we could expect people to participate with reasonable adherence for this study, which requires daily tasks. The 15-day trial splits the difference between these two extremes. Put another way, we chose to vary treatment period lengths by one day for the 5-day trial, three days for the 15-day trial, and five days for the 27-day trial. We could have selected a different design, such as treatment periods that are 1, 2 and 3 days long rather than 1, 3 and 5 days long for each group; however, to evaluate the impact of study durations and notification levels on completion rates, we reasoned it would be better to have a more extensive spread across the three groups.

Adherence

Treatment adherence is recorded as true for days when a participant completes a cognitive assessment and does not report treatment nonadherence. A participant is instructed to report any treatment nonadherence (eg, a missed treatment or the use of caffeine on a baseline day) in the app during the trial. At the end of the trial, participants are prompted to review a summary of their treatment adherence and may, if necessary, record missed treatments at this time as well. Assessment adherence is recorded as true when a participant completes all three cognitive tests in a daily cognitive assessment according to the user-specified schedule. Otherwise, assessment nonadherence is recorded (for both incomplete assessments and assessments that were not started). Daily adherence is recorded as true when a participant achieves both treatment adherence and assessment adherence for a given day during the trial.

We will also measure trial adherence, which is defined as the proportion of total actions completed by a participant during a trial. Here total actions are defined as the number of requested treatment actions (to take a treatment or abstain from all treatments) plus the number of requested assessment actions (take a cognitive assessment) during a trial. During the baseline period, participants take two actions per day in the form of abstaining from treatments and completing one cognitive assessment. During a treatment period, participants take two actions per day in the form of taking one treatment plus completing one cognitive assessment. The total number of actions requested, and the minimum number of actions required for each study duration are outlined in Table 2.

Table 2. Total number of actions requested, and the minimum number of actions required for each study duration.

Study duration	Total number of actions requested	Minimum number of actions required to avoid study failure
5-day study	10	10
15-day study	30	10
27-day study	54	22

Motivation and Notification Levels

Before the trial begins, we will ask participants to self-report their motivation level to learn their results on a 5-point ordinal scale (see Multimedia Appendix 2). Also, participants will be randomized into two notification levels (light or moderate). However, since Apple does not allow iOS apps submitted to the App Store to require that users allow app notifications, we will also record the number of participants that turn off notifications. We anticipate that the number of individuals that turn off notifications will be rare, in part due to a warning message we included as a modal in the app that discourages this behavior, due to the likelihood of failure to complete study tasks according to the user-specified daily schedule (see Multimedia Appendix 1).

Proportion of Trials That Yield Statistically Meaningful Results

For each study duration, we will also measure the proportion of completed N-of-1 trials that yield statistically meaningful results as determined by the N1 app, for the comparisons: (1) caffeine versus baseline; and (2) caffeine plus L-theanine versus baseline. As described elsewhere, the N1 app considers a trial to have yielded a statistically meaningful result if the coefficient of treatment effect is significantly different from zero at the 80% confidence level in at least one of the three cognitive tests (eg, if taking caffeine relative to baseline, with or without L-theanine, produces an effect on cognitive performance measured by at least one of the three cognitive tests) [6]. The 80% confidence level is arbitrary, and we anticipate future versions of the N1 app will allow individuals to select the confidence level they seek.

Exit Survey

We will also invite enrolled participants to provide feedback about the N1 app and the Brain Boost Study through an optional exit survey administered at the time of study completion, during voluntary withdrawal, or at study failure via an automated email with a link. The anonymous survey will not be linked with individual user accounts. The exit survey includes a modified version of the 2-item Usability Metric for User Experience (UMUX-Lite) and up to 15 optional questions related to the participant experience with the app and the study (see Multimedia Appendix 3) [7]. The survey will be conducted in a browser outside of the N1 app.

Bug Reports and App Crashes

We will record the number of software bug reports submitted anonymously by users through a third-party tool linked from inside the N1 app. We will also record the number of app crashes recorded from those users who have opted-in to share their diagnostics and app usage information with app developers in App Store Connect, an administrative platform for managing and monitoring iOS apps submitted to the Apple App Store [8].

Other Collected Data

We collect sex (male, female, other) and year of birth (YYYY). For each participant in a trial, we will also timestamp planned and completed actions, and record the following dates: planned trial start and end dates, dates of adherence and nonadherence (treatment and assessment adherence), and dates of early withdrawal or completion.

Power and Sample Size

The study will be sufficiently powered (>80%; alpha=0.05) if 640 individuals begin the study, are randomized into 3 study lengths (5, 15, or 27 days) according to a randomization percent allocation of 20%, 60%, 20%, and achieve rates of completion of 30%, 20%, and 10%, respectively (see Table 3).

Table 3. The minimum number of participants we aim to enroll in each study duration.

Study duration	Randomization allocation (%)	Participants who begin study (n)	Estimate of completion rate (%)	Participants who complete study (n)
5-day study	20	128	30	38
15-day study	60	384	20	77
27-day study	20	128	10	13
Total	100	640	60	128

For the sample size estimate, the Hsieh sample size correction for multiple logistic regression was used, which assumes correlation among covariates and therefore adjusts the sample size accordingly [9]. We estimated this correlation to be equal to 0.25. With these assumptions, 97 completed studies are required to discern whether the study length and notification level are associated with the rates of study completion. To estimate how precise we may be, we used sample size tables for each predictor (see Multimedia Appendix 4).

Data Analysis Plan

Primary Analysis

All study data, unless otherwise noted, will be collected through the N1 app, and stored in Health Insurance Portability and Accountability Act (HIPAA)-compliant cloud storage. Statistical analyses will be conducted primarily using R version 3.6 (The R Foundation, Vienna, Austria). We will use a multiple logistic regression model to discern the relationship between study duration and notification level with the proportion of studies completed among participants who begin a study. Participants who begin a study are defined as those who achieve both treatment adherence and assessment adherence for at least one day during the baseline period. Participants that do not begin the study will be removed from the analysis. We will adjust these results for any variance in completion rate by age and sex.

Exploratory Analyses

We will also use descriptive statistics to summarize measures collected in the Brain Boost Study. We will compare the proportion of studies completed and trial adherence across the six groups of participants (three study durations and two notification levels), removing from this analysis anyone that turned off notifications. We will also compare the proportion of completed trials that are deemed by the N1 app to demonstrate a meaningful difference in treatment response on any of the cognitive tests, across the three study durations.

We also want to learn about the factors that influence the measure of trial adherence to improve future study designs. We will use Bayesian methods for exploratory analysis to get a baseline for future analyses, which we expect will also use Bayesian methods of analysis. The exploratory analysis will utilize a Bayesian survival-style model with semicompeting risks throughout the study. It will be assumed that a participant is in the study up until the time of study completion, voluntary withdrawal, or involuntary withdrawal (ie, study failure). Daily adherence will be assessed among all participants in the study on a given study day. There will be two types of events considered: (1) daily nonadherence, as a nonterminal repeating event; and (2) early withdrawal (including both voluntary withdrawal and involuntary withdrawal due to study failure) as a terminal (nonrepeating) event. The daily rate of nonadherence and early withdrawal will be modeled as a Poisson process with the rates impacted by several covariates, including study day (number of days since the start of the study, estimated with a random walk prior), notification level (light versus moderate); self-reported motivation level (5-point ordinal scale), day of the week (if distinguishable from study day), and subject-specific shared frailty term.

The cumulative probability of early withdrawal can be used to estimate the inverse probability of study completion. Also, the daily rates of adherence can be used to improve study design for future participants, depending on self-reported motivation and subject-specific characteristics. As in the primary analysis of the study completion rate, we will additionally adjust this analysis of adherence for age and sex.

Results

Platform Development and Testing

We have completed extensive internal testing of the N1 app, as well as beta testing on a convenience sample of 12 users. We did not collect completion rates or adherence for the beta testers because the app was still under development at the time that testing was performed. We iteratively improved the N1 app over the past two years through more than 75 builds until we achieved a stable release and a feature set suitable for launch.

Ethics Approval

The Institutional Review Board at the Icahn School of Medicine at Mount Sinai has approved this study (IRB-18-00343, IRB-18-00789).

Enrollment

The Brain Boost Study on the N1 app opened enrollment to the public in October 2019.

Discussion

Primary Findings

The N1 App aims to facilitate the design, administration, and analysis of N-of-1 trials. The Brain Boost Study will be the first experiment available on the platform that is open to the public. As a wellness-related study that evaluates the effect of commonly used supplements on cognitive performance, this study also provides an opportunity to socialize N-of-1 methods to much broader audiences. While the first intentionally designed crossover treatment trial dates to the late 1700s and N-of-1 trials like how we conceive of them today have been practiced for decades, adoption remains low [10-12]. Opportunities for the public to apply these methods to their treatment dilemmas are similarly scarce outside of a limited number of clinical settings with expertise in the design, administration, and analysis of N-of-1 trials.

Digital tools, like the N1 app, provide a promising new avenue for making N-of-1 trials more accessible. However, many challenges remain, especially around participant engagement and adherence in app-based research [13]. Sustained engagement of participants has been elusive for many digital health studies to date. In a pooled analysis of 8 app-based digital health studies representing over 100,000 participants, 850,000 study days, and 3.5 million app-based tasks, the median time participants engaged in the study during the first 12 weeks was only 5.5 days, and the median time participants performed active tasks was only two days [14]. To deploy an effective app-based N-of-1 trial, one must reconcile many trade-offs that span study design, technology, and user characteristics. To our knowledge, this will be the first study to rigorously evaluate multiple factors associated with study completion and adherence in the context of app-based N-of-1 trials. One other app-based N-of-1 trial platform has recently evaluated usability and user acceptance of an app in the context of pain-related N-of-1 trials [15,16]. Our findings should be of significant interest to practitioners seeking to design N-of-1 trials using similar methods and tools to support data-driven treatment choices.

Strengths and Limitations

N-of-1 trials are designed as for-benefit trials that promote informed decision-making among individuals that participate in them [3]. As such, this study of factors that influence study completion in the context of N-of-1 trials is unlikely to be generalizable to other types of digital health studies (eg, observational studies, RCTs) where there is no likelihood of personal benefit. However, insights from this study may apply to future trials in the N1 app and other app-based N-of-1 trial platforms.

The N1 app was designed to be flexibly adapted to other N-of-1 trials that, by definition, will share a few common elements, including notifications to keep a participant on track with a schedule of alternating treatments and regular outcome measures. We anticipate that even within app-based N-of-1 trials, there may be marked differences in adherence and completion rates depending on the nature of the trial and the characteristics of the target population, such as the magnitude of decisional conflict an individual confronts related to treatment selection or the nature and severity of the underlying health condition, respectively. Moreover, the number and difficulty level of actions requested in an N-of-1 trial is likely to influence completion and adherence rates. The collection of outcome measures through the integration of apps, devices, or wearables that reduce the number of actions required of an individual to complete in app-based N-of-1 trial is an area where digital health research may defy the law of attrition and is a promising future direction.

This protocol requires participants to record treatment nonadherence, rather than to record treatment adherence positively. This choice was made to reduce the number of daily actions required of participants under the assumption that a participant is likely to complete a daily cognitive assessment only in the circumstance where a treatment was taken according to schedule. Since the results of the cognitive assessment are hidden until the completion of the trial, a participant does not stand to benefit by taking a cognitive assessment for reasons that are outside the purpose of the trial.

We anticipate that most participants will schedule their treatments at the beginning of the day since caffeine consumption is a typical morning ritual. This represents two challenges for participant engagement that may not be generalizable across other N-of-1 trials. First, a recent survey of eight app-based digital health studies observed the highest levels of engagement in the evening [14]. Second, the act of abstaining from caffeine consumption for the duration of the baseline period may be perceived as a significant challenge for some individuals in a manner that may be altogether absent were we to be running a trial that compares two treatments of a different nature.

The estimation of completion rates in the total enrolled population for each study duration is a challenge because it not only depends on factors being evaluated in this study but also on recruitment and user characteristics that are uncontrolled outside of very permissive inclusion/exclusion criteria that focus on the safety of caffeine consumption. The novelty of app-based research, for example, may attract people that are more curious about the app or methods than they are committed to learning their results, which is why we included the question about motivation level as an exploratory measure. For example, one recent app-based research study on asthma experienced very high initial recruitment followed by rapid attrition and a small number of highly engaged participants [17]. The relationship between intrinsic motivation and treatment adherence has been examined elsewhere, such as long-term antiretrovirals for HIV/AIDS, weight loss, and various public health initiatives that involve behavior change [18].

One limitation of the collection of only minimal demographic information is that we will not be able to determine if the enrolled study population is representative of the general population outside of age and sex, which will limit the generalizability of our results. The most extensive study to date on retention in digital health studies showed a relationship between age and retention, with older populations having higher retention than younger participants [14]. They observed no relationship between sex and retention [14].

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Examples of notifications and permissions in the N1 app.
[ZIP File (Zip Archive), 4799 KB - resprot_v9i1e16362_app1.zip]

Multimedia Appendix 2
Motivation survey.
[DOCX File , 14 KB - resprot_v9i1e16362_app2.docx]

Multimedia Appendix 3
Exit survey.
[DOCX File , 16 KB - resprot_v9i1e16362_app3.docx]

Multimedia Appendix 4
Sample size tables.
[DOCX File , 17 KB - resprot_v9i1e16362_app4.docx]

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Abbreviations

HIPAA: Health Insurance Portability and Accountability Act
RCT: randomized controlled trial

UMUX-LITE: 2-item Usability Metric for User Experience

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Protocol

Caring Near and Far by Connecting Community-Based Clients and Family Member/Friend Caregivers Using Passive Remote Monitoring: Protocol for a Pragmatic Randomized Controlled Trial

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Abstract

Background: Significant chronic disease challenges exist among older adults. However, most older adults want to remain at home even if their health conditions challenge their ability to live independently. Yet publicly funded home care resources are scarce, private home care is expensive, and family/friend caregivers have limited capacity. Many older adults with chronic illness would require institutional care without the support from family member/friend caregivers. This role raises the risk of physical health problems, stress, burnout, and depression. Passive remote monitoring (RM), the use of sensors that do not require any action by the individual for the system to work, may increase the older adult's ability to live independently while also providing support and peace of mind to both the client and the family member/friend caregiver.

Objective: This paper presents the protocol of a study conducted in two provinces in Canada to investigate the impact of RM along with usual home care (the intervention) versus usual home care alone (control) on older adults with complex care. The primary outcome for this study is the occurrence of and time to events such as trips to emergency, short-term admission to the hospital, terminal admission to the hospital awaiting admission to long-term care, and direct admission to long-term care. The secondary outcomes for this study are (1) health care costs, (2) client functional status and quality of life in the home, (3) family/friend caregiver stress, and (4) family/friend caregiver functional health status.

Methods: The design for this study is an unblinded pragmatic randomized controlled trial (PRCT) with two parallel arms in two geographic strata (Ontario and Nova Scotia). Quantitative and qualitative methodologies will be used to address the study objectives. This PRCT is conceptually informed by the principles of client-centered care and viewing the family as the client and aims at providing supported self-management.

Results: This study is supported by the Canadian Institutes for Health Research. A primary completion date is anticipated in fall 2022.

Conclusions: Findings from this real-world rigorous randomized trial will support Canadian decision-makers, providers, and clients and their caregivers in assessing the health, well-being, and economic benefits and the social and technological challenges of integrating RM technologies to support older adults to stay in their home, including evaluating the impact on the burden of care experienced by family/friend caregivers. With an aging population, this technology may reduce institutionalization and promote safe and independent living for the elderly as long as possible.

Trial Registration: International Standard Randomised Controlled Trial Number (ISRCTN) 79884651; http://www.isrctn.com/ISRCTN79884651

International Registered Report Identifier (IRRID): DERR1-10.2196/15027

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KEYWORDS

home care; family caregiver; friend caregiver; remote sensor; older adults; caregiver burden

Introduction

Older adult Canadians (aged 65 years and older) experience significant chronic disease challenges [1], yet most older adults want to remain at home even if their health conditions challenge their ability to live independently [2].

There is evidence that "...when home care is appropriately managed and properly integrated into the health care system, it can improve the health and well-being of many seniors and their families and reduce the costs of care in hospitals and long-term care facilities" [3]. However, evidence suggests that there is room for improvement in current home care service delivery. Recent studies showed that 25% of Canadian older adults receive only partial home care services and experience unmet home care needs that create a cascade of events resulting in deterioration of older adults' health and the need for institutionalized care [2,4]. Older adults want to be assured that their health care needs can and will be effectively addressed [5].

Part of the challenge in caring for older adults in their homes lies in providing suitable home care services and ensuring that older adults can safely follow their established treatment plan (eg, adherence to medication protocol). From a health care perspective, we have yet to feel the full effects of the impact of older adult health care challenges [6]. The transfer of health care services to the home setting is a strategic move intended to accommodate the desire of many older adults to remain at home and minimize acute care costs [7]. Yet home care resources are tenuous due, in part, to challenges in attracting and sustaining a work force (eg, nurses) that will be paid lower wages than in the hospital sector [3,5].

Deficiencies in availability of publicly funded home care means that family/friend caregivers are increasingly called on to play a larger role in the care of older adults within the home setting [3]. As the care needs of older adults increases, the average number of hours of care provided by family/friend caregivers increases significantly in contrast to the limited publicly funded home care service provision [3]. There is growing recognition that the majority of older adults would not be able to stay in their homes without the support from family/friend caregivers [5,8]. Family/friend caregivers in Canada are providing unpaid care to approximately 97% of home care recipients [8]. A Statistics Canada report indicated that in 2012 family/friend caregiving was provided by more than 8 million Canadians [9] at a conservative cost estimate of $25 billion (US $19 billion) in health care service [10]. These spouses, adult children, friends, and neighbors [8] provide transportation; prepare meals; clean and maintain the home; schedule and coordinate appointments; advocate for care services; manage finances; help with medical treatment; and provide emotional support and personal care such as bathing, feeding, and toileting [11]. The presence (physically or virtually) of family/friend caregivers is key to whether or not older adults with complex care needs can remain in their own home [3,12]. Yet for the family/friend caregiver, this role creates increased risk of physical health problems, stress, burnout, and depression [12].

Family/friend caregiver stress constitutes a depletion of personal resources and is reflected by family/friend caregivers' distress, anger, or depression as a consequence of an accumulation of tasks and responsibilities that impacts their sense of independence and freedom [13]. A study by Duxbury et al [6] of employed family caregivers (eg, spouse, adult child) in Canada found that the average caregiver maintained their supportive role for about 5 years; many taking on the role because they cared deeply about their family member. However, approximately 40% of family/friend caregivers reported that they assumed the caregiver role by default; there was no one else to take on the responsibility for care. There are significant costs to Canadian family/friend caregivers of an elderly family member related to altered work patterns, loss of career advancement, and increased use of Canada's health care system [6,8,14]. Family/friend caregivers are also at risk of financial strain associated with poorer physical and mental health, greater work-life conflict, increased workplace absenteeism, lower job satisfaction, and a higher number of visits to the emergency room and hospital. Fast et al [14] estimated an annual loss of income of $336.8 million (US $256 million) is associated with family/friend caregiver employment disruptions.

Health information technology and specifically remote monitoring (RM) technologies can support older adults to remain in their homes [15]. Remote technologies act by notifying, in this case, a family member or friend of a possible untoward

incident (ie, a fall, failure to take medications, wandering). Active RM monitoring applications require individual participation, such as pushing a button, whereas passive RM technologies such as sensors do not require any action by the individual for the system to work. Active and passive RM can increase client confidence in their self-health care and in their ability to live independently at home [16]. RM is especially helpful in tracking behaviors of older adults with cognitive decline (eg, forgetting to take medications) and allowing caregivers to intervene quickly [15]. These technologies can also benefit home-based older adults and their family/friend caregivers in the short-term by increasing communication and collaboration between and among all stakeholders [15].

We are proposing to develop and evaluate a technology-enabled RM model of home care (RMHC) to address current gaps in home care for older adults requiring the kind of complex care that includes (1) stretched health human resources, (2) partial home care services and unmet home care needs, (3) reliance on unpaid family/friend caregivers to sustain home care services with limited support to conduct this care work, (4) a chronic disease model of health care that assumes and expects client and caregiver ability for self-care, (5) lack of direct support for or involvement of family caregivers in new models of home care, and a (6) lack of innovative strategies to expand home care. RMHC is enabled by passive RM technologies (eg, sensors and cameras) and is conceptually informed by the principles of client-centered care, family as client, supported self-management, and stakeholder collaboration [4,5,17,18].

The purpose of this study is to examine the use of passive RM technologies in the home as a means of supporting older adults to safely remain in their home and avoid or delay the need for higher levels of care.

Methods

Study Design

This 4-year study is an unblinded pragmatic randomized controlled trial (PRCT) with two parallel arms [19-22]. PRCTs are well-suited to supporting decisions about complex interventions tested in the real world when comparing with usual care [23,24]. The objective of the study is to examine the effectiveness of the RMHC versus usual home care in maintaining the client in their place of residence and delaying or preventing admission to higher levels of care such as hospitalization or long-term care.

This study builds on the findings of previous pilot studies conducted in the provinces of New Brunswick, Alberta, Nova Scotia, and British Columbia. The primary aims of this study are to test whether (1) RM along with usual home care (the intervention) versus usual home care alone (control) allow older adults with complex care needs to remain in their home longer and delay or avoid admission to higher levels of care (eg, hospitalization and long-term care), (2) intervention is cost effective, and (3) intervention will improve the quality of life for clients and family/friend caregivers. The primary outcome for this study is the occurrence of and time to events such as terminal admission to hospital awaiting admission to long-term care and direct admission to long-term care. The secondary outcomes for this study are (1) health care costs, (2) client functional status and quality of life in the home, (3) family/friend caregiver stress, and (4) family/friend caregiver functional health status.

Setting

The PRCT will take place in two study sites: the provinces of Nova Scotia and Ontario.

Selection Criteria

PRCTs are meant to capture real-world situations and clients, therefore we have purposely selected broad inclusion criteria for this study (Textbox 1). To be assessed as at risk for higher levels of care, the clinical provider identifies that within the next 12 months the client is likely to be admitted to long-term care. For this research, participants must be recruited in client-caregiver dyads because the RM technology requires that older adults have a family member/friend caregiver who is willing to receive system notifications. These criteria were developed in collaboration with the regional health care partners.

Textbox 1. Participant recruitment selection criteria.

Inclusion criteria:

- Aged 65 years and older
- Assessed as requiring complex publicly funded home care
- At risk for admission to a higher level of care
- Have a caregiver (family member or friend or neighbor) willing to receive notifications from the remote monitoring system
- Willing to have remote monitoring technology installed in their home if they are randomized to the intervention group
- Able to read/write English or French
- Have decisional capacity to consent or have a substitute decision-maker consent to participate in study

Exclusion criteria:

- Assessed for immediate admission for higher level of care
- Lack a family/friend caregiver
- Not competent to consent to participate in study or do not have a substitute decision-maker for consent

Sample Size Calculation

The sample size calculation is based on data from one health region included in the study to estimate the study's main outcome (time to higher levels of care). The following criteria were used to estimate sample size: the total institutionalization proportion among controls being equal to 0.41 and the proportion or the experimental subjects at 0.27 (ie, a 34% reduction compared to controls); a 10% dropout and/or lost to follow-up rate; a power of 80% and a statistical significance level of alpha=.05. This resulted in an estimate of 160 participants for the intervention group and 320 for the control group for a total target study size of 480 participants across the study sites [25,26]. We opted to increase the study power by using a 2:1 ratio of controls to intervention subjects due to the cost of the intervention.

Recruitment

Participant enrollment in the PRCT is supported by the respective provincial regional authority. Home care recipient participants will be assessed by the case coordinator or case manager in the regional authority against the inclusion and exclusion criteria (see Textbox 1).

Consent to participate in the study will be obtained at the first meeting with the researcher and the patient and family/friend caregiver. Once consent is obtained from the participants (client and their family/friend caregiver), research staff will collect baseline data before initiating random allocation into control and intervention groups. Using block randomization, participants will receive either usual home care or RM with usual home care [27]. Randomization will occur as follows:

- Twelve ping pong balls will be placed in a container
- Four of each of the ping pong balls will be numbered 1 to 3
- Each block of 3 participants will be numbered sequentially from 1 to 3 as they appear on the master recruitment list
- A ping pong ball will be pulled from a container and whatever number that ball is will correspond to the numbered participant; it is that participant who will receive the intervention
- The remaining 2 participants will be in the control arm (no intervention)

Allocation bias will be addressed through allocation concealment; neither the case coordinator/case manager in the home care agency or research staff will know to which group the individual will be assigned a priori.

Control and Intervention Groups

Control

Clients will receive usual publicly funded home care services provided by their provincial or regional home care agency including but not limited to home visits by assistive personnel for activities of daily living, nursing care, and other supports deemed necessary by the home care case coordinator or case manager. In both study sites, home care assessments are conducted by the regional authority case coordinator or case manager. Once the assessment is completed and care services are decided, service delivery is provided by a contracted home care agency.

Intervention

Clients will receive RMHC in addition to usual home care services. The intervention group will receive passive RM sensors to detect a combination of the following behaviors/movement patterns: medication administration, opening refrigerator/cupboards, getting in and out of bed, movement in the bathroom, use of exit doors, movement detection, and for observation (cameras). The study technology partner, CareLink Advantage (www.carelinkadvantage.ca), will cover the equipment and monitoring costs. Once enrolled in the study, clients and their family/friend caregivers will have a home visit by the technology partner (or designate). They will receive written and verbal overview of the various RM options. Based on the assessment by the technology partner along with client and family/friend caregiver preferences, the RM options will be customized and implemented. The intervention will be offered to the client for 12 months at which time the client will be transitioned to usual care. Notifications of atypical events (eg, missed medication, atypical length of time in bed) will be sent to the family/friend caregiver via either email, text message, or phone call. Action, based on the notification, may include a telephone call to prompt the client or check on the client's safety, deployment of assistive home care supports, or emergency action (eg, ambulance). During the study, researchers will not receive any notifications. However, at the end of the study notification patterns and trends will be analyzed.

Data Collection

Prior to initiating the PRCT, all research team staff in Nova Scotia and Ontario and study site care coordinators/case managers will receive training on the study protocol and data collection measures. In addition, research staff and home care agency staff will be educated about the RM equipment by the industry partner (CareLink Advantage).

Phase I: Survey Data Collection

Researchers will meet with clients and family/friend caregivers in the home of the client or by phone at baseline, 6 months, and 12 months to collect data. It is expected the interviews will last no more than one hour. Paper format questionnaires including standardized instruments and researcher-developed questions will be used to collect data at each time point (see Measures). Data on reasons for leaving the study will also be collected. A demographic form will be used to collect basic demographics including age, education, sex, marital status, income, and individuals' provincial health insurance number. The provincial health insurance number will be used for data linkage to provincial administrative health care databases in order to conduct the economic evaluation.

Phase II: Administrative Data Linkage

To address the primary outcome of the study, data will be obtained from the regional health authorities related to the occurrence of and time to events such as trips to emergency, short-term admission to hospital, terminal admission to hospital, and direct admission to long-term care.

Phase III: Qualitative Interviews and Focus Groups

Qualitative data will be collected in the form of semistructured interviews to understand the perspectives of clients, family/friend caregivers, health care professionals, and health care decision-makers on the use of RM in the home. Eight to 12 individuals each of clients, family/friend caregivers, health care professionals, and health care decision-makers will be interviewed. Interviews will be audio recorded and transcribed verbatim. To ensure accuracy of the transcribed data, a random selection of transcripts will be validated with audio recording. Interviews will focus on understanding views on the technology itself including acceptability/resistance (eg, privacy), the model of care (eg, client-centered), enhancements/improvements, and benefits of the model for clients, family/friend caregivers, health care professionals, and health care decision-makers. These data will assist with understanding implementation and evaluation of the model, inform modifications to the model for potential scale-up, and integrate end user perspectives into model refinements.

Measures

The primary outcome of the study is the occurrence of and time to leaving one's home for a higher level of care such as long-term care. This will be assessed using the following variables available in the Discharge Abstract Database for Ontario and Nova Scotia: terminal admission to hospital (yes/no) and direct admission to long-term care (yes/no).

Secondary outcomes are described below along with their specific measures. All standardized instruments have been validated in previous studies. Different versions of researcher-developed instruments were developed for clients and family/friend caregivers.

Health Care Costs

Health care cost to the Ministries of Health (ie, hospitalization, emergency room visits, and home care services) will be captured from administrative databases (from provincial and regional authority databases).

Older Adult Functional Status and Quality of Life

Older adults' functional status, mood, well-being, and social supports will be assessed using the following:

- Hospital Admission Risk Profile [28]
- Participant self-reported perception of safety and quality of care (researcher-developed)
- Mini-Mental State Examination [29]
- Satisfaction with RM (researcher-developed)
- Older People's Quality of Life Questionnaire [30]

Family and Friend Caregiver Functional Status and Quality of Life

Measures include adapted versions of the following:

- Selected Caregiver Assessment Measures [31]
- California Caregiver Resource Centers Uniform Assessment Tool [32]
- Zarit Burden Interview [33]
- Positive Aspects of Caring [34]
- Stanford Presenteeism Scale [35]
- Todtman Financial Impact Scale [36]
- Satisfaction with in-home monitoring assessment (researcher-developed)

Remote Monitoring Data

Sensor notifications are atypical events (eg, missed medication, lack of movement from the bed) of client's activities of daily living that will trigger a message sent to a family/friend caregiver. Currently, all system (ie, client) activity is logged and viewable on a dashboard available to authorized individuals via computer or on a mobile device. As well, a history of the clients' activity/nonactivity is logged (eg, fridge door opened, bathroom motion idle). The system has a search function such that client activity can be determined by sensor (eg, bed, medication) over several months to determine emerging and changing patterns. Patterns will be identified by the application of algorithms. Alternatively, all activity of a day can be viewed in chronological order to generate a description of the clients' daily behavior patterns. The notification data has the potential to form a baseline of participant (client) behavior in the home, and trends or models of a participant's usual activity or behavior can be established and then used to identify changes. Data collected from camera sensors will not be assessed.

Data Analysis

Quantitative Data

Quantitative data will be analyzed at baseline, with subsequent analysis of primary/secondary outcomes at 6 months and 12 months. Using SPSS Statistics version 25 (IBM Corp) statistical software, descriptive statistics will provide a profile of study participants including demographics, current diagnoses, length of home care before the study, and model of care (RMHC versus usual care). The provisional effect of the intervention on the primary outcome will be tested using a prospective chi-square test of independence (continuity-corrected) between the experimental and control groups (Fisher exact test). Repeated measures analysis of variance will measure mean differences between groups on continuous variables. We intend to use multivariate survival analyses methods using a relevant time dependent outcome based on the ability to accurately track the main event of interest (ie, institutionalization) [24]. We will conduct within and between province analyses on secondary outcomes. Subgroup analyses will include examining differences based on sex (male/female) in both clients and family/friend caregivers.

Notification Data Analysis

Notification data from RMHC sensors will be analyzed for patterns and trends of clients' activity in the home. Data will be downloaded from the technology provider database quarterly and analyzed by the researchers. Exploratory pattern analysis will include reviewing each individual's pattern of notifications. In addition, data will be aggregated to examine patterns that might inform understanding of the population (eg, common issues such as medication delay, sleep/wake patterns). These data will provide broader insights about daily patterns of older adults living in their home that may lead to other interventions to support home care service planning.

Economic Analysis

An economic analysis will be undertaken by the study health economists to examine health care costs from the perspective of the health system. The objective of the economic analysis is to compare the costs associated the RMHC model against those of the usual publicly funded home care received by control group participants. The economic analysis will be conducted using primary data from the study and secondary data from the administrative databases (from provincial and regional health authority databases—ie, the Ontario Institute for Clinical Evaluative Sciences, Health Data Nova Scotia) for costs associated with older adult health service use (ie, hospitalization, emergency room visits, and home care services) along with costs associated with home care delivery. The costs of the delivery (service fees for installation and monthly maintenance) of the RM intervention will also be included. With data on health service use, costs for each older adult participant will be calculated by multiplying the individual resource use (from the study and home care database) with unit costs (from provincial standard costing sources such as the Schedule of Benefits [36-39]). We will analyze the total cost variable as a dependent variable, using regression, to estimate the difference in expected health care cost between the RMHC model of care and usual care. The intervention variable will be the primary independent variable, and the model will adjust for previously mentioned potential confounding variables. Ordinary least squares model produces unbiased estimates even if the data are skewed [40]. Subgroup analyses (eg, by sites, by sex) will be explored.

Qualitative Analysis

Qualitative data analysis will be conducted using an interpretive description approach. Semistructured interviews will be used. The interview guide will be developed based on data discovered from the baseline and 6- and 12-month interviews. Clients and caregivers will be interviewed separately. Interpretive description is an inductive analytic approach designed to analyze clinical phenomena with the intent of identifying thematic patterns within participants' experiences to inform clinical understanding and application [41]. The focus of this approach is not only intent on describing phenomena but on developing explanations which have meaningful application thus aligning this approach to data analysis with identifying and addressing practice issues, informing the development of policy and planning of home care services. Using NVivo version 10 (QSR International Pty Ltd) qualitative software, at least two researchers will independently code the data to ensure reliability in the coding. Data will be analyzed for emergent themes relevant to the study outcomes and to inform scale-up of the RMHC model.

Results

The end of data collection for the primary outcome (occurrence of and time to terminal admission to hospital awaiting admission to long-term care and direct admission to long-term care) will be winter 2020. Data collection for the secondary outcome (health service use) will continue for up to 5 years after the 12-month participant interview. Qualitative data will be collected during study years 3 through 5.

Discussion

Impact

Research evidence indicates that the real challenge in using RM technologies is not about the number and placement of sensors in the home but rather the ability to make sense of and respond in a timely manner to the data streams from clients [42]. To be effective, the notification data could be tailored to and uniquely presented to providers, older adults, and family/friend caregivers. RMHC notification to family/friend caregivers with the option to share this information with home care service providers (1) enhance family/friend caregiver support, (2) inform decision-making regarding client care to determine safety (eg, proper medication administration, falls), and (3) generate observations of daily living from client data for historical analysis for trending, modeling, and prediction [43]. With historical data, there is potential to model older adults' behavior to identify patterns that can be used to identify changes in behavior over time.

In the RMHC model, we redefine the term client to include both older adults in the home and their family/friend caregivers [5,12]. Although family/friend caregivers play an integral role as part of the care team to support older adults in the home, health care assessments remain largely focused on the needs of the individual client. The extended health care responsibilities taken up by older adults and their family/friend caregivers create care work. Family/friend caregivers in the RMHC model will also be recognized as clients with unique care needs [5,12]. Many family/friend caregivers also experience a decline in their health but continue to provide care. In light of this, researchers have concluded that a reasonable outcome for family/friend caregivers is one where caregiver stress is held constant [44]. Minimizing family/friend caregiver stress in light of the evolving care challenges of older adults in the home may be unrealistic [44]. In the RMHC model careful attention is given to the caregiver experience.

Conclusion

The societal impact of RMHC intervention may contribute to resolving the challenges of limited health human resources within home care and create greater benefits for family/friend caregivers. Collecting data on older adults' behaviors creates the opportunity to efficiently monitor and address the needs of home care clients but also to aggregate data into large datasets to be analyzed and used to inform the development of best practices for older adults with complex care needs and their family/friend caregivers within the home care setting.

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Conflicts of Interest

None declared.

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Abbreviations

PRCT: pragmatic randomized controlled trial
RM: remote monitoring
RMHC: remote monitoring model of home care

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Protocol

Using Augmented Reality to Motivate Oral Hygiene Practice in Children: Protocol for the Development of a Serious Game

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Abstract

Background: New technologies create possible new ways of action, interaction, and learning which is extremely relevant in the field of oral health education. There is a lack of protocol in using an immersive interactive ludic-educational interface to motivate oral hygiene practice in children by means of augmented reality.

Objective: This study aims to present a protocol on the development of a serious game to motivate oral hygiene practice in children.

Methods: A serious game will be designed by augmented reality techniques to improve toothbrushing effectiveness of children aged 6 to 10 years. The functional structure of this interface is activated by means of movements recognized by Kinect (Microsoft Corp). The toothbrushing technique will be available in the game, enabling the children to execute the movement in the virtual environment. By identifying errors, this game will be tailored to improve the oral health of children by correcting the technique and teaching the user the adequate toothbrushing method. A template analysis will be performed to identify barriers and facilitators in each scenario.

Results: After the implementation of the virtual interactive and immersive panels, enrollment will begin and evaluations will be made by means of questionnaires distributed to participants who interact with the game. Thus, an analysis of the product efficacy will be conducted. The expected outcome will be to obtain a digital instrument to motivate oral hygiene practice and enhance health awareness in children.

Conclusions: The serious game will support the prevention of oral diseases by sharing scientific research in the school environment and community.

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KEYWORDS

video games; education, dental; user-computer interface; computer simulation; pediatric dentistry

Introduction

Teaching processes conducted in virtual environments are becoming more prevalent in order to improve quality of life for the population [1,2]. Increasingly, these virtual environments employ augmented reality (AR) as a learning tool and provide a more realistic experience to the students. AR is composed of simulation, association of virtual reality with physical materials, instruments, and feedback to train students and verify their acquired knowledge on specific subjects. The interaction occurs through object manipulation, aiming at specific targets. AR is popular because of its applicability providing the user with unique experiences and great interaction yet promoting activities that stimulate learning. Studies comparing traditional and simulation technology–based learning showed that students had better knowledge retention indexes with the latter [3].

The recent literature reports the use of artificial intelligence to aid in developing children's personal skills inside a healthy environment [4]. Interactive interfaces directed to the parts of the human body related to oral health by using AR will share scientific knowledge on dentistry in the community, specifically regarding children [5,6]. Kinect (Microsoft Corp) is an interactive interface innovation designed not only for entertainment but also for other purposes such as health education, making the interaction between person and machine more effective. It allows the user to interact with the device only with gestures and movements, without the need of a joystick. These movements are captured by cameras and sensors, providing real interaction, also allowing users to explore the content with commands activated in a ludic or nonludic way. Kinect has several resources (sound, image, depth, infrared, and movement engine) with a high level of accuracy and synchronicity in one single device. These resources offer a series of innovative possibilities of interaction between users, services, and computing applications. Educational and motivational methods play an important role in informing individuals about oral diseases and changing their hygiene habits, starting as soon as children develop their motoric coordination [4]. This study aims to present a protocol on the development of a serious game (immersive virtual environment using AR) to motivate oral hygiene practice in children.

Methods

Interactive Panel Configuration

General Features

A serious game will be designed using AR techniques to improve toothbrushing effectiveness in children aged 6 to 10 years. The functional structure of this interface is activated by means of movements and recognized by Kinect. The programming language will be based on C#, which has been greatly influenced by the Java programming language. It is oriented toward objects and considered to be simple, with a great performance. Some C# characteristics:

- Language: low complexity; being projected in a simple way
- Object-oriented: classes, attributes, methods, and objects
- Strongly typed: avoiding attribution errors
- Managed language: all the management contained in the memory is done by runtime via Garbage Collector
- Version control: once assembly is formed, it contains information on the code version, either dynamic link library or executible file

However, for programming purposes, the framework Kinect for Windows SDK 2.0 (Microsoft Corp) will be used. This is a free tool for people who want to develop their own games that has a robust yet friendly interface and allows the development of applications based on Kinect (both for PC and the Xbox 360 Console, also Microsoft Corp) [7]. The toothbrushing technique [8-10] will be available in a game, enabling the children to execute movements in a virtual environment. This game will be tailored to improve the oral health of the children by correcting technique and teaching the user the adequate brushing method after identifying errors [11]. This method is easily trackable via the motion control ludic interface provided by Microsoft.

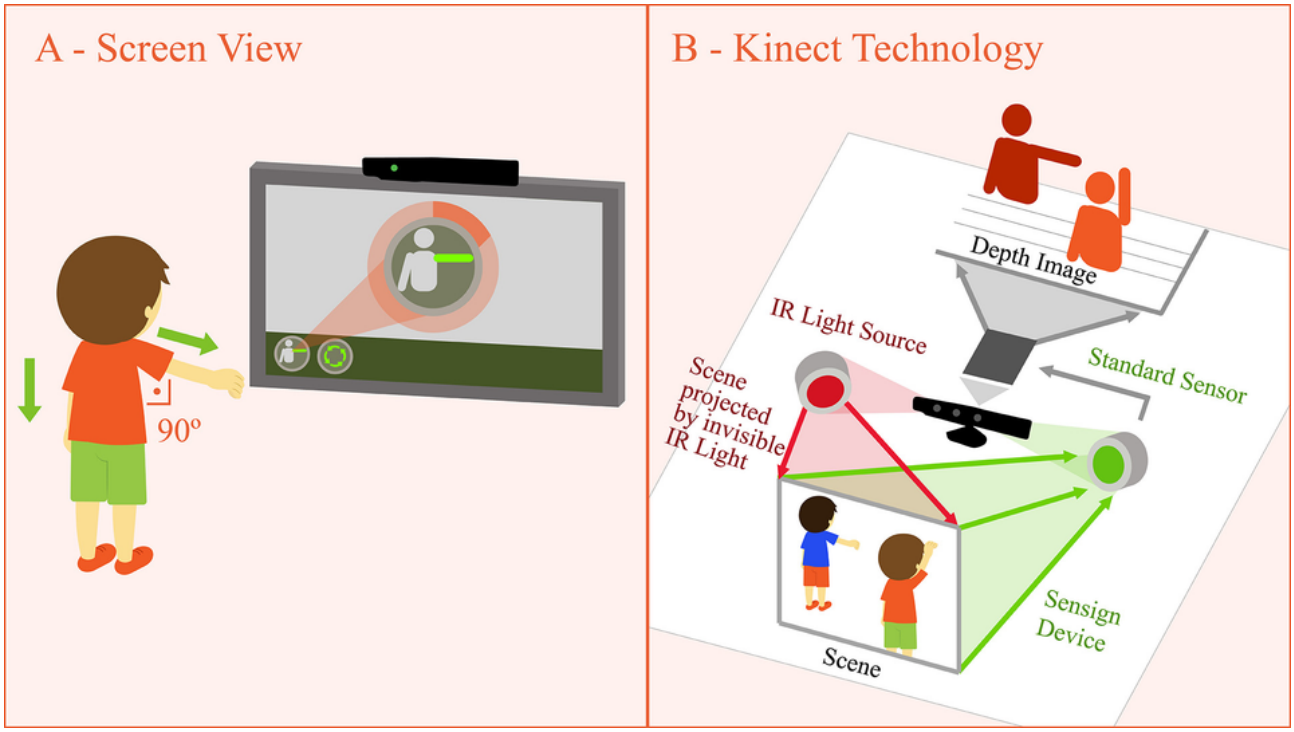
In the final stages, an open-source framework for mobile development compatible with Android and iOS devices and licensed by Adobe Systems will also be used. However, motion control will not be available in mobile devices. Instead a gesture-based control on the device's screen will be used to track users' movements.

Connected Devices

- Development suite: Kinect for Windows SDK 2.0 (freeware)
- Unity 3D engine platform
- Audio editors: Audacity and FormatFactory (freeware)
- Kinect Xbox 360 sensor (Microsoft Corp)
- High-definition 3D XL2420T monitors (2; BenQ Corp)
- High-performance desktop computers (2), with Intel Core i7 processor, 32 GB RAM memory, 2TB internal storage, and Nvidia Quadro graphics card
- High-performance notebooks (2): ASUS G74SX-DH73-3D 17.3" display, Core i7 2670QM processor, 12 GB RAM memory, 750 GB HDD + 750 GB HDD internal storage and 3D Vision Kit graphics card
- External hard drive: AirPort Time Capsule (Apple Corp) 2TB sharing station
- Television with ultra-high-definition technology

An ultra-high-definition television will be used to see the whole game interface and interaction with the Kinect sensor (Figure 1). This process happens hundreds of times per second, thus making the immersion real. This changes the user's old behavior into a new one, characterized by dynamic and intuitive reactions, stimulating curiosity and creativity.

Figure 1. Resources offered by Microsoft's Kinect device.



Interactive Panel Use

Interactive Interface

An interactive interface with an educative instructional aspect results from the intersection of three technological processes: game, computational application, and learning objects [12]. The use of games in school contexts applies the following aspects: (1) anxiety, (2) limits, (3) autonomy, (4) capability of achievement, (5) motor coordination, (6) spatial organization, (7) segmental control, (8) attention and concentration, (9) anticipation and strategy, (10) auditory discrimination, (11) logical reasoning, (12) creativity, and (13) figure and depth perception. In this context, the game is a very appropriate learning tool because it uses its power to attract the interest of students and creates social and personal experiences, triggering new discoveries and maturing their personalities [13]. Furthermore, by enabling innovative and attractive educational practices, these educational interfaces can become important accessories to the process of teaching and learning. The AR interface allows the user to see the real world together with virtual objects [14], consisting of a serious game where the player controls and executes actions by means of corporal movements. The body movements are interpreted as data entry and associated with specific commands to the game, transforming the tridimensional movement of the physical space into an entry into a computational system.

Game General View

In the construction of the game prototype, the technology employed involves virtual reality combined with the Kinect device. Through sensors, Kinect enables a more efficient interaction between the child and the game, allowing a ludic and immersive interaction in topics related to oral health (Figure 2). This is an essential and important issue for the prevention of dental caries and other related oral diseases.

Figure 2. Users' representation by game characters.

Interface Elements

The opening screen (Figure 3) shows three options to choose from: character, toothbrushing techniques (Fones or Stillman), and the option to quit. In the character option, the player can choose according to gender (male/female). In the toothbrushing option, the player can choose the technique and the training goal (Figure 4).

Figure 3. Opening screen of the digital interface with usage options.

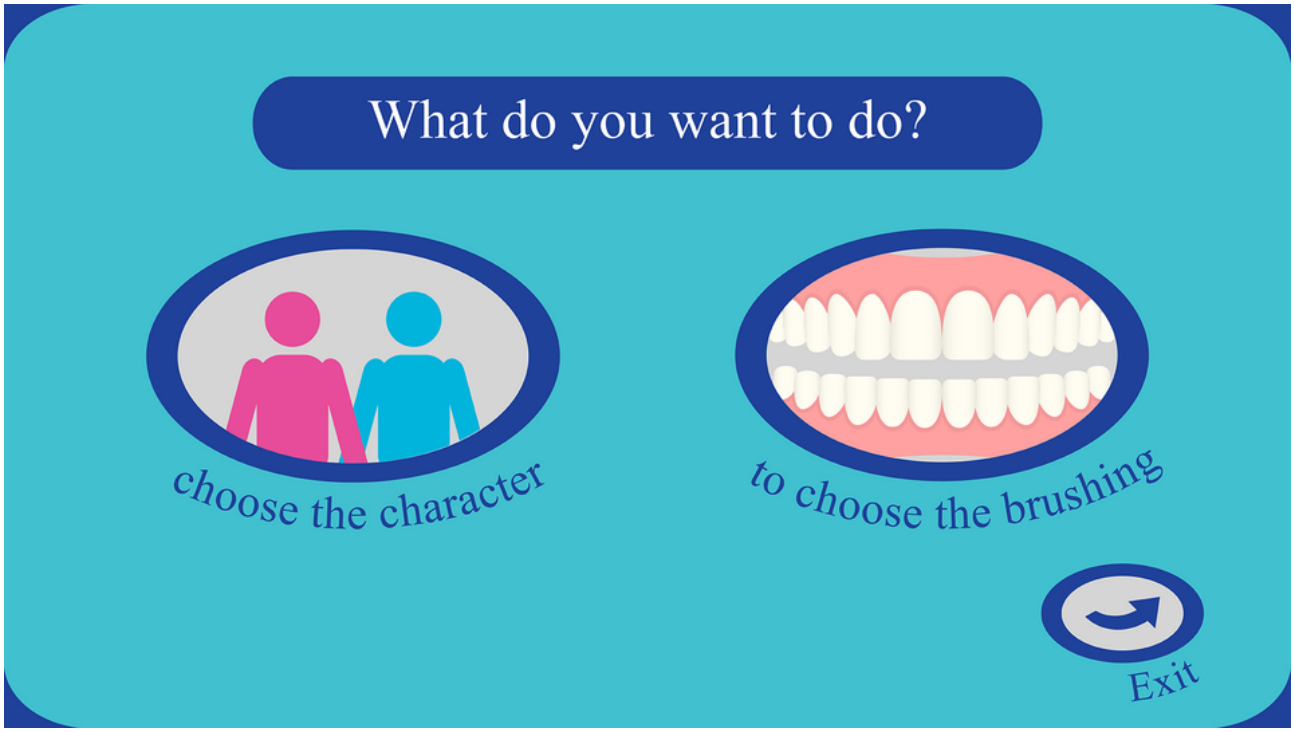
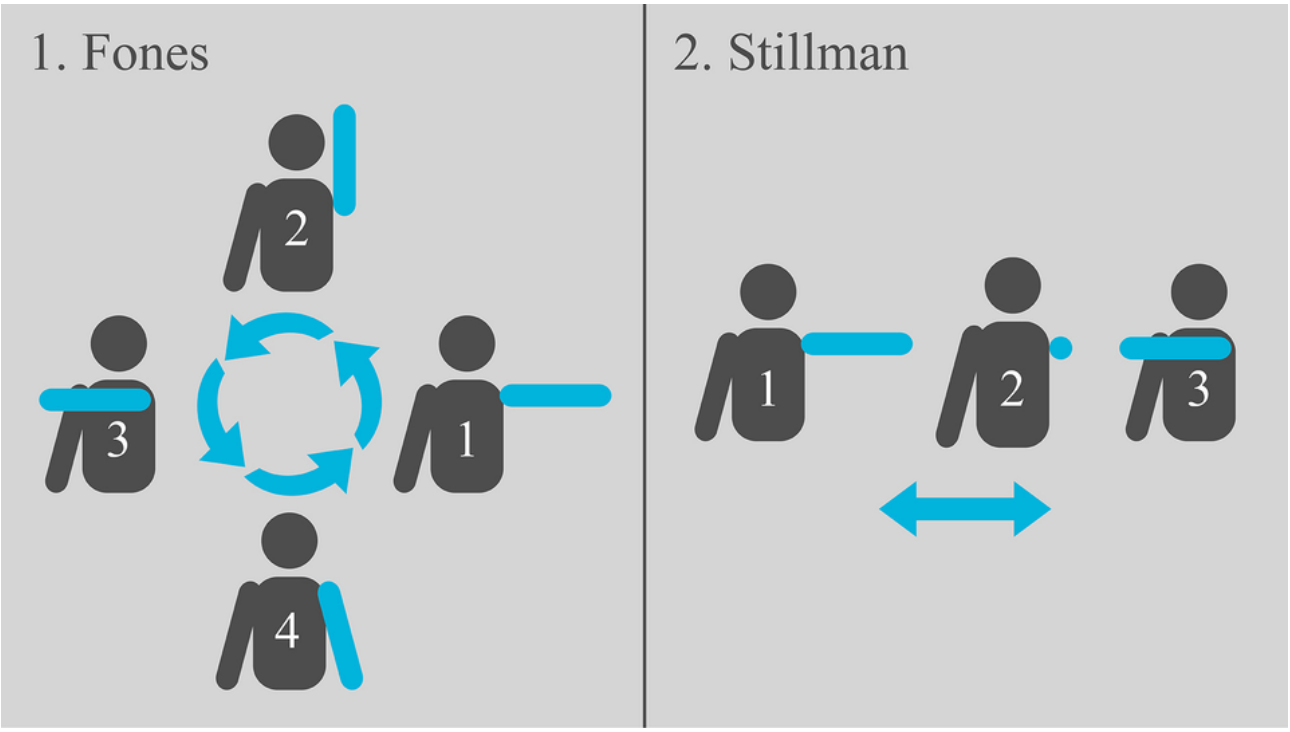


Figure 4. Movement simulations of the proposed techniques (Fones and Stillman).



Movement Detection and Error Identification

For movement detection, it will be necessary to (1) habilitate the capture of the human skeleton by the Kinect device, (2) create a code to establish connection between the device and software, (3) create an array (vector) of the skeleton type, attributing data to the vector, (4) verify the vector is being monitored, (5) attribute a variable to the body part to be monitored (in this case, the hands), and (6) create the desired modification (ie, a desirable response whenever the movement executed by the player's hands is closer to the movements expected in the chosen brushing technique).

For movement capture, the Kinect sensor uses a programming code that processes its reading and sends the data in a specific format to the system. The player's movement while performing the toothbrushing technique in the expected way will be detected. Then, after four successful repetitions of valid toothbrushing positions and movements, the user will be directed to another screen to execute the same movements, this time with the character's mouth in a frontal position. The toothbrushing movements must be repeated both for the maxillary and mandibular teeth. Figures 5 and 6 show the interaction between user and serious game using Kinect. Through the integration of Unity 3D and Kinect, it will be possible to effectively capture the movements of Fones and Stillman toothbrushing techniques and send them to the game, in real time, on the screen.

The game has also an error identification implementation. Whenever the player executes the chosen brushing technique incorrectly (ie, if the player does not reproduce the expected movements in the correct speed, time, and angle), the system provides a visual response with an on-screen indication on the avatar's mouth region. An arrow indicates the format, speed, and angulation of the movement the player should have been executing (Figures 7 and 8).

Figure 5. User interaction in the serious game with Kinect using the Fones brushing technique.

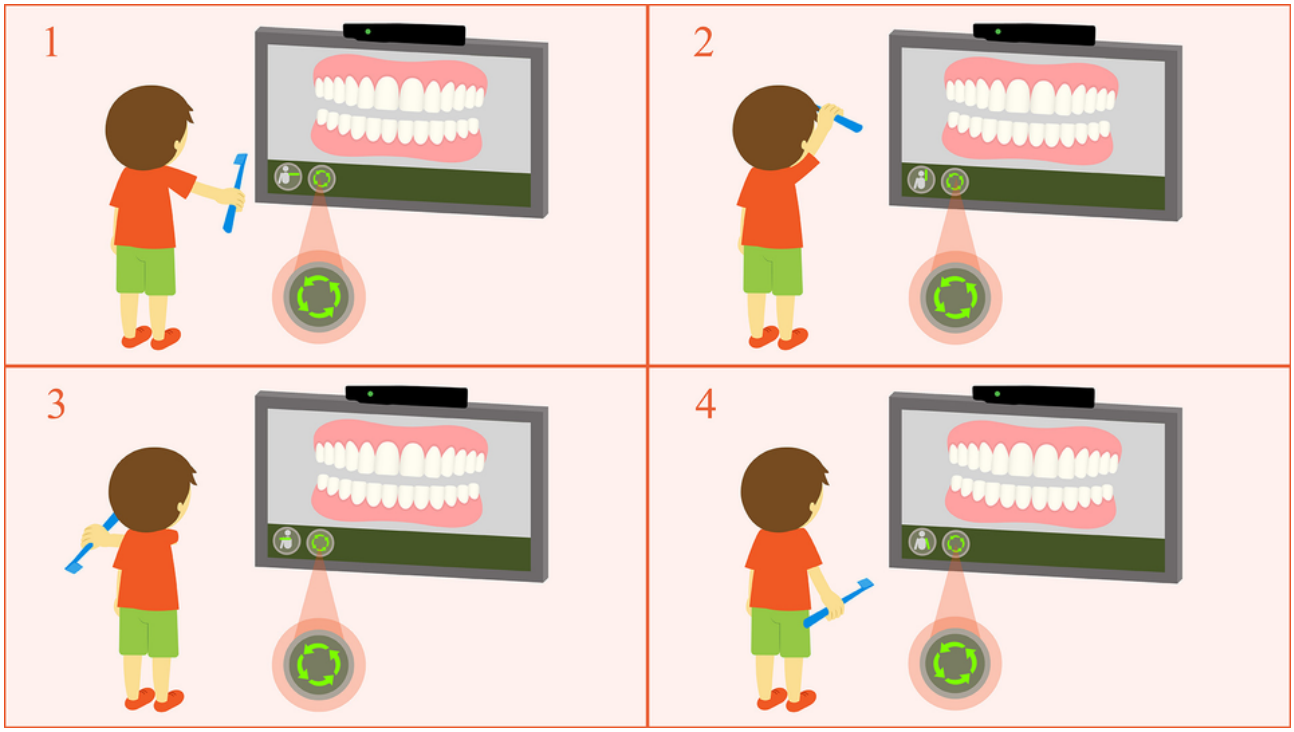


Figure 6. User interaction in the serious game with Kinect using the Stillman brushing technique.

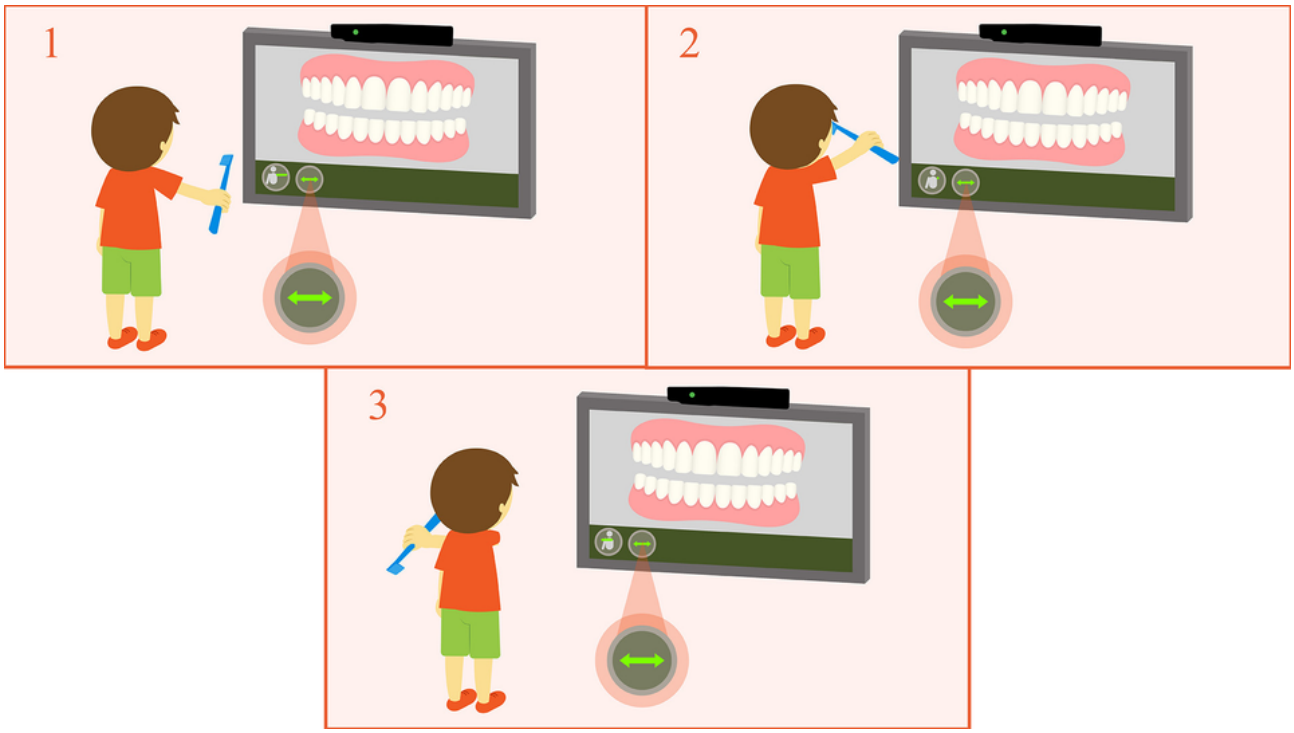


Figure 7. Indication of the Fones technique movement.

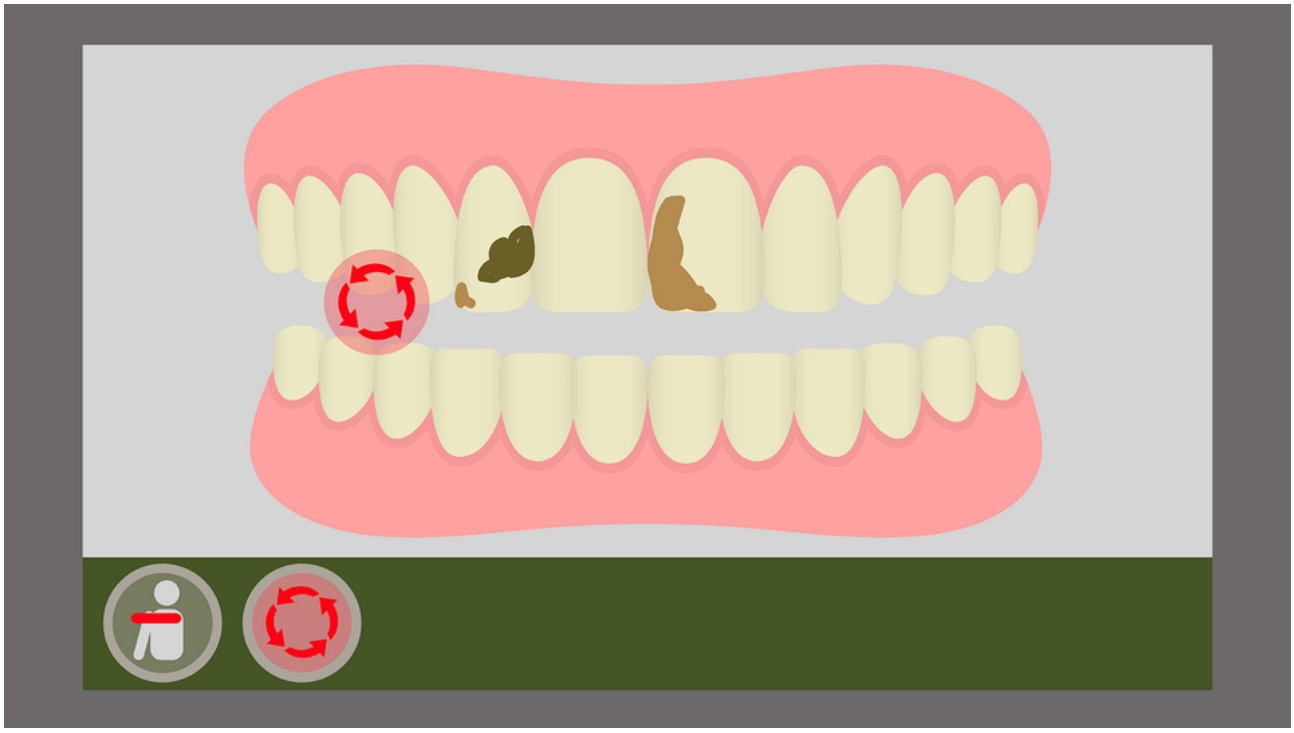
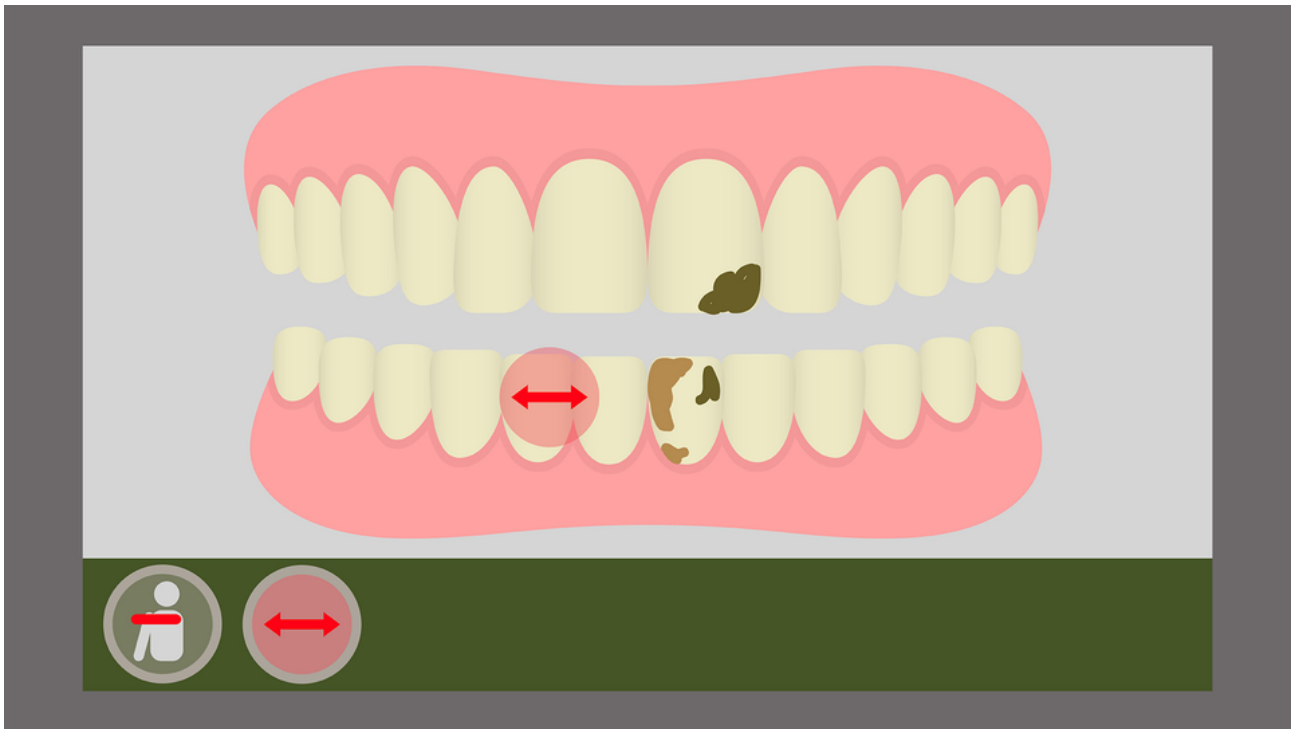


Figure 8. Indication of the Stillman technique movement.



Furthermore, the game provides a metric for an effective toothbrushing. For this purpose, several challenges are presented to the player as food residues represented graphically and in a ludic way on the character's tooth surface. On the scene, the player must remove the residues by reproducing the toothbrushing movements. Therefore, not only must the child execute these chosen toothbrushing technique movements correctly, they must also reproduce these movements on the sites (movement angle, height, and amplitude) where the residues are located to remove them completely. This is measured by means of a scoring system: if the player only executes the movements but does not remove the residues, they will receive a lower score at the end of the game; if the player manages to remove all residues, the score will be higher, according to the amount (partial or total) of elements removed during the toothbrushing (Figures 9 and 10).

Figure 9. On-screen representation of the Fones movement with residue fixation.

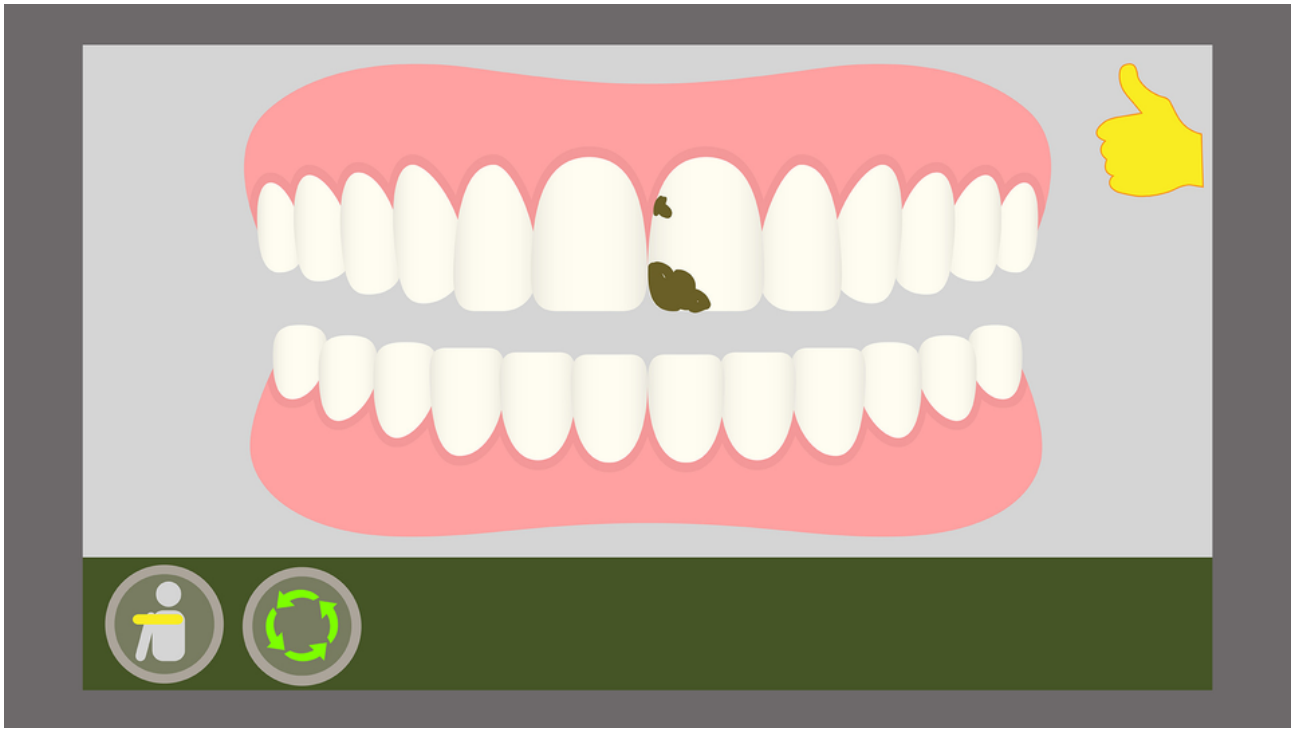
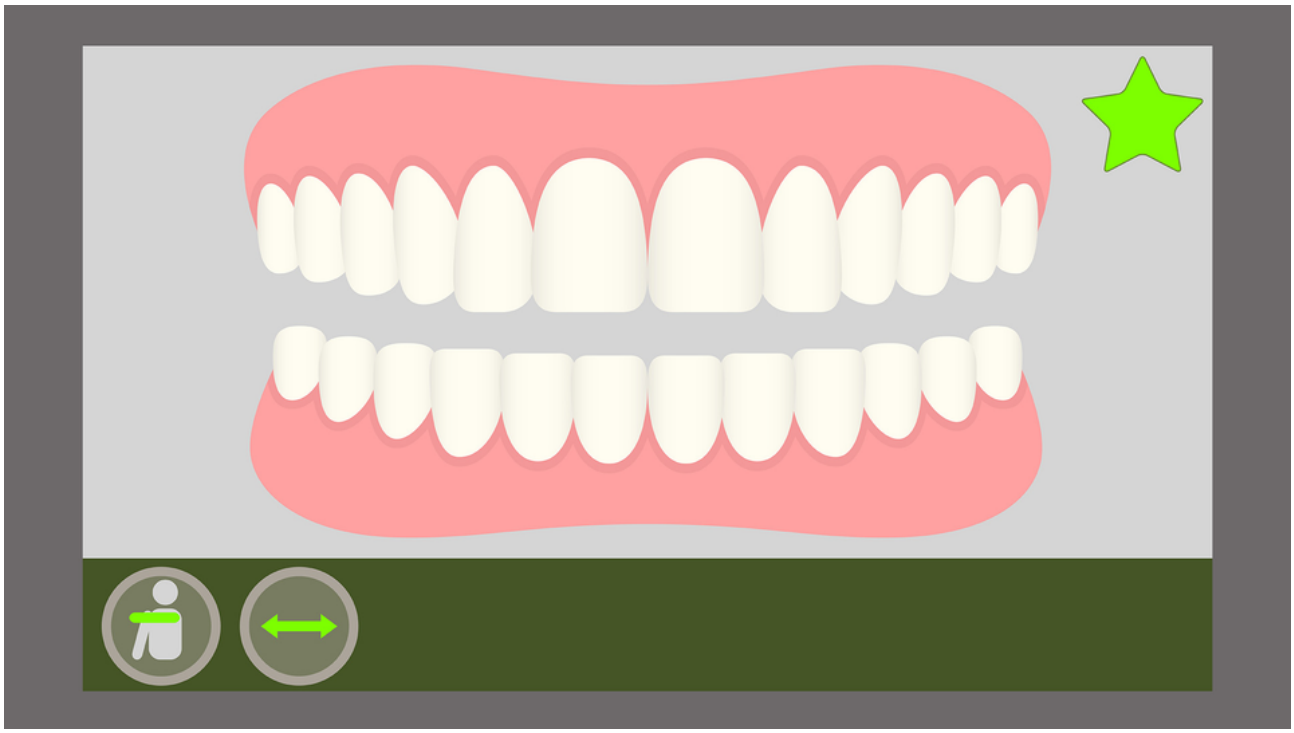


Figure 10. On-screen representation of the Stillman movement with total residue removal.



Results

This study protocol defines the use of AR on oral hygiene practice by means of an interactive interface that makes use of the Kinect movement sensor. The training of toothbrushing techniques will become more feasible, effective, and accessible to children. After the implementation of the virtual interactive and immersive panels, enrollment will begin and evaluations will be made by means of questionnaires distributed to participants who interacted with the game. Thus, an analysis of product efficacy will be conducted. The expected outcome is to provide a digital instrument to improve oral hygiene practice in children and also motivate the prevention of oral diseases by sharing scientific research in the school environment and community.

Discussion

This study presents the development protocol of an instructional immersive interactive environment using projection and

computational resources. From a methodological and technological point of view, the innovation of this tool will allow the effective interaction of the target audience. The serious game will be able to be edited for updates and changes, making this tool an instrument of scientific teaching and research on different levels of learning. New technologies create possible new ways of action, interaction, and learning, which is relevant in the field of education. It is worth highlighting that digital design applied to health education is a subject still little explored but with a significant and relevant potential for social contribution and improvement of oral health. There is a lack of protocol in using an immersive interactive ludic-educational interface to motivate oral hygiene practice in children by means of AR.

The process of dissemination and consolidation of the use of technology applied to education and health increases the use of digital technologies. This digital access led to the birth of generations with visibly distinct characteristics regarding information, the so-called "digital natives" and "digital immigrants" [15]. These terms are used to describe, respectively, individuals who were born immersed in digital technologies and individuals who were raised with no contact with such technologies. This generation gap was identified [16] and discussed throughout the first decade of this century as a challenge to be faced by the fields of resources and professional development in the educational area. The new generation of digital natives is looking for new content and activities that might encourage them to study and learn.

The virtual realism may be associated with static or dynamic objects [17]. In the training of this applied study, users will be able to visualize and interact in a virtual environment, feeling it as real; that is, the more immersion the simulator is able to provide, the more realistic it will be considered [17].

After the implementation of the virtual interactive and immersive panels, the concept proof will be applied (ie, technical and computational performance tests that evaluate the functionality requisites). The concept proof aims to enable the best performance during the simulation, within the specific characteristics of realism of the 3D realistic virtual model. After that, the application and use of the product will be validated and the learning object applied in other projects.

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Conflicts of Interest

None declared.

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Abbreviations

AR: augmented reality

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Protocol

Relationship Education and HIV Prevention for Young Male Couples Administered Online via Videoconference: Protocol for a National Randomized Controlled Trial of 2GETHER

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Abstract

Background: Young men who have sex with men have a high HIV incidence, and a substantial proportion of incident infections occur in the context of main partnerships. However, romantic relationships also provide numerous benefits to individual health and wellbeing. 2GETHER is a relationship education and HIV prevention program for young male couples, and the 2GETHER USA randomized controlled trial (RCT) was launched to establish the efficacy of an online version of 2GETHER.

Objective: The objective of 2GETHER is to optimize relationship functioning in young male couples as a method to improve communication about sexual risk behaviors and reduce HIV transmission. In the 2GETHER USA study, 2GETHER was adapted for online administration to couples across the United States via videoconferencing. The intervention in question aims to address the unique needs of couples from varied racial/ethnic backgrounds and geographic regions.

Methods: This is a comparative effectiveness RCT of 2GETHER USA relative to existing public health practice (control). 2GETHER USA is a hybrid group- and individual-level intervention that delivers three weekly online group discussion sessions for skills delivery, followed by two individualized couple sessions that focus on skills implementation in each couple. The control condition differs by participant HIV status: (1) the Testing Together protocol for concordant HIV-negative couples; (2) medication adherence and risk reduction counseling for concordant HIV-positive couples; or (3) both protocols for serodiscordant couples. Follow-up assessments are delivered at 3-, 6-, 9-, and 12-months post-intervention in both conditions. Testing for rectal and urethral Chlamydia and Gonorrhea occurs at baseline and 12-month follow-up. The primary behavioral outcome is condomless anal sex with serodiscordant serious partners or any casual partners. The primary biomedical outcome is sexually transmitted infection incidence at a 12-month follow-up.

Results: As of October 11, 2019, the trial has enrolled and randomized 140 dyads (Individual N=280). Enrollment will continue until we randomize 200 dyads (N=400). Assessment of intervention outcomes at 3-, 6-, 9-, and 12-months is ongoing.

Conclusions: 2GETHER is innovative in that it integrates relationship education and HIV prevention for optimizing the health and wellbeing of young male couples. The 2GETHER USA online adaptation has the potential to reach couples across the United States and reduce barriers to accessing health care services that are affirming of sexual minority identities for those who live in rural or under-resourced areas.

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KEYWORDS

HIV/AIDS; relationship education; male couples, randomized controlled trial

Introduction

Background

Young men who have sex with men (YMSM), including those in late adolescence and young adulthood, bear a disproportionate burden of the HIV epidemic in the United States [1]. However, there has not been a commensurate prevention response to curb the continued high incidence of new infections among these youth. Steady or main partnerships account for a large proportion of new HIV infections in men who have sex with men (MSM) (35-68%) [2,3], and this proportion may be much higher amongst YMSM (79-84%) [3]. Importantly, romantic relationships are much more than vectors of HIV risk for MSM; extant research on different-sex couples indicates that romantic relationships improve the health and wellbeing of individuals [4,5], and evidence suggests that these health promotive effects also apply to same-sex couples [6,7]. Thus, we developed the 2GETHER program to improve relationship functioning in young male couples and reduce the risk of HIV transmission [8]. The purpose of this manuscript is to describe the protocol for a randomized controlled trial (RCT) examining the efficacy of 2GETHER, delivered via videoconferencing technology to young male couples across the United States.

HIV Transmission Risk in Young Male Couples

The large proportion of new HIV infections among YMSM that is attributable to main partnerships [2,3] is driven by multiple factors. First, YMSM are substantially less likely to use HIV preventive behaviors (eg, condoms, preexposure prophylaxis [PrEP]) when they enter into serious or main partnerships [3,9-11]. Further, nearly half of YMSM aged 13-24 who were HIV-positive in 2016 were not aware of their HIV status (29.1% of HIV-positive men who were 25-34 years old were unaware of their status) [1], so many HIV-positive YMSM may be entering into romantic relationships, reducing or eliminating their use of preventive behaviors, and then unknowingly exposing their partners to HIV.

Many male couples build “relationship agreements,” or arrangements that describe whether their relationship is monogamous or nonmonogamous and specify rules that delineate the conditions under which outside sexual partners are permissible [12,13]. Relationship agreements may be highly effective at minimizing the risk of HIV transmission or acquisition while maximizing satisfaction when the rules of such agreements are clear to and adhered to by both members of the dyad. Studies report varied estimates of the number of male couples who do not have an agreement in place [14]; however, several studies have found that a substantial proportion of those who do have an agreement disagree about their agreement rules [8,15,16], which may result in exposure to HIV (though we note that some studies have found less partner disagreement [17]). Further, breaks in relationship agreements (ie, noncompliance with agreement rules) are common in male couples (approximately 46% report breaks) [15]. When these breaks are not promptly disclosed to partners, couples risk damaging relationship trust, and if condomless or otherwise unprotected sex occurred, exposing one another to HIV. Key to building and maintaining relationship agreements is effective communication, and strategies are needed that provide YMSM with skills to establish and maintain effective agreements.

Binge-drinking and drug use have consistently been linked to engagement in HIV risk behaviors among MSM [18], and some evidence suggests that this link may be stronger among YMSM in relationships [19]. Further, substance use has been linked to a higher likelihood of breaking relationship agreement rules in male couples [20], as well as a higher likelihood of having condomless anal sex with extradyadic partners [21]. Finally, heavy alcohol and drug use are robust predictors of relationship discord, particularly when partners report discrepant patterns of use [22,23]. Thus, it may be particularly important to enroll young male couples who binge-drink or use illicit drugs in couples-based relationship education and HIV prevention efforts. However, we note that focusing exclusively on heavy substance-using samples may overlook the important risks to both sexual and relationship health of those who use substances but do so less frequently.

Relationship Education and Couples-Based HIV Prevention

Existing approaches to couples-based HIV prevention have primarily focused on the provision of HIV testing and sexual risk reduction counseling in a couples format, particularly in Africa and other global settings [24]. Testing Together (formerly Couples HIV Testing and Counseling) is a Centers for Disease Control and Prevention–endorsed single-session HIV prevention strategy that is increasingly being used with HIV-negative YMSM in seroconcordant and serodiscordant (ie, one partner HIV-negative, one partner HIV-positive) relationships domestically [25]. This HIV testing strategy, which addresses some aspects of relationship functioning (eg, relationship agreements), has been adapted for remote administration via videoconferencing [26], and it has been enhanced to address substance use in male couples [27] and to include medication adherence counseling for HIV-positive individuals in serodiscordant couples [28]. However, given that it is a single session, Testing Together does not provide comprehensive relationship education content, which is key to establishing and maintaining safe and effective relationship agreements. Other couples-based HIV prevention programs that teach HIV risk reduction to both members of the couple simultaneously have

been developed for heterosexual couples domestically and globally, with some providing more comprehensive relationship education skills training to enhance HIV prevention uptake [24,29,30]. However, very few such programs have been developed for male couples, and those that do exist have tended to focus on heavy substance-using couples [31].

There are several important gaps in couples-based HIV prevention for young male couples. Many YMSM, particularly those in serious relationships, are uninterested in programs that solely focus on HIV prevention, but YMSM report a strong interest in relationship education [32]. Thus, providing YMSM what they want (eg, relationship skills) while giving them needed HIV prevention skills, is a promising strategy for improving young male couples' health and wellbeing. Further, most existing couples-based approaches do not adequately address secondary prevention among HIV-positive YMSM (ie, onward transmission of HIV from HIV-positive persons). Even those programs that do include HIV-positive individuals most often focus on reducing HIV transmission in serodiscordant couples, rather than the broader sexual health needs of HIV-positive persons, including those of seroconcordant HIV-positive couples. Further, YMSM have unique developmental needs (eg, lack of relationship experience, family stigma) that affect their ability to navigate sexual health in their relationships [33], and existing couples-based HIV prevention protocols do not address these issues.

Relationship education is a field that aims to promote long-term couple health by teaching skills to form and maintain healthy relationships, thus improving dyadic functioning in the present and preventing future discord [34]. Relationship education programs place a heavy emphasis on building effective communication and conflict resolution skills. These strategies' effectiveness is supported by meta-analysis, which concluded that relationship education is effective in improving conflict-management skills and global relationship satisfaction [35]. Whitton and colleagues conducted some of the seminal work to adapt evidence-based relationship education programs for same-sex couples, and they have demonstrated acceptability to both female and male couples, as well as positive effects on couple communication, conflict resolution, and relationship quality [36,37].

The 2GETHER intervention's unique contributions are that it uses evidence-based relationship education as a platform to deliver HIV prevention and sexual health promotion skills and that it has adapted this integrated relationship education and HIV prevention program to the unique developmental needs of YMSM [8]. Briefly, 2GETHER utilizes a hybrid group and individual format to teach various skills related to relationship and sexual health. The intervention demonstrated evidence of feasibility and high acceptability in a nonrandomized pilot trial with 57 young male couples in Chicago [8]. Further, the pilot trial showed evidence of preliminary efficacy, including significant posttest reductions in HIV transmission risk behaviors and improvements in HIV prevention motivation, mutual understanding of relationship agreement rules, and relationship investment. 2GETHER was the first program to integrate relationship education and HIV prevention for young male couples of any HIV status arrangement, including prevention content for concordant HIV-negative, concordant HIV-positive, and serodiscordant couples. Further, 2GETHER places an equal emphasis on relationship skills acquisition and sexual health, while existing programs have either emphasized HIV prevention or relationship education.

Telehealth and Implications for Couples-Based HIV Prevention

The vast majority of health care services that are affirming of lesbian, gay, bisexual, transgender, and queer (LGBTQ) experiences are concentrated in the nation's largest urban centers, creating wide disparities in access to services for individuals who live in suburban and rural locations. Indeed, rural MSM are substantially less likely to have received HIV/sexually transmitted infection (STI) testing and other preventive services and are more likely to report experiences of discrimination and bias due to sexual orientation [38]. Rural MSM in romantic relationships may be especially prone to stigma-based experiences because being partnered is a visible indicator of one's sexual orientation. However, at the same time, a healthy and supportive couple relationship may help to buffer against the negative impact of such experiences [6]. Telehealth is an extensive field that focuses on enhancing health care, public health, health education, and service delivery using a variety of telecommunications technologies [39]. This strategy for service provision may help to reduce the gap in access to LGBTQ-affirming services between rural and urban MSM, but very few such telehealth programs exist for these populations.

As technology continuously advances, as does the media through which telehealth can be administered. Synchronous telehealth approaches are those in which interactions between the patient and provider occur in real-time, through telephone, videoconferencing, or real-time text interactions [40]. Asynchronous interventions, on the other hand, are those in which patient-provider interactions do not occur in real-time, and include Internet sites, Internet-based modules, or educational videos [41]. 2GETHER primarily utilizes a synchronous telehealth approach in which intervention content is delivered in real-time by live facilitators via videoconferencing technology to most closely mimic health care services delivered in vivo. 2GETHER uses asynchronous components (ie, narrated videos) to supplement live facilitation and minimize participant fatigue (described in more detail below).

Synchronous telehealth uses a variety of transmission technologies and devices, including telephones, computers, and personal communication devices [42]. Telephone-delivered treatments have been shown to be as effective as in-person treatments [41], but they are limited in their ability to capture nonverbal communication (eg, facial features, body positioning), which can be crucial in establishing rapport [43]. More recently, high-speed fiber-optic broadband networks have improved on these limitations and enhanced the capabilities of synchronous telehealth, bringing it closer to the experience of in-person treatment [44]. Advances in videoconferencing technology have also allowed for group video chat, so patients in different locations can participate in synchronous interventions in which they interact with one another, as well as with a health care provider [45]. Not only do group interventions allow for a larger

patient-to-provider ratio, and thus are often used in settings where services are scarce [46], they also foster group unity and togetherness among participants [47]. Telehealth is also uniquely situated to overcome barriers commonly experienced with treating couples, in that: (1) coordination of multiple schedules is easier when couples can participate from home; (2) couples may be more open to sharing their experiences when they are not sharing the same physical space as facilitators and other couples; (3) there is a low likelihood that couples will run into facilitators or other participants in the real world; thus increasing willingness to participate; and (4) stigma associated with seeking treatment in brick and mortar settings at which they may be identified as a sexual minority is reduced [48].

The number of online HIV prevention programs designed for young and adult MSM is steadily increasing, but the vast majority of these interventions use an asynchronous approach that involves little to no live interaction with a facilitator [49,50]. Although asynchronous electronic health approaches are critical to improving the reach of LGBTQ-affirming and effective interventions, it is our belief that these automated approaches are not a replacement for the impactful live interactions with providers or facilitators that synchronous telehealth interventions provide. Concerning couple health, the ability to receive live coaching about relationship skills and sexual health allows couples to make changes in the moment, experiment with skill utilization, and observe the impact of these changes in vivo.

Objectives and Aims

The goal of the current study is to conduct a comparative effectiveness randomized controlled trial to assess the efficacy of 2GETHER relative to existing public health practice in reducing HIV transmission risk and improving relationship functioning. We are recruiting a national sample of young male couples, who will complete intervention sessions remotely via videoconference. The purpose of this manuscript is to describe the protocol of the RCT.

Methods

Study Design

We are conducting a comparative effectiveness RCT to test the efficacy of 2GETHER relative to a control condition based on existing available public health practice. The control public health practice intervention will consist of a single session of either Testing Together [25], Medication Adherence Counseling [51], or both, depending on the HIV status of individuals in the dyad. We will randomize 200 dyads (individual N=400) to the 2GETHER intervention or public health practice, and we will examine primary and secondary outcomes at 12-months postintervention, with interim follow-up at 3-, 6-, and 9-months postintervention. The primary HIV risk behavioral outcome will be the occurrence of condomless anal sex acts with serodiscordant or unknown status partners (all casual sex partners will be considered unknown status), and we will account for the reduced risk of condomless anal sex in the context of PrEP use and undetectable viral load (eg, condomless sex while one has an undetectable viral load may be considered no risk). The primary biomedical HIV risk outcome will be STI incidence (ie, urethral/rectal Chlamydia and Gonorrhea). Secondary HIV-related outcomes will be indicators of engagement in the HIV continua of prevention and care, including HIV testing, PrEP use, and adherence for HIV-negative participants, and antiretroviral therapy adherence and self-reported viral suppression for HIV-positive participants. Other secondary outcomes include alcohol and drug use problems and indicators of relationship functioning. We will test for dose effects and decay in effects over time, and we will examine substance use problems and relationship functioning as mediators of change in HIV transmission risk. All primary outcomes will be measured at the individual level (not couple-level). This is advantageous because HIV risk may also occur with partners outside the relationship. Also, relationships may dissolve during the follow-up period, so measuring individual-level outcomes allows us to examine the effects of 2GETHER behaviors after relationship dissolution.

Inclusion and Exclusion Criteria

Couples are eligible for this study based on the following inclusion criteria: (1) both members were assigned male at birth and currently identify as male; (2) both members are at least 18 years of age, and at least one member is aged 18-29; (3) both members consider one another to be their "main partner" (defined for participants as "…someone you feel committed to above anyone else. This would be someone you call your boyfriend, partner, or significant other"); (4) couple reports oral or anal sex with each another in the last three months; (5) at least one member reports having condomless anal sex with a known serodiscordant serious partner or with any casual sexual partner; (6) at least one member reports binge-drinking (ie, five or more drinks on a single occasion) or illicit drug use in the last 30 days; (7) both read and speak English at eighth-grade level or better; (8) both have access to the Internet; and (9) both agree to audio recording of intervention sessions.

Couples are ineligible if staff identify inconsistencies between information provided in the eligibility screener and baseline assessment (ie, a participant was faking eligibility or eligibility changed between screener and baseline), if issues arise that might hinder participation (eg, serious mental illness, intoxication), if both individuals are unable to be in the same place for the intervention sessions (ie, no long-distance couples), or if there is imminent risk for harm due to intimate partner violence. If either individual reports intimate partner violence (ie, their current partner has ever "hit, slapped, punched or physically hurt you" or "forced you to have sex when you didn't want to") at the baseline visit, study staff reach out via email to assess safety and provide resources. If participants report that they do not currently feel safe in their relationship, they are not eligible to participate in the study. These same procedures are followed if participants disclose intimate partner violence during their participation in the intervention sessions.

Concerning participant age (criterion 2), YMSM between the ages of 18-29 years old fall into the groups that currently have the highest HIV incidence [1], but we will allow one partner's age to be 30 or older because age discordant partnerships are a risk factor for HIV acquisition among YMSM [52]. We require that there be some indication of HIV transmission risk (criterion 4) to increase the relevance of HIV risk reduction content. A

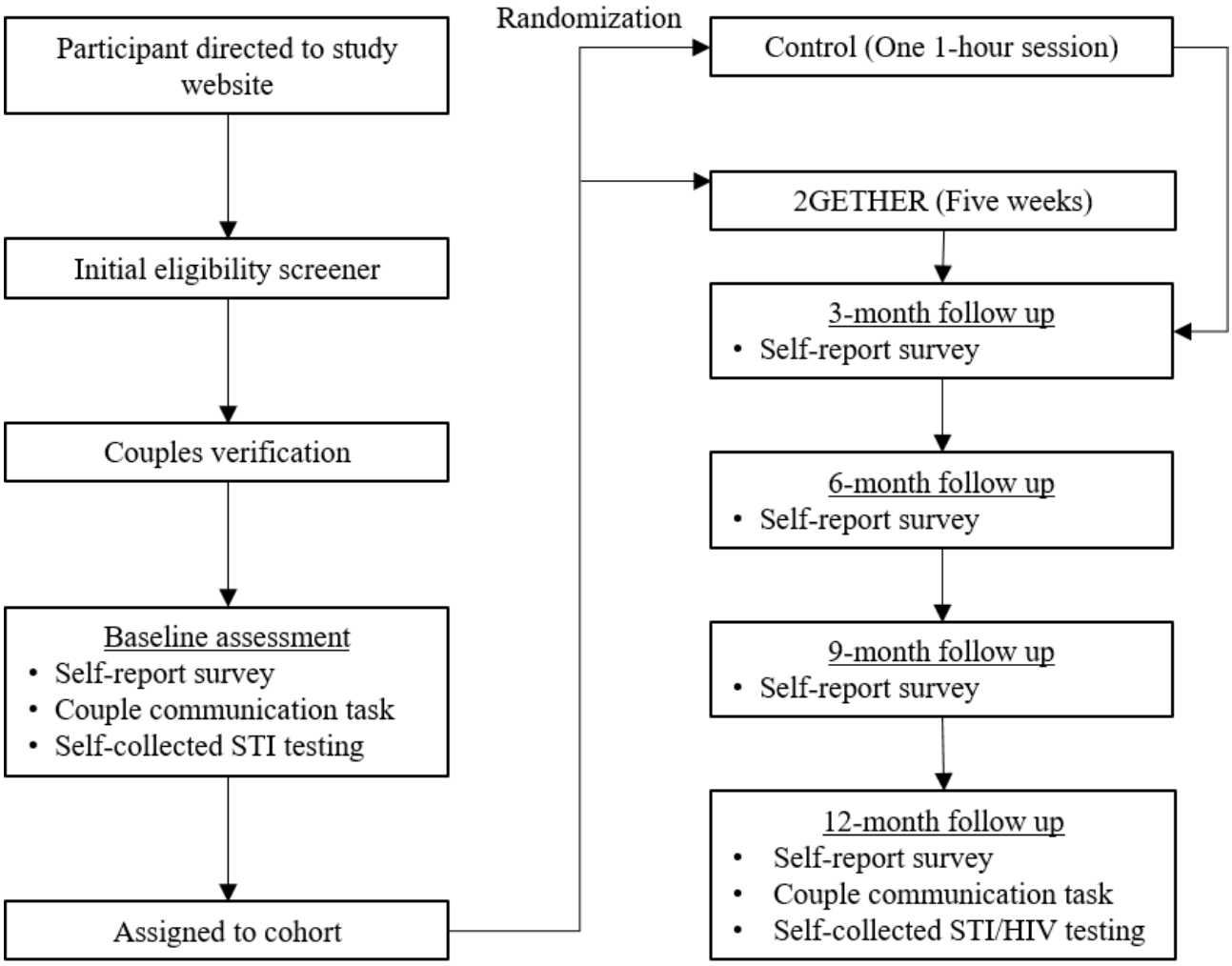
past 30-day substance use criterion (criterion 5) will enroll couples for whom substance use is more likely to contribute to HIV-risk behavior and relationship conflict. Finally, we do not require a minimum relationship length, because our research has found that YMSM stop using condoms and other preventive behaviors when they consider their relationship to be "serious," which often occurs very early in a new relationship (ie, less than three months) [9,53].

Recruitment, Eligibility Screening, and Couple Confirmation

Participants are recruited using paid advertising on social media sites (eg, Facebook, Instagram), geospatial dating/hookup apps, and organic online engagement through social media posts (eg, Reddit, Twitter). Advertisements and posts direct the initially recruited participant (ie, "partner 1") to a brief online eligibility survey, which includes an infographic illustrating study timeline and details. Eligibility surveys are administered via REDCap [54]. "Partner 1" is given the option to provide study staff with their partner's contact information, so that we may send a confidential link to the eligibility survey for "partner 2." If not provided, study staff contact "partner 1" to provide more information about the study and obtain the contact information of "partner 2."

Upon completion of eligibility screening of both partners, preliminarily eligible couples will complete a verification process. Study staff will perform phone call verification with each member of the dyad individually to confirm participant contact information and ask a series of questions to determine whether the couple is indeed two individuals in a romantic relationship. Couple verification includes asking questions about the participant's partner (eg, "How old is [partner name]?", "What is your partner's address?") and relationship history (eg, "How did you two meet?", "Where was your first date?"). Once both calls are completed, the study staff will determine the couple's eligibility to proceed in the study based on the response consistency of both members of the dyad. Individuals in eligible couples are then sent a link to the online informed consent and the baseline self-report survey and will be mailed materials and instructions for STI testing. After both members of the couple complete all components of the baseline assessment, couples will be scheduled for intervention sessions and randomized to one of the two intervention conditions. See Figure 1 for the flow of events for participants.

Figure 1. Flowchart of Study Timeline. STI: sexually transmitted infection.



Randomization to Treatment Arm

Couples will be scheduled into a group of 2-6 couples based on availability, and randomization occurs at the group level. Groups are assigned to either the active (2GETHER) or control (public health practice) condition using a covariate-adaptive randomization method [55,56], known as minimization. Minimization can control imbalance in baseline variables more efficiently than simple or restricted randomization and can manage a higher number of prognostic factors compared to stratification [57]. Minimization is uniquely suited to the current study design that schedules couples into groups, as it allows sequentially recruited clusters (eg, 4-12 individuals) to be treated as single units while balancing both individual- and couple-level prognostic variables [58]. For this trial, we used the range metric of imbalance in the minimization function and biasing probability of 0.80.

The allocation algorithm controls the imbalance on the following baseline factors: couple-level HIV-status (serodiscordant and seroconcordant positive), couple-level age discordance (one partner aged 30 or older), individual-level STI results (any positive result), and the total count of participants. We selected these prognostic factors because HIV risk (ie, outcome) may vary based on couples' HIV status arrangement and may differ for age discordant partnerships; using these variables in the minimization algorithm will control against the chance of a large imbalance that may result in biased inferences. Positive STI result at baseline was added to the algorithm on October 15, 2018 (after 38 couples had been randomized) to control imbalance across conditions in this important variable that is linked to outcome.

Allocation concealment is assured in several ways. Participants are not eligible for randomization until all baseline components are complete, and at least two couples have committed to the same group session date(s). Dates are not, *a priori*, associated with study arm or intervention type. When a group is finalized, the data manager is immediately responsible for implementing the randomization algorithm and delivering the results to session facilitators. The randomization algorithm is stored in a secure, restricted, electronic location: only the data manager has access. The probability of assignment to the intervention yielding the least imbalance according to the algorithm (referred to as the biasing probability) is P=.80. Thus, there is always a random component to allocation to prevent against deterministic assigning and corresponding selection bias.

Treatment Conditions

2GETHER (Active)

Overview

2GETHER is a relationship education and HIV prevention program for young male couples that was developed based on formative mixed-methods research [19,32,59] and integration of components from the Strengthening Same-Sex Relationships program [37]. 2GETHER was initially designed as an in-person intervention, consisting of two group sessions focused on didactics, and two individualized couple sessions focused on skills implementation.

2GETHER teaches couples to use relationship education skills (ie, communication skills training, coping skills, problem-solving, acceptance) as a platform for optimizing their relationship functioning, improving their sexual health, and reducing HIV transmission risk. 2GETHER addresses HIV transmission risk in couples regardless of HIV status; couples learn to use behavioral and biomedical approaches to prevent both HIV acquisition (eg, HIV testing, condom use, PrEP) and transmission (eg, medication adherence to reduce viral load). Intervention content has been described in detail in manuscripts describing the nonrandomized pilot feasibility and acceptability trial [8] and a practical paper aimed at describing the implementation of relationship education for HIV prevention [60].

Online Adaptation and Pilot Trial of 2GETHER USA

To address the specific needs of young male couples outside of urban areas, we adapted 2GETHER for online administration (hereafter referred to as "2GETHER USA") in two phases: (1) an initial content adaptation; and (2) a small pilot feasibility trial (N=10 dyads/20 individuals). During Phase 1, the study team reviewed the technical and usability merits of various videoconferencing platforms, followed by run-throughs of the group and individual sessions using the most promising platforms. We elected to use BlueJeans (BlueJeans Network, San Jose, California, United States) as our videoconferencing platform because it allowed for the highest degree of functionality (eg, hosting group chats, streaming video content live) and usability while minimizing technical issues (eg, strong connectivity, few interrupted sessions). Next, we completed several more rounds of internal content run-throughs and finalized study protocols for the Phase 2 small pilot feasibility trial. This involved finalizing protocols for national online recruitment strategies, remote baseline completion (including STI home testing and remote completion of couples communication tasks), and videoconference implementation of intervention sessions. We also made several alterations to address participant fatigue and enhance participant rapport, based on staff feedback and review of the telehealth literature [42]. First, we split the two group sessions into three sessions to minimize any loss of attention during remote sessions. Second, the group sessions involve a fair amount of didactic presentation, which is harder to follow for extended periods on videoconference. Thus, we prerecorded videos of the narrated didactic material (ie, PowerPoint presentations) and sent them to participants one week before group sessions (ie, three 20-minute self-paced modules per week). This facilitated briefer, more focused group sessions that emphasized discussion of intervention content and participant experiences that were already present in the original protocol. The structure and content of the individualized sessions, including live remote facilitation, were retained in 2GETHER USA. Finally, we developed specific training protocols to assist facilitators in speaking more clearly and conveying affect, which is more difficult through videoconference, in order to optimize rapport.

In Phase 2, we conducted a pilot trial of the adapted intervention with ten dyads (individual N=20). Participants were diverse in terms of race/ethnicity, HIV status, and geographic location. Participants completed a baseline assessment, consisting of

three components: (1) online self-report questionnaire; (2) at-home testing for urethral and rectal Chlamydia and Gonorrhea; and (3) video-recording a couple communication task. They then completed group skill-building sessions, followed by individualized couple sessions for skill implementation. Upon completion of the intervention, participants completed a 2-week posttest and exit interview.

Regarding feasibility and acceptability, recruitment was rapid (ie, all participants recruited and enrolled January-February 2018), and couples were diverse in terms of demographics. All participants completed all intervention sessions and study components and reported few concerns with format or content. With regard to baseline assessment, some participants struggled to complete at-home STI testing and the video-recorded communication task promptly. We thus simplified instructions for these tasks and allowed couples to schedule appointments with staff to record the communication task remotely. We experienced occasional connectivity issues during videoconference sessions and difficulty coordinating participant schedules across time zones. We modified protocols to minimize these barriers (eg, simplifying technical instructions, scheduling by time zone).

2GETHER USA Content Overview

The final 2GETHER USA program, after adaptation, piloting, and refinement based on participant and facilitator feedback, is comprised of five sessions. First, couples complete three videoconference group sessions aimed at skills building. Before each session, participants view three, 20-minute, self-paced video modules that address communication skills, coping with stress (both general and sexual minority-specific stress), relationship sexual satisfaction, and HIV transmission risk within the dyad and with outside partners. After viewing these modules, weekly one-hour videoconference group discussions led by two facilitators reinforce core concepts through structured conversations about how skills apply to couples' relationships. We cannot guarantee that couples viewed the video modules, so each group session contains a review of core content. Participants are asked if they were able to watch the videos in order to guide the extent to which core content needs to be reinforced during group discussion. Videoconference groups are attended by 2-6 couples (both members of the couple must attend and be collocated) who can all see one another, with the screen enlarged on whomever is currently speaking, which helps to build community and facilitate group learning. If a couple does not show up to a group session, we proceed with the session (even if only one couple attends) and conduct a make-up session with the missed couple. In rare cases, couples may proceed with the intervention without having completed one or more group sessions, but we seek to incorporate missed content into remaining sessions.

Next, each couple completes two individualized couple sessions via videoconference with a program facilitator (with no other couples attending), aimed at skills implementation. The first individualized session focuses on communication skills coaching and problem-solving, in which couples discuss up to two areas of disagreement. Each partner communicates concerns, actively listens to their partner, and discusses problem-solving, with guidance and corrective feedback from the facilitator to facilitate effective use of these skills. The second individualized session, and the zenith of the intervention, focuses on sexual health. Utilizing effective communication skills, couples discuss sexual satisfaction within the dyad, their preferences for a monogamous or nonmonogamous relationship agreement, and biomedical and behavioral HIV prevention strategies. HIV-negative and unknown status participants receive HIV testing during this session, while HIV-positive participants and HIV-negative participants on PrEP receive medication adherence counseling, based on the Life-Steps protocol [51]. If participants test preliminary HIV positive, we provide participants with resources for confirmatory testing and linkage to care in their area of residence. At the end of the sessions, couples draft a detailed relationship agreement, which includes specific rules about monogamy or nonmonogamy and HIV prevention practices. After establishing an agreement, the couple discusses strategies for maintaining or altering the agreement in the future, as well as how they will handle agreement breaks if they occur.

Existing Public Health Practice (Control)

The public health practice intervention that couples in the control condition receive depends on the HIV-status of the partners: HIV-negative/unknown status participants receive a single-session of Testing Together [25], HIV-positive participants receive a single session of Medication Adherence and Risk Reduction Counseling [51], and serodiscordant couples receive both protocols in a single session. Testing Together, previously known as Couples HIV Testing and Counseling, is a public health strategy designed for two or more persons who are in, or planning to be in, a sexual relationship who receive HIV testing services together (including their HIV test results). Testing Together facilitates communication and disclosure of HIV status between the two partners, while also supporting linkage to HIV medical care, PrEP, and other appropriate services. Testing Together creates an opportunity for couples to discuss and prepare a risk-reduction plan based on the HIV status of both partners. Couples in which at least one member is HIV-positive receive Medication Adherence and Risk Reduction Counseling, which was developed based on Safren and colleagues' Life-Steps protocol [51]. Based on cognitive-behavioral therapy principles, this session focuses on identifying motivations for and barriers to antiretroviral adherence, as well as making a plan for optimizing medication adherence and reducing HIV transmission risk. For serodiscordant couples who receive both Testing Together and Medication Adherence Counseling, the protocol emphasizes engaging each partner as an equal participant in both interventions, with the ultimate goal of reducing transmission risk within the dyad and with outside partners.

Facilitator Training, Fidelity, and Supervision

All intervention facilitators hold a bachelor's degree at minimum and have direct experience working in research or social service settings with young adults or MSM. Instead of emphasizing advanced education and training, our hiring practices prioritize community-based and direct service experience, including HIV testing and counseling, health education, teaching, counseling, research administration, and program coordination. Using

bachelors-level facilitators (instead of mental health professionals) with relevant community-based experience means that the program will be easier to implement in community settings, which is an important consideration when designing interventions that contain group and individual session components. Given that all public health practice control content is also presented in the 2GETHER USA active condition, this study utilizes the same facilitators for the active and control conditions.

Each facilitator completed an intensive eight-week training protocol, which included Communication Skills Coaching, HIV Test Specimen Collection and Interpretation, HIV Risk Reduction, Testing Together, and session-specific intervention content. As part of the training, all facilitators completed mock session run-throughs with the Principal Investigator, Coinvestigator/Supervision Lead, and Project Coordinator for feedback. To reinforce facilitator skill-building, facilitators completed mock sessions with patient simulators who were given a case description (ie, individual characteristics, relationship history, relationship dynamics, and session-specific scripts). Patient simulation allowed facilitators to experience "real-life" sessions, as well as how to handle potentially negative or hostile situations, deliver HIV-positive test results, and guide and direct effective communication practice among dyads.

Facilitators will receive weekly supervision on their audio-recorded individual 2GETHER USA couples' sessions. Supervision is primarily provided by one of three doctoral-level clinical psychologists and a masters-level HIV test counselor in a group setting. During group supervision, relevant segments of audio are played to illustrate both areas for improvement and ways facilitators skillfully handled difficult situations. As facilitators master the 2GETHER USA content, they are given opportunities to provide mentored peer supervision. Supervision for the public health practice control condition is conducted separately using an analogous format, led by a masters-level HIV testing counselor. Given that this trial uses the same facilitators across conditions, supervision aims to minimize drift in content across conditions by identifying moments when facilitators break condition fidelity.

To ensure fidelity to the intervention manuals, and thereby the essential components and content of the intervention, facilitators audio-record all 2GETHER USA and public health practice sessions. A total of 20% of sessions (both group and individualized couple sessions) are randomly selected for review by an independent assessor to validate appropriate content delivery. All staff members trained in intervention delivery will assist with fidelity monitoring. Facilitators are eligible to conduct fidelity assessments only for those couples with whom they did not work in either group or individual sessions to minimize bias. Fidelity monitoring assessors will complete a dichotomous checklist indicating whether or not the central components of each intervention session were completed and delivered effectively by facilitators. They will also rate facilitator time management, completion of collaborative activities, addressing participant concerns and questions, stimulating conversations, familiarity with session content and materials, and ability to develop a rapport with participants.

Study Assessments

After participants complete couple verification, each individual in the dyad is sent materials to complete their baseline assessment, which consists of a self-report survey hosted on REDCap, a video-recorded couple communication task, and self-collected STI testing for urethral and rectal Chlamydia and Gonorrhea. The "baseline kit" contains detailed instructions for completing each component of the baseline. Based on prior work conducted in our group [61], we provide a guide for self-collection of STI samples and instructions for mailing the materials to the lab. STI testing results are delivered to each participant individually via phone, including referrals for treatment in the participant's area of residence. Participants complete self-reported questionnaires at all follow-up points (ie, 3-, 6-, 9-, and 12-months postintervention), and they complete the couple communication task and self-collected STI and HIV testing at the 12-month follow-up. If a couple breaks up during the follow-up period, each individual still completes follow-up surveys and STI testing. If individuals then enter into new relationships, we gather information on their current relationship functioning in order to assess whether skills generalize to future relationships. Participants are compensated US $50 for completing each assessment time point, for a total of up to US $250 for each member of the dyad. See Figure 1 for the flow of events for participants and Table 1 for a list of primary and secondary outcomes by assessment timepoint.

Table 1. Primary and Secondary Outcomes and Assessment Schedule

Outcome type, construct	Measure/Operationalization	Measurement schedule				
		Baseline	3 months	6 months	9 months	12 months
Primary						
HIV risk behavior	Condomless anal sex with a serodiscordant main partner or any casual partner [62]	✓	✓	✓	✓	✓
STI[a] incidence	Urethral and rectal Chlamydia and Gonorrhea: Aptima Combo 2 GC/CT nucleic acid amplification test [63]	✓				✓
Secondary: dyadic HIV risk						
Relationship agreements	Partner concordance in (non)-monogamy agreement type and rules	✓	✓	✓	✓	✓
Agreement breaks	Past 3-month breaks in (non)-monogamy agreement rules	✓	✓	✓	✓	✓
Secondary: HIV prevention and care continua						
HIV/STI testing	Assessing past 3-month HIV and STI testing history	✓	✓	✓	✓	✓
PrEP[b] use and adherence	Current & past 3-month PrEP use; adherence over 7-, 30-, and 90-days [64-66]	✓	✓	✓	✓	✓
ART[c] adherence and viral suppression	Adherence over 7-, 30-, and 90-days; self-reported viral load (detectable/ undetectable) [65]	✓	✓	✓	✓	✓
Secondary: relationship functioning						
Relationship satisfaction	Couples Satisfaction Index: 4-items [67]	✓	✓	✓	✓	✓
Communication (self-report)	Communication Skills Test: positive and negative scales adapted [68]	✓	✓	✓	✓	✓
Communication (objective)	10-minute recorded communication task [69-71], coded with Interactional Dimensions Coding System [72]	✓				✓
Secondary: substance use						
Alcohol problems	Alcohol Use Disorders Identification Test [73]	✓	✓	✓	✓	✓
Marijuana problems	Cannabis Use Disorders Identification Test-Revised [74]	✓	✓	✓	✓	✓
Other drug use	Past 3-month use of prescription and illicit drugs [75,76]	✓	✓	✓	✓	✓

[a]STI: sexually transmitted infection

[b]PrEP: preexposure prophylaxis

[c]ART: antiretroviral therapy

Analytic Plan

Chi-square tests and analysis of variance will be used to test for randomization imbalances on demographic factors, primary outcomes, and prognostic variables (ie, couple-level HIV-status, age discordance, and individual-level STI results) at baseline among the two treatment conditions. Observed imbalances will be adjusted for using baseline data in all subsequent analyses of treatment effects.

The primary biological outcome, change in STI prevalence rates between baseline and 12-month follow-up, will be examined using a Cochran-Mantel-Haenszel test of two independent binomial proportions. This test will allow for stratification while testing for significant associations between two binary variables. The primary behavioral outcome, condomless anal sex with casual partners or with serodiscordant main partners, and secondary outcomes will be assessed using multilevel growth modeling to adjust for the nested nature of our data. Initial power analyses to determine the sample size for 2GETHER was conducted based on individual-level outcomes so that partnerships breaking up throughout the study would have a limited effect on power, and power analyses assumed an approximate 20% attrition at 12-months. Latent growth curve factors will be formed for each outcome using data from the four follow up surveys (3-, 6-, 9-, and 12-month). Models will include the latent intercept and slope formed at the individual level for each outcome. The 2GETHER treatment condition

will be entered as a dyad-level predictor of the latent intercept and slope. Significant treatment differences on the intercept will indicate differences in the outcome at the 3-month follow-up. By changing the referent time point for the intercept, we will also test for differences at 6-, 9-, and 12-months. Significant treatment differences on the slope term will indicate different trajectories of change for that outcome among the two study conditions.

For outcomes where significant differences have been identified based on treatment condition, relationship functioning, and substance use problems will be explored as potential mediating factors within the multilevel growth modeling framework described above. Variables will be identified as suitable mediators if, like the outcome, the treatment effect is related to change in the potential mediator. Mediated pathways will be identified using a parallel process approach where the treatment effect predicts change in both the mediator, which will be modeled as a lagged effect to maintain the temporal order necessary for mediation, and the outcome [77]. The indirect effect of the treatment on the outcome through the lagged mediator will be calculated using a percentile bootstrap test. To address partners who break up in analyses where relationship functioning is the mediator, we will incorporate data about their new serious partner if the participant reports one or treat that variable as missing if they report no serious partner at that follow-up.

Results

This efficacy trial is ongoing. As of October 11, 2019, 140 dyads (individual N=280) had completed all baseline assessment components and had been randomized to either 2GETHER USA or public health practice. At the conclusion of the study, we will have enrolled and randomized 200 dyads, or 400 individuals. The final sample will be diverse in terms of race/ethnicity, HIV status, geographic region, and urban or rural location.

Discussion

Although YMSM are the group at highest risk for HIV in the United States [1], relatively few preventive interventions have been developed that take into account the unique developmental needs of this population [78]. Further, a large proportion of new HIV infections in MSM occur in the context of serious romantic relationships [2,3], particularly among YMSM [3]. 2GETHER's unique approach of integrating relationship education and HIV prevention for young male couples has a strong potential to reduce HIV transmission risk among those at the highest risk.

In addition to establishing the efficacy of a novel HIV prevention program for YMSM, this evaluation of 2GETHER makes several innovative contributions to HIV prevention. First, although the number of available HIV prevention programs for YMSM is on the rise [78], very few couples-based preventive interventions are available for YMSM in serious relationships. 2GETHER is also unique in that it integrates primary and secondary HIV prevention by enrolling both HIV-positive and HIV-negative individuals (in any arrangement of HIV statuses within dyads). Further, it moves beyond simply advocating for condom use by integrating information about both behavioral and biomedical prevention strategies that are relevant to individuals of any HIV status. This comprehensive approach to sexual health is especially important when working with couples because they are simultaneously trying to build dyadic intimacy and pleasure while also preventing HIV/STI transmission, goals which may be at odds with one another if they are not navigated effectively.

Even among the minimal number of available, couples-based approaches to HIV prevention for MSM, 2GETHER was the first published pilot trial of an intervention that placed an equal emphasis on relationship education and sexual health (including HIV prevention) in young male couples, and we now aim to assess its efficacy. It is our belief that if a couple can optimize their relationship functioning first (eg, improve communication and satisfaction), then they will be better able to navigate complex conversations about sexual health and safety. Indeed, we assert that our approach of leading with relationship education has the potential to provide health benefits beyond HIV prevention, including couples-based mental health treatment and substance use reduction. This is important because YMSM report fatigue associated with HIV prevention messaging, but they express a desire for programs that address their health more broadly, including relationship education [32]. Since the completion of our original pilot trial, 2GETHER is now one of several interventions that addresses both HIV prevention and relationship skills [26,79]. For example, the We Prevent program [79], which is in its initial phases of testing, is adapting relationship skills for adolescent MSM in romantic relationships in order to prevent HIV transmission.

Finally, the online adapted version of 2GETHER described in this manuscript offers specific innovation above that provided by the original, in-person version of the program. Specifically, the delivery of 2GETHER to couples across the country via videoconference provides much-needed relationship education and sexual health services for couples that often lack LGBTQ-affirming health care (eg, rural YMSM). While asynchronous telehealth programs also have the potential to increase the reach of affirming and effective services to nonurban populations, they do not offer the opportunity for participants to interact in vivo with a facilitator and receive in-the-moment feedback about the implementation of their skills. If efficacious, the approach used in 2GETHER has tremendous potential to fill the health care needs of YMSM who lack access to care in physical spaces in their area of residence.

There are several limitations inherent in the trial design. First, participants are likely not blinded to their intervention condition, given that the control condition is not attention-matched and is a single-session protocol based on existing public health practice. Second, intervention facilitators conduct sessions for both the active and control conditions. Supervision focuses on minimizing drift in condition content, but facilitators may periodically compromise fidelity to a given protocol because they facilitate sessions for both conditions. Finally, while recruiting participants from across the United States increases the ability to make inferences about generalizability, the final sample will not be representative. Despite these limitations,

2GETHER is a highly innovative and promising approach for improving relationship functioning and reducing HIV risk in young male couples. This RCT will provide important information about the efficacy of couples-based HIV prevention and relationship education, adapted for remote administration via videoconference, for a diverse group of young male couples across the United States.

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Conflicts of Interest

None declared.

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Abbreviations

LGBTQ: lesbian, gay, bisexual, transgender, and queer
MSM: men who have sex with men
PrEP: preexposure prophylaxis
RCT: randomized controlled trial
STI: sexually transmitted infection
YMSM: young men who have sex with men

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Protocol

Behavioral, Nutritional, and Genetic Risk Factors of Colorectal Cancers in Morocco: Protocol for a Multicenter Case-Control Study

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Abstract

Background: Colorectal cancer (CRC) has been reported as the third most commonly diagnosed cancer worldwide and is currently considered as a major public health concern. A peak increase in incidence has been noted in economically transitioning countries like Morocco where industrialization started shifting from a traditional lifestyle and diet toward a more westernized diet and lifestyle.

Objective: This paper aims to present the protocol of a large-scale Moroccan case-control study that aims at investigating associations of diet, other lifestyle factors, and genetic traits with CRC risk in Morocco.

Methods: A case-control study was conducted between 2009 and 2017, including 3032 case-control pairs (1516 cases and 1516 controls) matched on sex, age, and center in 5 major public health hospitals in Morocco. Questionnaires on sociodemographic data, lifestyle, family history of CRC, and nonsteroidal anti-inflammatory drugs (NSAIDs) were completed by trained investigators during face-to-face interviews. In addition, participants completed a semiquantitative food-frequency questionnaire, developed to assess food intake in the Moroccan population. Information regarding genetic factors was recorded for cases, and paraffin blocks (with embedded tumor tissues) are available in 3 collaborating hospitals. Conditional logistic regression analysis is planned to assess associations between diet and CRC risk. Binary logistic regression is considered to predict associations between mutations and nutritional risk factors including only CRC case series.

Results: Altogether, 2966 cases-control pairs (1483 cases and 1483 controls) were considered eligible and included in this study. Both cases and controls did not differ significantly with respect to age (P=.36), sex (P=.51), center (P>.99), marital status (P=.30), and NSAID use (P=.08). However, participants in the control group were significantly more likely to have a high income level and live in urban areas and to have a high level of education than cases.

Conclusions: This is the first study investigating potential risk factors of CRC such as lifestyle, diet, and genetic factors, originating from a southern Mediterranean country with low but increasing CRC prevalence. Identified risk factors allow the establishment of evidence-based preventive actions regarding nutrition and other lifestyle habits adapted to the Moroccan context. In brief, this study will promote cancer research and prevention in Morocco.

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KEYWORDS

diet; colorectal cancer; Morocco; case-control study; study protocol

Introduction

Background

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide [1,2]. The high CRC incidence and magnitude make it a real public health concern [3]. Therefore, it is essential to determine its risk factors as a basis for evidence-based prevention strategies. The risk factors of CRC are complex and involve genetic and environmental factors [4,5]. Indeed, 30% to 70% of CRCs are considered to be because of environmental factors such as lifestyle and eating habits [6-8].

According to the recent World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) 2018 report, high red and processed meat intake, high body fatness, high consumption of alcoholic drinks, and low levels of physical activity have been associated with increased CRC risk, whereas diets high in antioxidants, in particular fruits and vegetables, or fibers have been associated with reduced risk [9]. A high body mass index is associated with an increased risk of occurrence of large adenomas at the level of the colon and rectum [10].

CRC incidence is indeed particularly high in Western countries with high meat consumption, such as Australia and the United States [11], whereas lower in Mediterranean countries [1] which could potentially be attributed to the quality of the Mediterranean diet, including high consumption of fruits, vegetables, and olive oil [12].

Regarding genetic factors, epidemiological studies conclude that the risk of developing CRC increases with increasing first-degree family history [13]. Several recent studies attempt to show a potential interaction between genetic predisposition and dietary factors [14]. One of these interactions could involve the acetylator status [15]. Indeed, rapid acetylating subjects (rapid phenotype of N acetyl transferase [NAT2]) are more likely to develop CRC, particularly when consuming overgrilled meat, through greater activation of heterocyclic amines [15]. Another example demonstrating the importance of considering genetic status is the analysis of certain mutations that occur in the early stages of CRC such as Kirsten rat sarcoma (KRAS) and proto-oncogene B-Raf (BRAF) mutations. These mutations were associated with certain foods, nutrients, and micronutrients, and it has been suggested that the risk of KRAS and BRAF mutations may depend on dietary and lifestyle factors [13,16].

The majority of studies investigating CRC risk factors have been conducted in countries with high CRC prevalence [11]. Results from these high-prevalence studies are sometimes controversial and not always applicable to low-prevalence countries such as Morocco, which have started feeling the effects of the triple demographic, epidemiological, and nutritional transition [17-19].

According to the cancer incidence data from Globocan 2018, CRC ranks as the third most common cancer in Morocco after lung and prostate cancer in men and after breast and cervical cancer in women (8.7% and 7% of all types of cancer, respectively). Furthermore, this number of new cancer cases seems to increase each year [20,21]. According to the Cancer Registry of the Greater Casablanca Region (2005 to 2012), age-standardized incidence rates raised from 3.8 to 8.4 and from 2.6 to 7.4 per 100,000 in Moroccan men and women, respectively [20,21]. At the same time, cancer risk factors and behaviors of the Moroccan population are progressing rapidly owing to profound societal and industrial changes. This progression would also be linked to the nutritional transition that shows local specificities so far scarcely documented [22].

Moroccan food habits are characterized by their tradition and culture but also by profound changes to a Western lifestyle [22]. Increasingly, the westernization of food fads that is characterized by more consumption of red meat, processed meat, alcohol, and *junk food* is observed, all this in a context of a sedentary and stressful lifestyle [11]. Given that the majority of these changes are considered to be CRC risk factors, this could explain part of the increasing incidence rates in a country supposed to be low in CRC incidence.

Objective

In Morocco, to our knowledge, no previous study has investigated associations between these risk factors and CRC. Therefore, we designed a multicenter case-control study to evaluate the relationship of the Moroccan diet, physical activity, and other lifestyle habits with CRC risk. This study will also describe the genetic profiles of CRCs in Morocco and their interaction with food intakes. Finally, we will also select CRC index cases that would identify family cancers in Morocco.

Methods

Design

This case-control study was conducted between September 2009 and February 2017 in 5 major public health hospitals in Morocco, namely, the University Hospital Center (UHC) Hassan II of Fez, UHC Ibn Sina of Rabat, UHC Mohammed VI of Oujda, UHC Ibn Rushd of Casablanca, and UHC Mohammed VI of Marrakech. The sample size estimation was based on red meat consumption as one of the main exposures of interest. According to the National Survey of Dietary Habits in Morocco, the proportion of Moroccan adults eating red meat at least twice a week was 62.7% [23]. The sample size was calculated using the following formula specific for individual-matched case-control studies (Figure 1) [24], considering a type I error (Cronbach alpha) equal to 5%, a statistical power of 90% (beta=.10), and a minimum difference in terms of risk of 43% as reported by the WCRF/AICR report [5].

Figure 1. Formula specific for individual-matched case-control studies.

$$n_c = \frac{[Z_\alpha(\psi+1) + 2Z_\beta\sqrt{\psi}]^2}{(\psi-1)^2(\psi+1)P_{O1}}.$$

n_c: Sample size for case-control pairs

ψ: OR Odds Ratio

P_o: The probability of obtaining a matched pair in which the case is unexposed and the control is exposed.

The number of pairs required for the study was 1496, that is, in each of the 2 groups 1496, which was rounded to 1500.

Definition of Cases and Controls

Cases were patients who had newly confirmed CRC diagnosis by histopathology less than 3 months before the interview and who did not start any therapeutic protocol (chemotherapy, radiation therapy, hormone therapy, or surgery) yet at the time of inclusion. However, for some patients included in the study, the diagnosis was done at the time of surgery. For the exclusion criteria, patients who had received chemotherapy, radiation therapy, or hormone therapy were excluded as they were not considered as newly diagnosed, and the therapy may affect their lifestyle habits.

Each case was matched with a control subject by age (±5 years), sex, and center. Other eligibility criteria included the following: at least 18 years old, no prior history of diabetes mellitus, capability to give consent, and ability to communicate and carry out the interview. Extra exclusion criteria were patients under exclusive palliative treatment and patients confined to their chairs or beds.

Controls were selected from the same local population and in the same hospitals as cases, among healthy subjects accompanying other patients or visitors. Eligibility criteria were the same as for cases, except that the controls should not have any personal history of CRC or any other type of cancer. Unfortunately, we did not have the funding to carry out a fecal occult blood test or colonoscopy for controls. However, to avoid (or minimize) the inclusion of false controls, questions about their medical history and clinical symptoms related to CRC were systematically asked to all controls.

Data Collection

Data were collected through face-to-face interviews conducted by trained investigators. All participants were asked to answer questionnaires on the following topics.

Sociodemographic Information

It includes age (obtained from personal identification numbers); sex; center (Rabat, Marrakech, Fez, Oujda, and Casablanca); residency (urban and rural); profession (employed, retired, unemployed, housewife, and student); marital status (single, married, divorced, and widow[er]); education level (illiterate, primary, secondary, and higher); income level (<2000 MAD [Moroccan dirham], 2000-5000 MAD, >5000 MAD); and type of habitat (luxurious habitats, new medina, slum habitats, modern habitat, and old medina).

Clinical Data

Clinical data were collected regarding their CRC diagnosis (the type of cancer, the date of biopsy, the stage of cancer, operated patient, and date and type of surgery), family history of CRC in first- and second-degree relatives, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Substances Use

It includes alcohol consumption and smoking status. Alcohol consumption was divided into 2 categories: never and current consumers. The current consumers were asked to precise the quantity and the frequency of consumption of the 5 proposed types of alcoholic beverages (red wine, white wine, pink wine, whisky, and vodka). Smoking status was defined according to the International Union Against Tuberculosis and Lung Diseases Guide [25]. Respondents were defined as current smokers (daily and occasional smokers) if they were smoking at the time of the survey and had smoked more than 100 cigarettes in their lifetime. They were defined as ex-smokers if they had smoked more than 100 cigarettes in their lifetime but stopped smoking during the past more than 3 months at the time of the survey; and they were defined as never smokers if they had never smoked or had smoked less than 100 cigarettes in their lifetime [25]. Thus, smoking status was divided into 3 categories: never smokers, ex-smokers, and current smokers.

Physical Activity Levels

To assess the physical activity levels, participants were asked the average time they spent on the following activities during the past year: physical activity at work, travel to and from home, and recreational activities. According to the Global Physical Activity Questionnaire [26], the number of hours per week spent engaging in each activity was multiplied by the corresponding energy expenditure, expressed as metabolic equivalent of task (MET), and the product was taken as the physical activity score expressed as MET-minutes per week. The intensity of physical activity was classified into 3 categories: light intensity (<600 MET-minutes per week), moderate intensity (600-3000 MET-minutes per week), and vigorous intensity (≥3000 MET-minutes per week).

Anthropometric Measurements

The anthropometric measurements included height and current weight at the time of the survey and have been extracted from

medical records, whereas all previous measurements (before the appearance of the symptoms), waist, and hip sizes were self-reported.

Dietary Data

Dietary data were collected using a validated semiquantitative Food Frequency Questionnaire (FFQ) that was developed to assess food intake in the Moroccan population [27]. It was inspired from the Global Allergy and Asthma European Network (GA^2LEN) [28] and validated in the Moroccan context [27].

Multimedia Appendix 1 depicts this FFQ that included 255 foods and the following 32 food groups: (1) bread, (2) breakfast with grains, (3) couscous (one of the traditional staple foods of Maghreb countries' cuisine prepared by durum wheat semolina), (4) pasta, (5) cake, (6) rice, (7) sugar, (8) sweets without chocolate, (9) chocolate, (10) vegetable oil, (11) margarine and vegetable fat, (12) butter and animal fat, (13) dried fruit, (14) legumes, (15) vegetables, (16) potatoes, (17) fruits, (18) juice, (19) nonalcoholic beverages, (20) coffee/tea, (21) beer, (22) wine, (23) other alcoholic beverages, (24) red meat and processed meat, (25) poultry, (26) sekat (offal and brain), (27) fish, (28) eggs, (29) milk of cow/soya, (30) cheese, (31) other dairy products, and (32) miscellaneous foods (Multimedia Appendix 1).

Participants, both cases and controls, recorded their food consumption of the past year before the interview. Frequency of food consumption was recorded in 8 different categories (never, 1-3 times per month, once a week, 2-4 times per week, 5-6 times per week, once a day, 2-3 times per day, and ≥4 times/day). Regarding seasonal foods, participants were asked to answer the question based on intakes during periods/seasons when these foods are available. The daily intake of the foods was then calculated according to the number of months per year that each seasonal food was available. To convert foods into nutrient intakes, we essentially used food composition data from Tunisia [29] and Morocco [30]. The nutrient and energy intakes were calculated by multiplying the daily intakes of each food item by the nutrient and calorie content (per 100 g) of all food items.

In addition, the reproducibility and validity of this FFQ were evaluated among 105 healthy Moroccan adults. The results showed a good relative validity (deattenuated correlations ranging from 0.24 for fiber to 0.93 for total monounsaturated fatty acids) and a good reproducibility (intraclass correlation coefficient ranging from 0.69 for fat to 0.84 for Vitamin A) [27].

Genetic Data

Pathology tumor samples were collected for 170 patients, whose anatomopathological tests were done in the UHCs and whose block tumors were available. In fact, the majority of patients are used to do their biopsies outside the university hospitals, in private sectors, which are difficult to access and not always willing to participate in research projects. For this reason, biopsies done in the private sector were not included in this study. In addition, only 3 out of 5 public health hospitals provided consent to participate in the genetics part of the study and because of financial difficulties, only a subsample of pathological tumor samples was obtained. The tumor samples were collected between February 2016 and July 2017 from 3 public health hospitals in Morocco (Casablanca, Oujda, and Rabat). In addition, all molecular analyses were done in the laboratory of genetics at the University Hospital Hassan II in Fez. A pathologist doctor classified the samples embedded in paraffin and registered and coded using consecutive and unique identification numbers. These stored paraffin-embedded tissues were collected from the 3 UHCs included in this study. DNA was extracted using an Invitrogen RNA/DNA isolation kit by manually scraping tissue from unstained slides. The BRAF and KRAS mutations will be determined by direct sequencing and analyzed by methylation-specific polymerase chain reaction.

Data Cleaning and Handling

In total, the study recruited 3032 subjects (1516 cases and 1516 controls). Table 1 depicts the data cleaning and handling by reporting the exclusions. Exclusions before starting statistical analysis included participants with unspecified primitive cancer (n=7), cases with old biopsies (6 cases), participants with missing dietary data because the FFQ was not well filled (n=10), duplicate records (n=2), and unmatched records (n=8).

Table 1. Exclusions of study participants (1516 cases and 1516 controls invited in the study) during data cleaning and handling (N=1516).

Exclusion criteria[a]	Excluded cases, n (%)	Excluded controls, n (%)
Unspecified cancer	7 (0.46)	0 (0.00)
Patients with old biopsies	6 (0.39)	0 (0.00)
Food-Frequency Questionnaire empty	10 (0.65)	10 (0.65)
Duplicate records	2 (0.13)	0 (0.00)
Unmatched cases/controls	8 (0.52)	8 (0.52)
Total	33 (2.17)	18 (1.18)

[a]Total individual matching (included in the study): 1483 cases and 1483 controls.

Participation Rate

The participation rate in this study was 97% (1516/1555) for cases and 0.75% (1516/2000) for controls. Table 2 depicts the missing data of all variables for the final sample included in this study (1483 cases and 1483 controls).

Table 2. Missing data for each variable (1483 cases and 1483 controls).

Variables	Subjects with missing information	
	Cases (N=1483), n (%)	Controls (N=1483), n (%)
Surgery type	1 (0.06)	0 (0.00)
Surgery date	18 (1.21)	0 (0.00)
Number of years of study	336 (22.65)	408 (27.51)
Current weight	8 (0.53)	15 (1.01)
Waist size	680 (45.85)	713 (48.07)
Hip size	1019 (68.71)	1006 (67.83)
Family history of colorectal cancer but type of family relationship unknown	2 (0.13)	1 (0.06)
Nonsteroidal anti-inflammatory drug use	2 (0.13)	3 (0.20)
Personal address	27 (1.82)	20 (1.34)
Heading of food groups	47 (3.16)	48 (3.23)
Cereals	15 (1.01)	5 (0.33)
Oils	4 (0.26)	2 (0.13)
Butter	1 (0.06)	0 (0.00)
Nonstarchy vegetables	3 (0.20)	9 (0.60)
Starchy vegetables	4 (0.26)	2 (0.13)
Soft drink	9 (0.60)	13 (0.87)
Tea	1 (0.06)	3 (0.20)
Coffee	1 (0.06)	1 (0.06)
Red meat	9 (0.60)	13 (0.87)

Ethics and Availability of Data

The protocol of this study has been reviewed and approved by the ethics Committee at the University of Fez in September 2009. Written informed consent was obtained from all participants before enrollment. Confidentiality of data is secured by removing personal identifiers from the datasets.

Statistical Analysis

The descriptive information of the categorical variables was presented as the frequency of each category and for the continuous variables by means and standard deviation. Differences between continuous variables were examined by using the student *t* test (2 tailed) for matched samples. Chi-square tests (McNemar) were used to examine differences among categorical variables.

Results

As of February 2017, we enrolled 2966 cases and controls (1483 cases and 1483 controls) considered eligible and included in our study. To date, the genetic part of the study is still ongoing. Table 3 shows the sociodemographic variables and lifestyle factors among CRC cases and controls. Both cases and controls did not differ significantly with respect to age (P=.36), sex (P=.51), center (P>.99), marital status (P=.30), and NSAID use (P=.08). However, participants in the control group were significantly higher educated than cases.

Table 3. Main characteristics of cases and controls in the Moroccan colorectal cancer case-control study.

Characteristics	Cases (N=1483)	Controls (N=1483)	*P* value[a]
Matching variables			
Age at recruitment (years), mean (SD)	56.45 (13.98)	55.51 (13.73)	.36
Sex, n (%)			
Female	746 (50.30)	746 (50.30)	.51
Male	737 (49.69)	737 (49.79)	—[b]
Center, n (%)			
Rabat	482 (32.50)	482 (32.50)	—
Marrakech	27 (1.82)	27 (1.82)	>.99
Fes	241 (16.25)	241 (16.25)	—
Oujda	251 (16.92)	251 (16.92)	—
Casablanca	480 (32.36)	480 (32.36)	—
General characteristics			
Residency, n (%)			
Urban	1021 (68.84)	1117 (75.32)	.001
Rural	462 (31.15)	366 (24.67)	—
Marital status, n (%)			
Single	142 (9.57)	146 (9.84)	—
Married	1128 (76.06)	1138 (76.73)	.30
Divorced	47 (3.16)	59 (3.97)	—
Widow(er)	166 (11.19)	140 (9.44)	—
Education level, n (%)			
Illiterate	936 (63.11)	748 (50.43)	—
Primary	281 (18.94)	276 (18.61)	.001
Secondary	178 (12.00)	271 (18.27)	—
Higher	88 (5.93)	188 (12.67)	—
Income level (Moroccan dirham), n (%)			
<2000	1216 (81.99)	1061 (71.54)	—
2000-5000	208 (14.02)	299 (20.16)	.001
>5000	59 (3.97)	123 (8.29)	—
Family history of colorectal cancer, n (%)			
Yes	83 (5.59)	12 (0.80)	.001
No	1400 (94.40)	1471 (99.19)	—
Past regular nonsteroidal anti-inflammatory drug use, n (%)			
Yes	105 (7.08)	126 (8.49)	.08
No	1378 (92.91)	1357 (91.50)	—

[a]Differences between continuous variables were examined by using student *t* test. Chi-square tests (McNemar) were used to examine differences among categorical variables.

[b]Not applicable.

Compared with controls, cases were more likely to have a family history of CRC. At last, cases were slightly but not significantly older than controls (mean 56.45 years, SD 13.98 years vs mean 55.51 years, SD 13.73).

Discussion

The primary aim of this study was to evaluate the relationship of diet, physical activity, and other lifestyle habits with CRC risk in Morocco. To our knowledge, this is the first study

designed to investigate this association in the Moroccan context. Similar studies have been conducted mostly in western countries [31-34] and few of them in some countries of the Middle East and the Northern African (MENA) region, 2 regions that are culturally quite similar to Morocco.

The studies conducted in the MENA region had low sample sizes, and their results could not be considered as representative. In addition, cases were not necessarily newly diagnosed with CRC [35,36]. This might affect the reliability of the results as cases may change their dietary habits after diagnosis. Moreover, the control groups were selected among patient's visitors, and the authors of these studies did not check for familial relationships between cases and their matched controls, what could potentially introduce selection bias and overmatching problems. Besides, all these case-control studies [37-42] used matching methods to control for some confounding factors such as age and sex. Nevertheless, they did not use the model of conditional regression for statistical analysis, which is highly recommended for this type of study design [43]. At the international level, many case-control studies have been conducted in Western countries with strong methodologies and great statistical power [44,45]. These reported strong evidence for the association between some foods and CRC risk, such as red and processed meat and dairy products [46-48]. Other associations are either controversial or not approved yet [10,49]. Furthermore, all these western studies did not include dietary habits from other regions of the world including the MENA region or Morocco. Moreover, the results drawn from some strong associations found for some foods, such as pork and alcohol [32,44], may not be applicable to the Moroccan context, where these types of foods are not commonly consumed for cultural or religious reasons. Therefore, this Moroccan case-control study checks whether or not the CRC-related factors are the same as in western countries. It also describes the specificities of Moroccan food habits in relation to CRC risk in Morocco.

This study has some potential limitations. The major one may be the recall bias that is known to be related to any retrospective study and was minimized in this study through the enrollment of the newly diagnosed patients who presumably remember their eating habits just before the onset of their illness better than after therapy or at more advanced cancer stages. The lengthy recall of dietary information can be considered as the second limitation. However, it could also be considered as an advantage of the study that very detailed dietary intake data were collected and available for statistical analyses; conversely, short dietary questionnaires may underestimate the true variation in food intake. Furthermore, the measurement error associated with the FFQ is another possible limitation of our study. To minimize the effect of these biases and errors and to avoid the likely influence of the lengthy recall of dietary information on data quality, interviewers were trained to help participants to fill in the questionnaire by clarifying questions if needed, which may increase the accuracy of answers. In addition, the dietary questionnaire has been validated, showing moderate to good validity.

The use of visitors as controls is another potential limitation of the study. In fact, recruitment of controls from outside the hospital setting was not feasible. Thus, we selected healthy subjects accompanying other patients or visitors as controls. As a condition of recruitment to avoid bias related to such controls, visitors must not be a relative or the patient's partner. We also made sure that they did not have the same family history and did not live in the same circumstances. The majority of those recruited were friends or neighbors of the patients.

The major strength of this study is that it is the first of its kind investigating potential risk factors of CRC such as lifestyle, diet, and genetic factors, originating from a southern Mediterranean country with low but increasing CRC prevalence. Its multicentric design and its large sample allow us to describe the national food habits as well as the epidemiological profile of Moroccan CRC cases. Moreover, dietary data were collected through a validated FFQ [27], in addition to a large battery of other lifestyle behaviors.

Identified risk factors will allow the establishment of evidence-based preventive actions regarding nutrition and other lifestyle habits tailored to the African, more particularly Moroccan, context. To conclude, this study will promote cancer research and prevention in Morocco.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Foods included in the validated Food Frequency Questionnaire (FFQ) for Morocco.
[PDF File (Adobe PDF File), 172 KB - resprot_v9i1e13998_app1.pdf]

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Abbreviations

AICR: American Institute for Cancer Research
BRAF: proto-oncogene B-Raf
CRC: colorectal cancer
FFQ: Food Frequency Questionnaire
KRAS: Kirsten rat sarcoma
MENA: Middle East and the Northern African
MET: metabolic equivalent of task
NSAID: nonsteroidal anti-inflammatory drug
UHC: University Hospital Center
WCRF: World Cancer Research Fund

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Protocol

Assessing Whether Meditation Improves Quality of Life for Adolescent Girls With Polycystic Ovary Syndrome: Protocol for a Randomized Controlled Trial

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Abstract

Background: Polycystic Ovary Syndrome (PCOS) is a common endocrine condition characterized by irregular periods and hyperandrogenism. Adolescents with PCOS have impaired quality of life (QOL) and increased psychological distress. Transcendental Meditation (TM) is a well-established self-management strategy that has been used to improve stress and well-being. A meta-analysis of TM trials has shown beneficial effects on stress and blood pressure in adults. Recent data are suggesting that another self-management strategy called a mindfulness stress management program has a role in improving QOL in women with PCOS, but there are no studies in adolescents.

Objective: This study aims to evaluate the effect of TM on QOL and psychological distress in adolescent girls with PCOS.

Methods: This study is a randomized controlled trial that will be conducted over eight weeks at the Women's and Children's Hospital in Adelaide, South Australia, to determine the effect of TM on QOL and psychological distress in adolescent girls (aged 12-20 years) with PCOS. A total of 40 girls will be randomized into either the TM (n=20) or control group (n=20). The TM group will be asked to practice TM in a comfortable sitting position with the eyes closed, for 15 minutes twice daily over eight weeks. The control group will be asked to sit quietly for 15 minutes twice daily for eight weeks. The primary outcomes are any effects on improving QOL and psychological distress, and the secondary outcomes are any effects on lowering blood pressure and salivary cortisol levels.

Results: The recruitment of study participants began in May 2019 and is expected to be completed by June 2020. It is expected that the adolescent girls with PCOS practicing TM over eight weeks will have a significant improvement in QOL and psychological distress compared to adolescents in the control group. Also, it is expected that adolescent girls in the TM group will have lower salivary cortisol levels and lower blood pressure.

Conclusions: This study will be the first to evaluate the effect of TM on QOL in adolescent girls with PCOS. The study will provide valuable information on a potential self-management strategy to improve QOL and well-being in adolescent girls with PCOS.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN1261900019010; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=376657&isReview=true

International Registered Report Identifier (IRRID): PRR1-10.2196/14542

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KEYWORDS

meditation; quality of life; polycystic ovary syndrome; adolescent

Introduction

Polycystic Ovary Syndrome

Polycystic Ovary Syndrome (PCOS) is the most common endocrine condition and affects 8-13% of women of reproductive age [1] and up to 6% of adolescent girls [2], depending on the diagnostic criteria used and the population studied [3-8]. Adolescent PCOS is characterized by irregular menstrual cycles and at least one of the following signs of hyperandrogenism (hirsutism, acne or hyperandrogenemia) [3-8]. PCOS is associated with increased weight, difficulties losing weight, insulin resistance, metabolic syndrome, infertility, and psychological distress (eg, depression, anxiety, and stress) [3,5,7-9].

Quality of Life in Polycystic Ovary Syndrome

Two systematic reviews have shown that women with PCOS have reduced quality of life (QOL) [9,10]. Women with PCOS are also at increased risk of psychological distress [5,7,8] and have reported higher scores in the Depression, Anxiety, and Stress Scale (DASS) questionnaire compared to women without PCOS [11]. Similarly, adolescent girls with PCOS are more likely to have anxiety and depression than age-matched healthy adolescents [12]. A mixed-methods study (including quantitative and qualitative data) showed that adolescent girls with PCOS are at an increased risk of depression [13]. Also, adolescent girls with PCOS have reduced QOL according to cross-sectional quantitative and qualitative studies [12,14,15].

General health and its perception, behavior, physical functioning, and the family activities domains of QOL are lower in adolescent girls with PCOS in comparison to healthy adolescents [12]. Specific symptoms of PCOS, such as hirsutism, excess weight, irregular menstrual cycles, and infertility problems, can affect QOL, as demonstrated by lower scores in the specific QOL questionnaire for PCOS [16]. Increased weight and body perceptions are essential contributors to reduced QOL as well as fears and concerns about future infertility [17,18]. In a Bulgarian study of women with PCOS, it was shown that hirsutism (predominantly in those <25 years of age), excessive weight gain, and infertility (in those >25 years of age) were independently associated with decreased QOL [19].

Strategies to Improve Quality of Life in Polycystic Ovary Syndrome

Most management strategies used in adolescent girls with PCOS have targeted symptoms such as irregular menstrual cycles, acne, and hirsutism, or have addressed excess weight and insulin resistance [5,7,8]. There are limited data directly evaluating interventions addressing psychological comorbidities in PCOS, such as reduced QOL and psychological distress [5,7,8].

In women with PCOS, there is increasing evidence for the role of complementary and alternative medicine [20] and self-management strategies, such as mindfulness-based stress reduction, in the management of stress, and improving QOL [21-23]. In adolescent girls with PCOS, however, there have only been two studies conducted that evaluated strategies to improve QOL [24,25]. One study was a small open trial with no control group that used cognitive behavioral therapy to target lifestyle goals, family functioning, and the effects of having PCOS [24]. This study showed a statistically significant improvement in health-related quality of life from a mean of 77 points (SD 20) from baseline to a mean of 82 points (SD 27) post-intervention [24]. In the other study, participants received a lifestyle modification program (ie, weekly discussions on nutrition and lifestyle changes and weekly structured group exercise sessions) that was associated with a significant improvement from 4.5 to 5.6 points on the specific QOL questionnaire for PCOS, which was calculated by averaging all domains of QOL related to PCOS [25].

Transcendental Meditation as a Strategy to Improve Quality of Life

Transcendental Meditation (TM) is a sitting meditation technique from ancient Vedic tradition that originated in India and has spread worldwide since the 1950s [26]. It is a well-established and easily practiced technique while sitting with the eyes closed in adults for 20 minutes twice daily, and in children for 15 minutes twice daily. The TM technique uses the sound value of a mantra to draw attention within the mind, leading to a relaxed but mentally alert state. Trained instructors taught TM in a standardized manner with careful attention to fidelity of the program by regular review sessions of the TM practice.

TM has been used in adults and adolescents to reduce stress in conditions such as cardiovascular disease and negative school behaviors [27-31]. Meta-analysis of stress reduction trials, including TM, has shown beneficial effects on stress and blood pressure in adults, with systolic and diastolic blood pressures of –4.26 mm Hg (95% CI –6.06 to –2.23) and –2.33 mm Hg (95% CI –3.70 to –0.97) respectively, compared to control groups [30,32], with increasing use recently [33]. Sitting meditation practices, including TM and mindfulness, may have

some beneficial effects in physiological, psychological, and behavioral conditions in children and adolescents [34]. Few randomized controlled trials in adolescents have demonstrated beneficial effects of TM on school behavior and blood pressure [27,35]. Also, TM has shown beneficial effects on cardiovascular outcomes, as measured by left ventricular mass index in a group of prehypertensive adolescents in comparison to the control group (–2.6 gm/ht$^{2.7}$ versus 0.3 gm/ht$^{2.7}$) [36].

To date, no trials have evaluated the effect of TM on women or adolescent girls with PCOS. This proposal aims to evaluate TM as a novel strategy, which is easy to implement once learned, to improve QOL and psychological distress in adolescent girls with PCOS using a randomized controlled trial.

Aims and Hypotheses

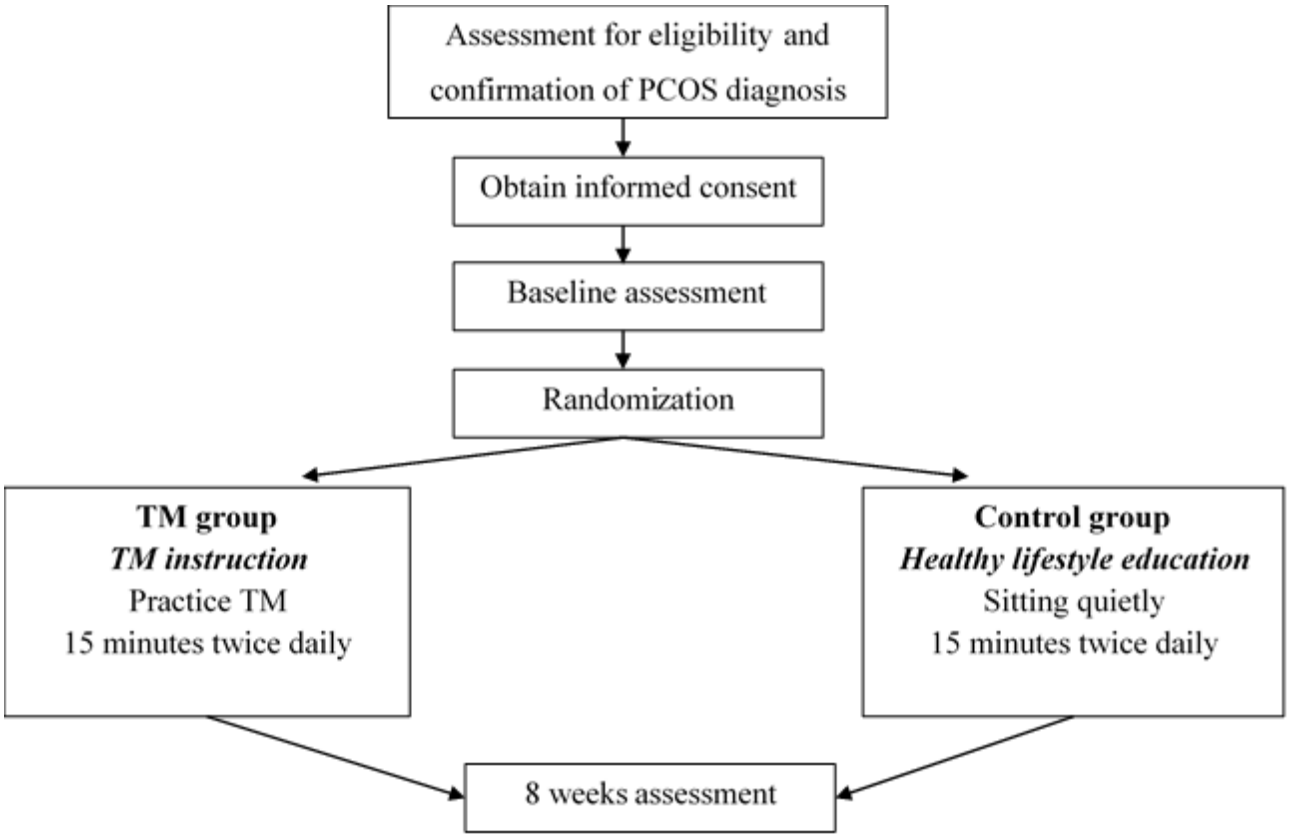
The primary objectives are to determine the effect of TM over eight weeks on QOL and psychological distress in adolescent girls with PCOS. The secondary objectives are to determine the effect of TM over eight weeks on salivary cortisol levels and blood pressure in adolescent girls with PCOS. We hypothesize that the adolescent girls with PCOS practicing TM over eight weeks will have a significant improvement in QOL and psychological distress in comparison to adolescents in the control group. We also hypothesize that those in the TM group will have lower salivary cortisol levels and lower blood pressure.

Methods

Study Design, Approval, and Registration

This is a randomized controlled trial that will be conducted over eight weeks at the Women's and Children's Hospital in Adelaide, South Australia. A flowchart of the study is depicted in Figure 1. The trial has been approved by the Women's and Children's Hospital Research Ethics Committee (HREC/18/WCHN/168, protocol version 2.0, dated January 11, 2019), and any modifications to the protocol will be sent to the Ethics Committee. This study has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619000190101).

Figure 1. Study design flowchart. PCOS: polycystic ovary syndrome.



Recruitment

A total sample of 40 adolescent girls, aged 12-20 years old and with a confirmed diagnosis of PCOS, as per the recent international evidence-based guidelines [5,7,8], will be recruited by authors from various outpatient clinics (adolescent gynecology and endocrine clinics, pediatric endocrine clinics, and gynecology clinics). These include clinics at the Women's and Children's Hospital in South Australia, from private gynecology clinics in South Australia, from the Polycystic Ovary Syndrome Association of Australia (POSAA) consumer support groups, Health consumer groups in South Australia, and the Women's and Children's Hospital consumer groups. If the adolescent is older than 16 years of age, written informed consent will be obtained from the adolescent. If the adolescent is under 16 years of age, written informed assent will be obtained from the adolescent, and written informed consent will be obtained from their parent/guardian. Participants can also either consent or not consent to the future use of study data in any other research project, provided the project has the approval

of the Women's and Children's Hospital Research Ethics Committee.

Inclusion Criteria

Each adolescent girl must meet the following criteria to be involved in this study: aged between 12-20 years old; diagnosed with PCOS according to the recent, international, evidence-based guideline of diagnostic criteria for PCOS, consisting of a clear definition of irregular menstrual cycles according to time post menarche and at least one of the following signs of hyperandrogenism (moderate to severe acne, hirsutism or hyperandrogenemia [high androgen levels]) after exclusion of other conditions that mimic PCOS [5,7,8]; for participants not recruited at the Women's and Children's Hospital, a review by the principal investigator (AP) will be done to confirm PCOS diagnosis as per recent guidelines [5,7,8]; on a stable medical regimen for at least the previous four weeks if on metformin or other hormonal therapy (contraceptive pill, medroxyprogesterone, or spironolactone); willingness and ability to participate in the TM instruction session and practice TM during the study; the willingness of one parent to be involved in facilitating and keeping a diary card of the TM or sitting activities in the control group.

Exclusion Criteria

Adolescent girls are excluded from the study if they meet any of the following criteria: significant coexisting chronic illness that may have a contributory effect on health-related QOL, such as diabetes (Type 1 or 2), gender dysphoria, or severe anxiety or depression treated with medications; psychological conditions, such as schizophrenia or bipolar disorder; high level of depression (DASS score>20), anxiety (DASS score>15), or stress (DASS score>26) as they will require immediate treatment; regularly practicing the TM or any other meditation/mindfulness program; substance use, as it will interfere with the TM practice; or inability to speak English.

Randomization

A randomization schedule was generated in Stata 15.1 (StataCorp, College Station, Texas, United States) by an independent statistician (SE). Randomly permuted blocks of size 2 or 4 and an allocation ratio of 1:1 (TM: control) was used. Unique identification codes and random group allocation will be generated for each participant. Sequentially-numbered, opaque, sealed envelopes containing each participants' group assignment will be created by a pharmacist not involved in the study. The allocation sequence will be unavailable to study investigators. Participants will be allocated to either the TM group or control group according to information contained in the sealed, opaque envelope. An envelope will only be opened after the participant has been enrolled and completed baseline clinical assessments. Analysis of the data will be performed by a statistician who was not involved in the initial randomization process (LG).

Participant Withdrawal

Any participant may withdraw from the study without giving a reason and without any disadvantage or interference with their care at their treating hospital. Reasons for withdrawal will be noted and reported.

Intervention

Transcendental Meditation

Participants allocated to the TM group will be asked to practice TM for 15 minutes, twice daily, for eight weeks. The instructional sessions for the TM technique will be delivered by a certified and experienced female teacher [37] at either TM Adelaide or the Adelaide South TM Centre in South Australia.

TM will be taught according to a standardized course. Before beginning this course, participants will be asked to attend a one-hour introductory presentation reviewing the origin of TM and the possible benefits of regular practice. The participant and one of the parents are required to attend this introductory session. If the participant is younger than 18 years of age, then the participant's parent will be required to provide a letter of support stating that they approve of their child's participation in the standardized course.

After the introductory presentation, there will be a one-on-one personal interview for the participant to provide the teacher with some basic information to aid in the personalization of their instruction (Table 1). On the first day of instruction, the participant will be given a personal mantra (sound or word) that will be used in every meditation. This sound will help draw attention within the mind, leading to a relaxed but mentally alert state. After the initial instruction, the participants will be instructed to practice TM for 15 minutes, twice daily, at home.

Following the personal instruction session, there will be check-up meditation sessions on three consecutive days during the first week and an additional day in week 2 to discuss the participant's experiences during meditation. This meeting will also assist with any practical issues encountered during practice, such as handling outside noise and timing of the meditation.

Practice review sessions will occur from weeks 3-6, where participants will be able to practice TM in a small group (Table 1). The TM teacher will reinforce the fidelity of the program by encouraging multiple practice review sessions after initial instruction and check-ups. Participants/parents will also complete a diary showing the frequency of meditation practice.

Table 1. Instruction, check-up, and practice review sessions for the transcendental meditation group.

Appointment	Timing	Activity	Duration
1	Day 1	Personal instruction to learn transcendental meditation	1 hour
2	Day 2	Check-up, including meditation	1 hour
3	Day 3	Check-up, including meditation	1 hour
4	Day 4	Check-up, including meditation	1 hour
5	Week 2	Check-up, including meditation	1 hour
6	Week 3	Practice review, including meditation	30 minutes
7	Week 4	Practice review, including meditation	30 minutes
8	Week 6	Practice review, including meditation	30 minutes

Control Group

Participants in the control group will be asked to sit comfortably for 15 minutes twice daily in a quiet room for eight weeks. Participants will be allowed to read a book, write, or listen to some music. The control group will receive a one-hour, healthy lifestyle education session and healthy lifestyle information via email/phone at similar times to the intervention group (Table 2). Participants/parents will also complete a diary, including sitting activities.

Table 2. Healthy lifestyle education session and information for the control group.

Appointments	Timing	Activity
1	Day 1	Healthy lifestyle education session (1 hour)
2	Day 2	Email or phone contact with healthy lifestyle information
3	Day 3	Email or phone contact with healthy lifestyle information
4	Day 4	Email or phone contact with healthy lifestyle information
5	Week 2	Email or phone contact with healthy lifestyle information
6	Week 3	Email or phone contact with healthy lifestyle information
7	Week 4	Email or phone contact with healthy lifestyle information
8	Week 6	Email or phone contact with healthy lifestyle information

Outcome Measures

Table 3 shows the primary and secondary outcomes that will be measured at baseline (preintervention) and eight weeks (postintervention) at the Women's and Children's Hospital.

Table 3. Primary and secondary outcome measures.

Outcome measure	Baseline	Eight weeks
Primary outcomes		
Pediatric QOL[a]	✓	✓
QOL related to PCOS[b]	✓	✓
DASS[c]	✓	✓
Secondary outcomes		
Salivary cortisol levels (3 samples over a day)	✓	✓
Blood pressure	✓	✓
Weight	✓	✓
Height	✓	✓
BMI[d]	✓	✓
BMI *z* score	✓	✓
Waist circumference	✓	✓
Hip circumference	✓	✓
Hirsutism score and acne score	✓	✓
Review of current symptoms and treatment	✓	✓

[a]QOL: quality of life

[b]PCOS: Polycystic ovary syndrome

[c]DASS: Depression, Anxiety and Stress Scale

[d]BMI: body mass index

Primary Outcomes

Quality of Life

General QOL will be assessed using the Peds QLTM 4.0 generic core scales [38]. The generic core scale consists of 23 items, which will be completed independently by participants and one of their parents. It includes four scales that measure physical, emotional, social, and school functioning.

Specific Quality of Life Questionnaire for Polycystic Ovary Syndrome

This questionnaire measures health-related QOL in PCOS over the previous two weeks. It consists of 26 items covering five domains (emotions, body hair, weight, infertility problems, and menstrual problems). Each item is graded with a 7-point scale ranging from 1 (maximum impairment) to 7 (no problems experienced) [16,25].

Depression, Anxiety and Stress Scale Questionnaire

This is a self-reported instrument that was designed to evaluate the three emotional states of depression, anxiety, and tension or stress [39]. This will also assist in the evaluation of the severity of symptoms to assess the eligibility of the participants.

Secondary Outcomes

Salivary cortisol levels will be measured as a marker of stress in adolescents [40]. Salivary cortisol will be collected with salivary cortisol sampling kits (Salivette). Specific instructions will be provided for proper collection. Three salivary cortisol samples will be collected as the cortisol levels change throughout the day (immediately after awakening in the morning, 30 minutes later, and before going to bed). Samples will be collected the day after baseline assessment and the day before the eight-weeks assessment. Salivary cortisol concentrations will be measured by IDS-iSYS Salivary Cortisol assay (Abacus ALS Pty Ltd, Queensland, Australia). Salivary samples will be deidentified before analysis. Salivary samples will not be retained for future use and will be put in the human biohazard bins for appropriate destruction immediately after completion of the analysis.

Also, weight will be measured in light clothing using a Tanita BC-418 segmental Body composition analyzer (Tanita, Tokyo, Japan). Height will be measured on a wall-mounted stadiometer (to 0.1 cm). Waist circumference will be measured with a flexible tape (0.5 cm) at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, and hip circumference will be measured around the widest portion of the buttocks, with the tape parallel to the floor, following World Health Organization guidelines [41]. Body mass index (BMI) percentiles and *z* score will be calculated using the EpiInfo database version 3.2.2 and the Centers for Disease Control and Prevention 2000 standardized reference charts [42]. Blood pressure will be measured using an automatic sphygmomanometer (Omron digital blood pressure monitor, Omron Healthcare, United Kingdom) with an appropriately sized cuff on the left arm, and the mean of 3 consecutive measurements will be recorded. We will also evaluate hirsutism using the modified Ferriman Gallwey score [43], and acne will be assessed using the Global Acne Grading System [44]. Finally,

a review of current symptoms and treatment will be documented at baseline and eight weeks posttreatment.

Adherence

Assessment of adherence to the study will be assessed using the diary that participants and parents complete about their time spent practicing TM or undertaking sitting activities. Also, the TM teacher will reinforce adherence to TM during check-up and practice review sessions.

Monitoring of Adverse Events

TM is a safe self-management strategy that has been used by many adults around the world, with rarely reported adverse events. These events occurred in individuals with severe psychiatric conditions, but participants with such conditions will be excluded from this study. TM practice can rarely cause mild headaches at the beginning if it is not done correctly. Teachers of the TM technique are trained to correct any difficulties with practice. Any adverse events noted will be reported to the ethics committee and documented.

Data Management and Statistical Analysis

Data collected during this study will be both hard copy (questionnaires and case report forms) and electronic (excel spreadsheets with participant's data) files. Hard copy data will be stored securely in the Department of Endocrinology and Diabetes at the Women's and Children's Hospital, and electronic data will be stored securely using password protected files. Documents will be retained for 30 years after study completion per current guidelines for data storage.

All data will be analyzed in the deidentified form. Statistical analysis will be performed using the intention-to-treat principle by LG, who will be blinded to the randomization status. A linear mixed-effects model will be used to compare the change in primary outcomes (QOL, specific QOL questionnaire for PCOS, and DASS questionnaires) and secondary outcomes (salivary cortisol levels and blood pressure) between the TM group and control group over the study period. The models will include a random effect for participants to account for the correlation between serial measurements within individual participants. Unadjusted and adjusted analyses will be conducted, with adjustment for important prespecified baseline covariates, including age and BMI (except for the analyses where BMI is the outcome).

While no studies have looked at the effect of TM on QOL in adolescent girls with PCOS, a change in QOL of 21.2 (SD 21.5) will be interpreted as clinically meaningful, as per our previous study in obese adolescents [45]. The sample size was calculated based on a change in QOL of 21.2 (SD 21.5) from baseline to 8 weeks in the TM group, compared to no change in the control group. Therefore, we would require 40 adolescent girls (20 in each treatment group) to have 80% power to detect a difference in the primary outcome of QOL between the TM group and control group (assuming alpha=0.05, and a two-sided statistical test), allowing for 10% attrition based on rates in previous studies that included adolescents in our center [46]. The sensitivity of the effect estimates to missing values will be evaluated using multiple imputation. Analyses will be conducted according to a pre-specified analysis plan using Stata version 15.1 (StataCorp, College Station, Texas, United States).

Results

Recruitment started in May 2019 and is expected to be completed by June 2020. It is expected that adolescent girls with PCOS practicing TM over eight weeks will have a significant improvement in QOL and psychological distress compared to adolescents in the control group. Also, it is expected that adolescent girls in the TM group will have lower salivary cortisol levels and lower blood pressure. The results from this trial are anticipated to be published by September 2020.

Discussion

PCOS is the most common endocrine condition affecting women of reproductive age and is associated with many comorbidities, which contribute to impaired QOL and increased psychological distress [3,5,7,8]. Currently, health care professionals have limited strategies to offer to improve the well-being of this population beyond hormonal and metabolic treatments. Evaluating the efficacy of a novel sustainable strategy in the management of PCOS will assist in the overall management of this condition from adolescence and into young adulthood, as once this strategy is learned, it can be practiced for life. Although studies are suggesting that mindfulness may have a role in improving QOL in women with PCOS, there are no studies conducted in adolescents and no studies of TM in women or adolescents with PCOS.

To our knowledge, this is the first study evaluating the effect of TM on QOL and psychological distress in adolescent girls with PCOS. The current study will evaluate a simple, translatable strategy to improve QOL and well-being in adolescent girls with PCOS. TM will be easy to implement in the long term, with no additional costs once the strategy has been learned. This intervention can also be potentially taught in schools as part of classroom activities.

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Conflicts of Interest

None declared.

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Abbreviations

BMI: Body mass index
DASS: Depression, Anxiety and Stress Scale
PCOS: Polycystic ovary syndrome
QOL: Quality of life
TM: Transcendental Meditation

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Protocol

Design and Development of a Viral Hepatitis and HIV Infection Screening Program (Hprolipsis) for the General, Greek Roma, and Migrant Populations of Greece: Protocol for Three Cross-Sectional Health Examination Surveys

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Abstract

Background: Although infectious diseases are globally on the decline, they remain a major global public health problem. Among them, the hepatitis B virus (HBV) or hepatitis C virus (HCV) and HIV infection are of primary interest. Valid prevalence data on these infections are sparse in Greece, especially for vulnerable populations.

Objective: This study aimed to present the design and methods of Hprolipsis, an integrated viral hepatitis and HIV screening program administered to adults (≥18 years) from the general, Greek Roma, and migrant populations. Its aims were to estimate the prevalence of HBV, HCV, and HIV; assess infectious disease knowledge level; design, implement, and assess population-specific awareness actions; and offer individual counseling and referral when indicated and HBV vaccination to susceptible Roma and migrants.

Methods: Multistage, stratified, random sampling based on the 2011 Census was applied to select the general population sample, and nonprobability multistage quota sampling was used for Roma and migrant sample selection. Trained personnel made home (general population) or community (Roma and migrants) visits. Collected blood samples were tested for Hepatitis B surface Antigen, Hepatitis B core Antibody, Hepatitis B surface Antibody, Hepatitis C Antibody, and HIV 1,2 Antibody. The surveys were conducted during May 2013 and June 2016. To estimate an HCV prevalence of 1.5% with 0.3 precision, the required general population sample size was estimated to be 6000. As migrants constitute 10% of the whole Greek population, the migrant sample size was set to 600. A feasible sample size of 500 Greek Roma was set.

Results: In total, 6006 individuals from the general population (response rate 72%), 534 Greek Roma, and 612 migrants were recruited. Blood test results are available for 4245 individuals from the general population, 523 Roma, and 537 migrants.

Conclusions: Hprolipsis is the first nationwide survey on HBV, HCV, and HIV. Its results will enhance our understanding of the health needs and disease burden of these diseases in the 3 studied populations. Its implementation provided useful recommendations for future studies, particularly in vulnerable populations.

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KEYWORDS

hepatitis; HIV; Greek general population; Greek Roma; migrants; health examination surveys

Introduction

Background

Although infectious diseases are on the decline globally, they are still of major public health importance, imposing significant burden on global economies and public health [1]. Among them, hepatitis B virus (HBV) or hepatitis C virus (HCV) and HIV infection are of particular interest in developed countries owing to their prevalence and associated disease burden.

In 2015, about 257 million people were living with chronic HBV infection and 71 million people with chronic HCV infection globally [2]. An estimated 36.7 million people worldwide were living with HIV at the end of 2015 [3]. Currently, highly effective therapies for HCV and long-term therapies for HBV and HIV infections are available. However, owing to their usually long asymptomatic period, only a minority of those infected with one of these viruses are aware of their infection, lacking thus the opportunity to take advantage of new treatments [4]. Delayed diagnosis has harmful implications not only for individual patients but also for public health owing to the ongoing viral transmission from undiagnosed incidents. The World Health Assembly, in 2016, introduced a global strategy for achieving viral hepatitis elimination by 2030 (reduce incidence by 90% and mortality by 65%) [5]. In addition, the Joint United Nations Programme on HIV and AIDS targets to curb the HIV epidemic by 2020, including diagnosis of 90% of those living with HIV, treatment of 90% of those diagnosed, and achieving viral suppression of 90% of those treated [6]. Valid estimates on prevalence, infection awareness, treatment uptake and the knowledge for HBV, HCV, and HIV are necessary to plan and implement effective prevention programs.

In Greece, until recently, estimates for HBV and HCV prevalence were derived from studies restricted to specific population groups (eg, patients undergoing hemodialysis, people who inject drugs, men who have sex with men, and blood donors) [7-11]. In 2015, a telephone survey was conducted in a representative sample of adults living in Greece. On the basis of self-reports, the (age-adjusted) prevalence (95% CI) of chronic HBV and HCV was estimated as 2.39% (1.88%-2.91%) and 1.79% (0.97%-2.61%), respectively [12]. Trends in HIV diagnosis are reported by the HIV/AIDS surveillance system operated by the Hellenic Centre for Disease Control and Prevention (HCDCP), but delayed diagnosis, duplicates, or missing information on key characteristics of the infected population cannot be ruled out [13].

Vulnerable populations, such as the Greek Roma and migrants, constitute special target groups since their adverse living conditions facilitate the spread of infections. Although data on Roma health are sparse and fragmentary, Roma communities appear to have unequal access to health services, high morbidity, especially regarding infectious diseases, and insufficient immunization compared with that of the general population [14,15]. The combination of increased risk factors for infectious diseases and lack of appropriate models for reaching, engaging, and informing Roma communities raises serious public health concerns [16,17]. In a recent study conducted in Slovakia, it was found that the Roma population has a higher prevalence of HBV compared with non-Roma populations [18]. In Greece, only a small proportion of Greek Roma is integrated into mainstream society, whereas the vast majority lives marginalized on the outskirts of inhabited areas [19]. The few available studies on Roma health have shown that they have been experiencing a higher prevalence of infectious diseases [20], lower vaccination coverage [21,22], and higher relative mortality from infectious diseases compared to non-Roma Greeks [23].

Migrants are another population group with increased incidence of infectious diseases. In Europe, migrants accounted for 40% of newly reported HIV cases between 2007 and 2011 [24]. The migration process itself increases the risk of infectious diseases [3]. Migrants are more likely to be exposed to social factors associated with poor health such as poverty and unemployment; they may face social exclusion, whereas legal and administrative issues may pose additional barriers to access to health services [3,25]. It has been shown that migrants infected with infectious disease are diagnosed later than native populations, limiting their treatment options and increasing the probability of transmission [3,25,26]. In Greece, data on viral hepatitis among migrants are limited; only new HIV diagnoses are reported to the HIV/AIDS surveillance system of the HCDCP.

Taken together, accurate data on the prevalence, awareness rates, treatment uptake, and knowledge related to HBV, HCV, and HIV in the general population and especially among specific vulnerable populations are currently lacking in Greece. To fill this gap, the Hprolipsis Survey, a Design and Development of Viral Hepatitis and HIV Infection Screening Program in the General Population and Vulnerable Populations, was set up. Hprolipsis, combining questionnaire data on health determinants, living conditions, high-risk behaviors, and knowledge on viral hepatitis and HIV with results from serological testing, provides a unique opportunity to study HBV, HCV, and HIV. It focused on 3 target populations: adult general population, Greek Roma,

and migrants. Experience gained through Hprolipsis implementation could provide valid guidelines for future studies. In this paper, we describe the design and methodology of Hprolipsis, and we discuss the challenges associated with organizing and implementing such a study focusing on difficult to reach populations, such as the Greek Roma and migrants.

Objectives of the Study

This study aimed to assess access to the public health care system; estimate the prevalence and determinants of HBV, HCV, and HIV infection in the 3 target populations; design and implement population-specific awareness-raising actions; offer anti-HBV vaccination to susceptible Greek Roma and migrants study participants; and offer individual counseling and referral to health care services for all individuals who were tested positive for any of these infections.

The specific objectives of the study were as follows:

1. To estimate HBV, HCV, and HIV prevalence and cascade of treatment in the 3 studied populations.
2. To assess knowledge level and effectiveness of the awareness-raising activities.
3. To investigate barriers and facilitators to access to care.
4. To provide counseling—referral to individuals who tested positive for any of these infection.
5. To offer HBV vaccination to susceptible individuals in vulnerable populations.

Methods

Study Design

Hprolipsis consists of 3 cross-sectional epidemiological surveys of 3 adult (≥18 years) populations: (1) the general population, (2) Greek Roma, and (3) migrants. It was funded by the European Union's (EU) structural funds and national resources, coordinated by the Department of Hygiene, Epidemiology, and Medical Statistics of the Medical School of the National and Kapodistrian University of Athens (NKUA), and conducted in cooperation with all the other Greek medical schools, the MSc International Medicine—Health Crisis Management of the Medical School of NKUA, and the nongovernmental organizations (NGOs) Doctors of the World Greek delegation and PRAKSIS. Hprolipsis was initiated in May 2013 and completed in June 2016. The general population survey was nested within the National Survey of Morbidity and Risk Factors (EMENO) health examination survey; EMENO aimed to investigate morbidity (focused on cardiovascular and respiratory diseases) and associated risk factors in the general adult population, which have been described in detail elsewhere [27].

Sampling Strategy

For the general population, a multistage stratified random sampling based on the 2011 Census was applied (for a detailed description of the sampling strategy, refer to the study by Nikolaidis et al [27]); the target sample size was 6000 individuals, allowing us to estimate a 1.5% prevalence of anti-HCV with 0.3% precision [23]. Nonprobability multistage quota sampling was applied to select Greek Roma and migrant populations.

Greek Roma Population

In the Greek national context, the Roma are Greek citizens who are not officially recognized as a national or linguistic minority. Thus, little reliable data about the Roma in Greece have been collected. Estimates of Roma populations in Greece range from 120,000 to 300,000 [22]. Greek Roma populations live mainly in 4 settlement types: (1) houses dispersed among the majority population, (2) settlements with houses, (3) settlement/camps with houses and shacks (mixed), and (4) shacks. For the purposes of this program, those living in houses dispersed among the majority population were excluded as they would be part of the general population survey. Balancing the available financial resources and feasibility/difficulty of running a health survey in Greek Roma settlements, the target sample size was set at 500 adults. To increase the representativeness of the sample, a 3-stage procedure was adopted.

Stage 1

An effort was made to collect and synthesize information on Greek Roma settlements by type of settlement and relevant population, and general living conditions in the camps. Data were collected from the Ministry of Interior, Greek Roma organizations, and the relevant literature.

Stage 2

On the basis of data retrieved from stage 1, 4 geographical regions were selected: Peloponnese (Western Greece), Thessaly (Central Greece), and Central Macedonia (Northern Greece) as regions with higher Greek Roma numbers [17], and Attica as the largest urban center in Greece. In each selected geographical region, areas representative of the 3 settlement types (houses, mixed, and shacks) were selected. Selected settlements were visited by specialists (social and/or health scientists), and the population demographics as well as the general living conditions in each selected settlement were recorded.

Stage 3

To increase the power of investigating potential differences by geographical region, we recruited the same number of people in each region (135 adults per region). Within each region, the recruited number of people from each type of settlement was broadly proportional to its size (Table 1) as recorded by the study staff (stage 2). Adults (≥18 years) from the selected settlements were invited to participate in the study. Only 1 adult from each family could participate. An effort was made to reflect in our sample the actual sex and age distribution of the settlement as recorded in stage 2 (ie, the required number of men and women by 10-year age groups was predefined).

Table 1. Planned and achieved Greek Roma population sample per region participating in the study and settlement type.

Selected settlements and settlement type	Houses	Families per household	Persons per household	Planned sample	Final achieved sample
Attica					
ST[a] 1[b]: Acharnes	300	2 to 3	5 to 10	45	45
ST 2[c]: Ano Liosia	300	2 to 4	5 to 8	45	43
ST 3[d]: Aspropyrgos	200 to 300	2	8	45	46
Region total	800 to 900	2 to 4	5 to 10	135	134
Western Greece					
ST 1: Kato Achaya	2000	1	9	95	93
ST 2: Sagianeika	150	3	20	30	20
ST 3: Riganokampos	20	3	15	10	30
Region total	2170	1 to 3	9 to 15	135	143
Thessaly					
ST 1: Nea Smyrni	400	1 to 3	5 to 10	53	54
ST 2: Tyrnavos	400	1 to 3	5 to 8	53	54
ST 3: Farsala	150 to 200	1 to 3	5 to 10	29	30
Region total	950 to 1000	1 to 3	5 to 10	135	138
Central Macedonia					
ST 1: Dendropotamos	500	2 to 3	6 to 10	45	36
ST 2: Agia Sofia	300	2 to 3	8 to 10	45	42
ST 3: Peraia	65 to 70	1 to 2	4 to 5	30	26
ST 3: Chalastra	20	1 to 2	5 to 8	15	15
Region total	885 to 890	1 to 3	4 to 10	135	119
Total	4805 to 4960	1 to 4	4 to 10	540	534

[a]ST: settlement type.

[b]ST 1: settlement with houses.

[c]ST 2: settlement with houses and shacks (mixed).

[d]ST 3: settlement with shacks.

Migrant Population

Lack of reliable data on the composition of migrants and their high mobility during the study period made it very difficult to select a random sample. To reduce the sampling error, it is recommended to approach migrants through multiple sources [22,28].

Migrants were defined as those who were born in another country. Excluded were those who originated from the EU-15 countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and United Kingdom), Norway, Switzerland, the United States, and Canada. Inclusion criteria were (1) aged 18 years or older at recruitment and (2) living in Greece for at least 6 months (self-reported); thus, new arrivals and/or those living in shelter camps were excluded to avoid confusing data on health care access. To select the sample, a 2-stage procedure was followed.

Stage 1: Preparation Phase

All available data from the Ministry of Interior, Asylum Service of the Ministry of Migration Policy, relevant literature, as well as data from the Hellenic Statistical Authority (ELSTAT) were reviewed. As undocumented migrants are likely to be unrepresented in the Ministry of Interior and Asylum Service of the Ministry of Migration Policy datasets, the most reliable data were considered those reported by the ELSTAT based on the 2011 Census. According to that census, the number of those born abroad was 911,929 persons, thus consisting of approximately 10% of the total population living in Greece. To keep the sampling fraction similar to that in the general population (about 10% of the total population), the required sample size was set as 600 adults. The distribution of the region of origin of migrants based on the 2011 Census is presented in Table 2. Most migrants originated from Albania. Albanians migrated to Greece in late 90s to early 2000s, and currently most of them are well integrated into Greek society; thus, they are expected to be included in the general population survey. As this survey focused on the most vulnerable populations, it

was decided to underrepresent those who originated from Albania (planned percentage 33.0% vs 54.7% in the population of migrants in Greece) and overrepresent those from regions more likely to be part of current migration flows, namely those originated from Africa and Asia (planned percentage 46.0% vs 21.0% in the population of migrants in Greece). The planned sample and the final achieved sample by region of origin are presented in Table 2.

Table 2. Planned and achieved migrant population sample according to country of birth.

Description	Proportion in the total adult population based on 2011 Census (%)	Planned number and proportion in the sample, n (%)	Achieved number and proportion in the final sample, n (%)
Country's total migrants[a]	100.0	600 (100.0)	612 (100.0)
Countries members of EU[b]	17.4	90 (15.0)	67 (10.9)
Non-EU European countries (except Albania)[c]	6.4	36 (6.0)	53 (8.7)
Albania	54.7	198 (33.0)	159 (26.0)
Africa	3.2	90 (15.0)	145 (23.7)
Asia	17.8	186 (31.0)	187 (30.5)
Other (Caribbean, South or Central America, Oceania)	0.5	N/A[d]	1 (0.2)

[a]According to our inclusion criteria: adults (≥18 years), excluded those who originated from the EU-15 countries, Cyprus, Norway, Switzerland, the United States and Canada.

[b]EU: European Union.

[c]According to our inclusion criteria, those who originated from Norway and Switzerland were not included.

[d]N/A: not applicable.

Stage 2: Recruitment of Participants

A comprehensive mapping of NGOs and refugee and migrant communities was made. A network of NGOs and especially of migrant communities was set up, and the survey's aims were disseminated to them. To implement the migrants' survey, an official collaboration with the 2 largest NGOs serving migrants in Greece was set up: Doctors of the World Greek delegation and PRAKSIS. These NGOs run open polyclinics in 4 large cities/regions in Greece where the majority of migrants live: Athens-Attica (Doctors of the World and PRAKSIS), Patra-Peloponnese, Western Greece (Doctors of the World), Thessaloniki-Central Macedonia, Northern Greece (Doctors of the World and PRAKSIS) and Chania-Crete (Doctors of the World), and Southern Greece (Doctors of the World). Eligible migrants attending the polyclinics were invited to participate in the study. As those attending polyclinics may have different characteristics from those in the reference population, eligible migrants were also invited through their communities to visit polyclinics on specific days and time.

Questionnaire Development and Measurements

A steering committee (SC) consisting of experts in epidemiology, medical statistics, virology, internal medicine, hepatology, and the representatives of the collaborating NGOs, migrants, and Greek Roma communities was set up to develop survey instruments. For the questionnaire, items previously validated were used, whenever possible. For that, an extensive systematic literature review was conducted. New questions were formulated by the SC. Two different questionnaires were created, for interviewers and physicians, with 3 different variations for the 3 target populations.

The Hprolipsis interviewers' questionnaire involved the following sections: (1) basic demographics, (2) socioeconomic situation, (3) addictive substances usage (smoking habits, alcohol consumption, and drug use), (4) medical history, (5) eating habits focusing on Mediterranean diet adherence, (6) a short 4-item questionnaire for evaluating symptoms of anxiety and depression, (7) use and access to public health services, (8) knowledge assessment of HBV, HCV, and HIV/AIDS, (9) sexual behavior, and (10) risky behaviors related to infectious diseases. A detailed description of questionnaire items can be found in Multimedia Appendix 1. The interview mode adopted was a computer-assisted personal interview, aided by self-administered laminated cards for the most sensitive questions (eg, sexual behavior). The vast majority of the questions were close ended. All items were administered to all 3 study populations (apart from the anxiety and depression questionnaire that was not included in the migrants' survey). Nevertheless, verbal modifications were made to adapt to each population's culture. In addition, population-specific questions were added to the Greek Roma and migrant questionnaires; these were related to living conditions or legal status (for migrants). An additional settlement-specific short questionnaire on the status of the settlement (distance from main roads, water, and electricity supply, etc) was also developed and administered to Greek Roma local representatives.

The physicians' questionnaire included general information about blood sampling procedure (visit outcome, place, and duration) and specific exclusion for blood sample draw criteria. Collected blood samples were tested for the following serological markers anti-HIV-1/2, anti-HCV, HBsAg, anti-HBc, and anti-HBs. Study standardized operating procedures (SOPs) were developed containing information on health surveys,

sampling procedure, interview techniques, detailed guidelines on filling each questionnaire item, and collection and management of blood samples.

Survey questionnaires were tested and validated (time, clarity of questions, comprehensibility, etc) in 30 volunteers from the general population [27], 4 Greek Roma volunteers, and 4 migrant volunteers from each cooperating NGO. Feedback from questionnaire testing led to minor modifications/corrections where necessary.

Ethics

Hprolipsis was approved by the Ethics Committee of the NKUA (date: March 4, 2015, protocol: 6141); the general population EMENO survey was approved by the same ethics committee (date: November 8, 2012, protocol: 1742) and by the Hellenic Data Protection Authority (date: December 7, 2012, protocol ΓΝ/ΕΞ/1069-1/07-12-2012).

All participants were given the time to carefully read the participant information and consent forms (PICF) and to ask relevant questions before they signed it. For Greek Roma participants, the PICF was linguistically simplified; usually, interviewers read it to the eligible adults. Cultural mediators were available, too. The migrants' PICF was available in 9 languages (Greek, English, French, Albanian, Romanian, Farsi, Urdu, Arabic, and Bengali). An interpreter was available, when necessary. Consent from migrants was provided by ticking the corresponding icon in the computer-assisted personal interview questionnaire. Consent was confirmed in writing by the physician and another person (NGO staff or study interviewer or migrant community representative or interpreter) during the signature procedure. This procedure was adopted to avoid paper-signed PICF being a potential barrier to participation, particularly for undocumented migrants [28].

A combination of digits demonstrating the population, region, interviewer, and serial number of the participant were used to prepare barcodes with unique individual codes. Barcodes were attached to all forms and questionnaires, referral forms for blood examinations, and aliquots. For aliquots, specific deep-freeze barcodes were used. Personal data and their associated individual code were safely stored in a separate file. Only physicians and coordinators of each population/area had access to these data which were used only to send thank-you letters, medical reports, and to facilitate linkage to the public health care system when needed.

Before any field work began, all researchers and physicians signed a confidentiality form, and prophylactic vaccination against HBV was recommended.

Implementation of the Study

Researchers' Training

Training materials on data collection through questionnaire, sampling, and blood collection were developed by the SC. All training materials were available on an electronic database, accessible by all researchers. For the general population, a 2-day training program was organized on September 12 and 13, 2013 [27]. For the Greek Roma and migrant populations, 2 training seminars took place on November 11, 2014, and October 23, 2014, respectively. All study staff (coordinators, interviewers, physicians, and intercultural mediators), as well as collaborating NGOs and Greek Roma and migrant communities' representatives participated in the course. The training course included information on the purpose and objectives of the study; the study design; portable computer usage; instructions on how to fill out questionnaires; and guidelines for blood sampling, storage, and administration of blood samples.

Information System

A total of 2 database-driven Web applications were developed for each population. One application was installed on each interviewer's laptop (for the general and Greek Roma populations) or tablet (for the migrant population), whereas the other one resided on a private server. The central databases were hosted on the central server, located at the Department of Hygiene, Epidemiology, and Medical Statistics of the Medical School of the NKUA. To achieve secure access and use of data, each database on the laptops/tablets was synchronized with each database on the central server over a private network, and local data (from laptops/tablets) were eventually deleted. Personal data (names and contact details of the participants) were saved in a separate file of the database, and the participant's code was used to connect all available information.

All data-related operations were made through secure transactions encrypted with 128-bit encryption, and compliance to atomicity, consistency, isolation, and durability was maintained in both databases of each population to ensure that all previously described operations were consistent, isolated, and durable.

Field Study Implementation

General Population

The principal investigator of each collaborating medical school was responsible for the field study in the nearby regions. The whole study was piloted in a sample of 160 adults from urban and rural areas, and study materials were adjusted when necessary. Study aims were disseminated through several means including central and local press conferences, advertisement in newspapers and on TV, informing meetings with local authorities, events in central locations near the sampling points, social media, and through the Hprolipsis website [29].

A letter was sent to the local police stations about the study procedure, and a notification letter was left in each house if the owner was not present at the researcher's visit. Following study standardized operating procedures, an adult was randomly chosen from all adults living in eligible households (ie, the one with the most recent birthday). After providing signed inform consent, an interview took place in the participants' houses during the scheduled appointments. Following the interview, physicians made house visits for blood sample collection. In some rural areas, blood sample collection took place at nearby health centers. A separate informed consent was required for testing blood for viral HBV and HBC and for testing for HIV. A more detailed description of the field study implementation in the general population is provided elsewhere [27].

Greek Roma

To reach Greek Roma populations, the most important step was to develop trust relationships. To do so, several steps, inspired by the document "A practical guide for implementing health promotion activities with the Roma people [30]," were taken: (1) cultural mediators, preferably living in the selected settlements, were recruited; in most settlements, 2 mediators (1 man and 1 woman) were employed to ensure communication with both male and female participants; (2) initial visits with Greek Roma community leaders facilitated by the cultural mediators were organized in the selected settlements to inform them about the study and its aims; (3) health care services provision in the involved communities, such as dental, pediatric, and ophthalmological preventive examinations were organized before and during the field study, in collaboration with various governmental organizations and NGOs (The Smile of the Child, Therapy Center for Dependent Individuals [KETHEA], Exelixis, Athens University School of Dentistry, etc); and (4) in collaboration with The Smile of the Child, children's clothes and toys were distributed.

Special information leaflets based on pictures and using simplified language were printed and distributed in the participating settlements to inform the community about the study aims and procedures. In collaboration with cultural mediators and Greek Roma community representatives, appropriate private places for interviewing and blood sample collection were identified in each selected settlement. Trained interviewers and physicians along with the cultural mediators visited the settlements several times, and cultural mediators invited people to participate. An effort to keep the predefined age and gender distribution of the participants was made. Physicians provided additional medical advice if requested.

Migrants

Initially, migrant communities and NGOs working with migrants were informed about the survey. Informative material was developed in 3 languages (Greek, English, and French) and was disseminated at the offices of the Doctors of the World Greek delegation and PRAKSIS, as well as in migrant communities and other relevant NGOs. Several events were organized in collaboration with migrant communities to further disseminate study aims and procedures. Social media was also used. In each polyclinic, an isolated office was chosen for interviewing and blood sample collection. Study interviewers and physicians visited polyclinics on prespecified dates and times and invited migrants to participate. In certain cases, interviewing took place in migrant communities' offices. In such cases, an appointment was arranged in the nearby polyclinic for blood sample collection. To facilitate communication with potential participants, interpreters were employed.

Blood Sample Management

Blood sampling protocol determined the procedure of collection and preservation of blood samples. Blood samples were kept in a cold environment (at 4°C) until transported, within 12 to 18 hours, to collaborating local laboratories for centrifugation. Centrifuged samples were stored at –80°C. All samples were sent to the central laboratory (National Retrovirus Reference Center, Department of Hygiene, Epidemiology, and Medical Statistics of the Medical School of the NKUA) for analysis.

Medical Notification/Counseling

To general population survey participants who tested negative for HBsAg, anti-HCV, and anti-HIV-1/2, a thank-you letter and a copy of their blood test results along with the physician's report (with corresponding recommendations) based on their personal medical findings were mailed. Participants who were notified if they had acquired or vaccine-induced anti-HBV immunity. Individuals susceptible to HBV were advised to be vaccinated. Participants who tested positive for HBsAg and/or anti-HCV and/or HIV-1/2 were contacted via telephone by a specialized physician. Individual counseling was provided, and medical referral was offered by organizing an appointment at a clinic belonging to a network of liver and infectious diseases public clinics set up at the beginning of the survey.

Participating Greek Roma settlements were visited several times to disseminate blood test results and to provide individual counseling and offer/organize referral when necessary. The whole procedure was set up carefully to ensure confidentiality of results. Migrant participants were called, and an appointment was arranged to disseminate blood test results and offer/organize referral for those with positive results. For those who did not respond to several attempts, an effort was made to get in contact with them through their communities or the collaborating NGOs. The turnaround time of results was around 3 months for the general population and 2 months for migrants and Greek Roma.

Hepatitis B Virus Vaccination

HBV susceptible individuals from Greek Roma and migrants' communities were offered the anti-HBV vaccine. To increase adherence to vaccination, a short vaccination scheme (first dose: day 0; second dose: 4 weeks; third dose: 16 weeks) was adopted (Multimedia Appendix 2). All susceptible individuals were informed, and the vaccine was offered to those who agreed and had no contradictions (ie, serious allergy to the components of the vaccine and acute febrile illness). Vaccination was performed in the participating settlements for Greek Roma and in the collaborating NGOs polyclinics for migrants.

Study Promotion and Awareness Activities

Before study initiation, study dissemination/promotion activities took place as described above. After field study completion, awareness activities were implemented with an aim to improve the knowledge level of HBV, HCV, and HIV infections and to promote safe sexual behaviors. Population-specific awareness models were developed and implemented. All activities took place after field study completion to allow us to evaluate their effectiveness.

Population-specific brochures on transmission routes, testing, and treatment opportunities were developed. Greek Roma brochures were based on simple illustrative sketches (provided by the Spanish NGO Salud Entre Culturas) with minimal text, whereas the ones for migrants combined illustrative drawing (created pro bono by the painter Venetia Psara) with minimal text in 9 languages (Greek, English, French, Albanian, Romanian, Farsi, Urdu, Arabic, and Bengali).

For the general population, awareness actions included: (1) television and radio spots design and creation, once approved by the National Council for Radio and Television, these were distributed to all TV channels and radio stations; the main idea was around the concept *you cannot see/hear it, but it exists*; (2) informative events organized in collaboration with participating municipalities; (3) in some regions, events in high school were organized in collaboration with corresponding municipalities and school directors.

Actions in Greek Roma took place in the participating settlements and involved all community. They included (1) projection of specially created audiovisual material (short video) on hygiene behaviors, (2) distribution of usable items (wristbands with a message, condoms, etc), (3) implementation of experiential games targeting stereotype elimination and perceptions and increasing knowledge. Actions for migrants included (1) disclosure of usable items (identity card-certificate card with logo, message-wristbands, key chains, and condoms) and (2) information events in both Greek and English at the Doctors of the World Greek delegation and PRAKSIS, as well as in migrant communities. Information events were also organized for migrants with drug addiction in at the KETHEA organization and for homeless migrants at the Municipality of Athens. Where necessary, interpreters were present to relay information in the participants' native language (eg, Ukrainian).

Assessment of Awareness Activities

The effectiveness of awareness actions was evaluated in the general and Greek Roma populations. The high mobility of migrants during the field study period (2015-2016) made it difficult, if not impossible, to reach the participants after all field study (including vaccination) had been completed; thus, the effectiveness of the awareness actions was not evaluated in this population. A questionnaire was developed that included the following sections: (1) basic demographic information; (2) all questions about knowledge and attitudes on infectious diseases under investigation that were included in the main study; and (3) questions evaluating the experience and satisfaction of participants from all stages of the study. Of the initial sample, 10% (ie, 600 individuals) of the general population was selected via systematic stratified sampling; participants in each region were ranked in ascending order based on their barcode, and 1 out of every 10 participants was selected. To ensure randomness and representativeness of the evaluation sample, the starting point varied by region: in one region, the selection procedure started from the smallest barcode, in the next from the second smallest and so on.

In the Greek Roma population, awareness actions were evaluated by visiting the selected settlements. A total sample of 100 individuals, equally distributed among the regions, was selected, that is, 25 individuals from each of the 4 regions participated in the evaluation study. The same procedure as for the general population was applied to select the subsample, although 1 every 5 individuals of the initial sample was selected.

The effectiveness of awareness activities was assessed by comparing the knowledge and attitudes score (derived by relevant questions) before and after the implementation of the awareness activities in the subsample of the general and Greek Roma study populations.

Cost

The total study implementation cost was around €772,000 (about €108 per participant). Total cost was distributed as 64% for personnel (academic and research); 20% for reagents; 5.2% for blood sample collection materials, transfer, and storage; 6.8% for study promotion and awareness activities materials; 2.7% for HBV vaccines; and 1.3% for portable computers and/or tablets for interviewing.

Statistical Analysis

The general population survey had a complex study design, with varying sampling fractions across regions. Thus, for the statistical analysis, sampling weights, being reciprocal of the probability of selection, will be applied. In addition, to adjust for potential discrepancies between the sample age and sex distribution and that of the reference population recorded in the 2011 Census, poststratification weights should be applied. As not all interviewed individuals provided blood samples, inverse probability weighting or multiple imputation methods could be applied to adjust for potential selection bias in all analysis involving the blood test results. A more detailed description of the statistical analysis for the general population survey is provided elsewhere [27].

The lack of sampling frame for vulnerable populations (Greek Roma and migrants) leads to a conventional sample. Initial analysis of Greek Roma and migrant data will be crude, ignoring deviations from the initially desired distributions. In the second stage, weighted analysis will be applied to adjust for such deviations.

Statistical analysis of the data is underway, and the first results are expected to be submitted during 2020. Questionnaire data will be combined with blood test results; the statistical analysis will focus on (1) prevalence estimates and treatment cascade of the investigated infections in the 3 study populations; (2) testing frequency and associated factors; (3) knowledge level and its determinants; (4) assessment of awareness-raising activities; and (5) access to health care and its determinants. For vulnerable populations, living conditions will also be investigated.

Results

Distribution of Study Samples

In total, 6006 individuals from the general population, 534 Greek Roma, and 612 migrants were recruited. The overall response rate for interviewing in the general population was 72.0%. The distribution of the final achieved sample compared with the planned one for Greek Roma is presented in Table 1 and for the migrant population in Table 2. Compared to the planned sample, settlements with houses and settlements with houses and shacks were slightly underrepresented, and settlements with shacks were slightly overrepresented in the final achieved Greek Roma survey. In the migrant sample, Albanians and those who originated from Europe were to some degree underrepresented, and those from Africa and Asia were

overrepresented in the final achieved sample compared with the planned sample.

Demographic Characteristics of Study Participants

From the 6006 individuals of the general population, 13 refused to provide their age, and as this variable is necessary to compute poststratification weights, all results provided were restricted to the 5993 participants with available age. Descriptive characteristics of the 3 study populations are presented in Table 3. After applying weighting, sex distribution was balanced in the general population sample. Compared with men, the proportion of women was higher in the Greek Roma sample and lower in the migrant sample. As expected, the Greek Roma and migrant study populations were substantially younger than the general population. Education level was relatively high in the general population and in migrants with about 23.6% (1222) from the general population and 12.4% (76) of migrants having a university or higher educational level. On the contrary, the majority (50.6%, 270) of the Greek Roma were practically illiterate (ie, not completed primary school). For all 3 populations, most of the participants were married or in cohabitation (Table 3). Reflecting the consequences of the financial crisis, the household income was low in all study populations, with family income below €900 per month for about 39.7% (2401) of the general population; around 26.6% (142) of Greek Roma reported no income at all, whereas personal income was less than €350 per month for 58.7% (359) of the migrants. The unemployment rate was high in all populations. The estimated unemployment rate (95% CI) for those over productive ages (≤65 years) in the general population was 28.7% (26.9%-30.5%). The unemployment rate was 59.0% (561) in migrants, whereas it was above 36.5% (195) in the Greek Roma population.

In the general population sample, among those with reported country of birth (N=5907), about 11.1% (580) were born in a country other than Greece/Cyprus, a result in line with the ELSTAT report from the 2011 Census. In the migrant survey, around 46.1% (282) described themselves as documented migrants, 24.4% (180) as asylum seekers or on refugee status, and 21.7% (133) as undocumented migrants. Only 2.8% (17) did not reveal their migrant status.

Among interviewed participants from the general population, 70.7% (N=4245) had serological tests, but 134 individuals (2.3%) had reasons to be excluded from blood sample collection (collaboration inability, pregnancy, anemia, and feeling faint); thus, among the eligible individuals, the response rate was 72.5% (4245/5859). In more detail, 4243 individuals were tested for HBV, 4245 for HCV, and 4233 for HIV/AIDS (Figure 1). The response rate was higher for Greek Roma reaching almost 98.0% (522/534) and 87.7% (537/612) for migrants. The numbers of Greek Roma and migrants tested for HBV, HCV, or HIV are presented in Figure 1.

Table 3. Demographic characteristics of study participants in the 3 study populations (general population, Greek Roma, and migrants).

Demographic characteristics	General population[a]	Greek Roma	Migrants
Gender, n (%)			
Male	2546 (48.5)	247 (46.3)	340 (55.6)
Female	3447 (51.5)	287 (53.7)	271 (44.3)
Unknown	0 (0.0)	0 (0.0)	1 (0.2)
Age (years), median (IQR)	47.7 (34-64)	35.0 (25-48)	36.9 (29.8-46.4)
Educational level, n (%)			
No school	0 (0.0)	270 (50.6)	46 (7.5)
Up to primary	2114 (28.9)	202 (37.8)	105 (17.2)
Up to secondary or postsecondary	2575 (46.2)	48 (9.0)	369 (60.3)
University or higher	1222 (23.6)	0 (0.0)	76 (12.4)
Other/unknown	82 (1.3)	14 (2.6)	16 (2.6)
Family status, n (%)			
Married or in cohabitation	3936 (61.0)	422 (79.0)	382 (62.4)
Single	1995 (38.0)	111 (20.8)	226 (36.9)
Unknown/no answer	62 (1.0)	1 (0.2)	4 (0.7)
Legal status (for migrants only), n (%)			
With legal papers	N/A[b]	N/A	282 (46.1)
Asylum seeker/refugee status/humanitarian status	N/A	N/A	180 (29.4)
Without legal papers	N/A	N/A	133 (21.7)
Unknown	N/A	N/A	17 (2.8)
Household income/month[c], n (%)			
Up to 900€[d]/no income[e]/up to 350€[f]	2401 (39.7)	142 (26.6)	359 (58.7)
900€-1700€[d]/<450€[e]/351-700€[f]	1658 (28.1)	305 (57.1)	96 (15.7)
>1700€[d]/≈450€[e]/701-900€[f]	606 (10.9)	63 (11.8)	14 (2.3)
—[d]/>450€[e]/>900€[f]	N/A	21 (3.9)	6 (1.0)
No answer	1328 (21.4)	3 (0.6)	137 (22.4)
Employment status, n (%)			
Employed	2088 (38.7)	140 (26.2)	160 (26.1)
Retired/household	2642 (35.4)	163 (30.5)	76 (12.4)
Unemployment	784 (15.3)	195 (36.5)	361 (59.0)
Other/unknown	479 (10.6)	36 (6.7)	15 (2.5)
Country of birth, n (%)			
Greece/Cyprus	5327 (88.9)	534 (100.0)	N/A
Balkans	294 (4.6)	N/A	221 (36.2)
East Europe/former Soviet Union	89 (1.6)	N/A	57 (9.7)
West Europe/Australia/Americas	101 (1.8)	N/A	1(0.2)
East/Central Asia	34 (0.7)	N/A	3 (0.5)
Middle East and North Africa	27 (0.5)	N/A	78 (12.8)
South Asia	17 (0.3)	N/A	124 (20.2)
Sub-Saharan Africa	18 (0.3)	N/A	126 (20.8)
Unknown	86 (1.4)	N/A	N/A

Demographic characteristics	General population[a]	Greek Roma	Migrants
Residence type (for Greek Roma only), n (%)			
Settlement with houses	N/A	165 (30.9)	N/A
Settlement with houses and shacks (mixed)	N/A	232 (43.4)	N/A
Shacks	N/A	137 (25.7)	N/A

[a]Weighted percentages.

[b]N/A: not applicable.

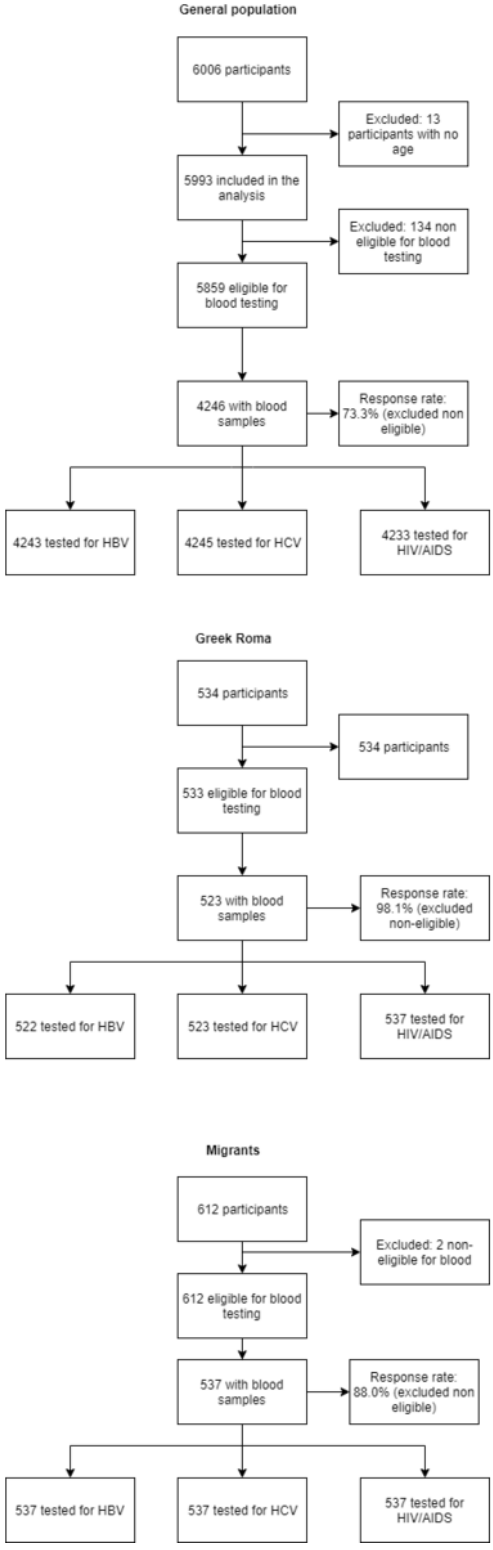
[c]For migrants, income refers to personal income, whereas for the other study populations, it refers to family income.

[d]General population.

[e]Greek Roma.

[f]Migrants.

Figure 1. Data flowchart of the 3 studied populations (general population, Greek Roma, and migrants). HBV: hepatitis B virus. HCV: hepatitis C virus.



Discussion

Strengths and Limitations

Hprolipsis is the first nationwide epidemiological study on infectious diseases HBV, HCV, and HIV. It was conducted not only in a random sample of the general population but also in two hard-to-reach populations, Greek Roma and migrants. In total, 6006, 534, and 612 from the general population, Greek Roma, and migrants, respectively, were recruited. Of those from the general population, 4243 were tested for HBV, 4245 for HCV, and 4233 for HIV/AIDS. The count for those tested for HBV, HCV, and HIV/AIDS in Greek Roma was 522, 523, and 523, respectively, and the count for those tested for HBV, HCV, and HIV/AIDS in migrants was 537, 537, and 537, respectively. Hprolipsis has 2 main advantages: (1) it combines extensive questionnaire data on several health indices with blood sample test results and (2) although one of its aims was to estimate the

prevalence of HBV, HCV, and HIV infections in the general adult population and in the 2 vulnerable populations, it was not only a research study but also an integrated program providing individual counseling, referral to all individuals who tested positive, and vaccination in vulnerable populations. The study was also involved in designing and implementing population-specific awareness actions, the success of which was evaluated by comparing the level of knowledge on the 3 investigated infections before and after awareness actions took place.

The expected benefits are multifaceted. Greece will be able to provide valid estimates of the prevalence of HBV and HCV infections in the general population, Greek Roma, and migrants. Such data, currently lacking, are particularly useful in an era where global efforts to control and ultimately eliminate these infections are being taken. Indeed, preliminary results on HCV prevalence, presented at international conferences [31], were used as the best currently available estimates on which the National Plan for eliminating HCV infection was based. In addition, data on testing, diagnosis, and treatment rates, overall and by risk group, region and sex, will provide the necessary evidence to construct disease-specific cascades of care and to identify potential inequalities. Dissemination of study results to health policy makers, relevant NGOs, and local authorities will help them to set up targeted prevention measures and to adjust health policies. Hprolipsis prevalence estimates can be used as baseline values to assess future changes and future disease burden. When combined with data on the use of health services and medicines in health economic models, future health needs and costs, necessary for public health policy planning, can be estimated.

Conducting a survey in migrant and in particular in Greek Roma populations is not an easy task (eg, [32-34]), and it becomes even more difficult when infectious diseases such as viral hepatitis and HIV are of main interest, owing to their stigmatization. Few such studies have been conducted worldwide (eg, [3,20,34-36]). Several issues, with the most important one being the establishment of trust relationships with target populations, must be considered. Despite the moderate deviations of the final sample, as compared with the planned one, within Hprolipsis, we managed to successfully complete the survey in Greek Roma and migrants. Conducting this study provided us with valuable experience. Dissemination of our study materials (study design, SOPs, guide on how to set up trust relationships, and lessons learned) will provide useful information for future studies on difficult-to-reach populations.

Data on the level of knowledge and misconceptions of HBV, HCV, and HIV routes of transmission and treatment opportunities as well as on prejudices against individuals testing positive are lacking in Greece. Such data, however, are necessary to design and implement awareness campaigns. In addition, knowledge, misconceptions and prejudices may differ by risk population. In Hprolipsis, we assessed the level of knowledge, misunderstanding, and prejudice in all 3 study populations. The analyses of these data will highlight the population-specific gaps in knowledge. Successful awareness campaigns must consider the specific cultural and social characteristics of the target populations. In Hprolipsis, populations-specific awareness-raising campaigns were designed and implemented, and their effectiveness was evaluated. Experience gained through this procedure, when shared with relevant governmental organizations and NGOs, could provide valuable information for designing future campaigns.

Finally, study participants gained numerous benefits. They were provided with HBV, HCV, and HIV blood test results, received personalized advice, and were personally informed about the routes of transmission and therapy opportunities for these infections. They also had the opportunity to discuss other health issues with the study physicians, if they wanted. In addition, previously undiagnosed cases took advantage of their early diagnosis, personal counseling, and referral to specialized clinics. Greek Roma people living in the selected settlements additionally benefited from all other provided services. Greek Roma and migrants susceptible to HBV also had the opportunity to be vaccinated for HBV.

Despite the significant advantages of the study, it also had some limitations. One major limitation was the lack of sampling frame for Greek Roma and migrants. Thus, a convenience sample was chosen. Despite our efforts to review all available data and assess sex, age, and ethnicity distribution and to imitate this distribution in our sample, representativeness cannot be assumed. However, in the Greek Roma survey, the sample was drawn from the regions where excessive number of Greek Roma live; across each selected region, representative settlements of all 3 types (homes, mixed, and shacks) were chosen to ensure that there will be enough people from each settlement type to enable investigation of the effects of the living conditions on health indices and that less privileged settlements were well represented in the sample. To increase representativeness, migrants were recruited from several sources, as suggested [22,28]. In the migrants' survey, we tried to catch the contemporary migrant flows. On the basis of all available data review, new arrivals mainly originate from Eastern European countries, Africa and, more recently, from Asia owing to the war in Syria. Those migrants are likely to be less privileged and with the most unmet needs. In our sample, a substantial proportion originated from Africa, Asia, and East European countries. In the general population survey, about 10% of the total sample was born in a country other than Greece (6% in a Balkan country, mainly Albania), in line with 2011 Census reports and justifying our decision to underrepresent Albanians in the migrants' survey. The sampling methodology for the general population ensures representativeness. However, the door-to-door approach that was adopted to recruit study participants, although quite common for conducting health screening, has some restrictions as well, mainly associated with increased costs, reducing response rate, and interviewers' safety [27,37,38]. Despite these limitations, the overall response rate in our study was quite high (72%).

Another limitation was that the migrants' field study was conducted during 2015 and 2016, a period of high migrant mobility. Although this could not be predicted at the study design phase, it had some serious side effects, the most important of which was that, despite multiple attempts, some participants could not be easily traced to provide them with test results, counseling, and referral or vaccination if needed.

Therefore, for future studies in displaced people, fourth-generation rapid tests for HBV, HCV, and/or HIV should be recommended. Despite their higher cost, rapid tests minimize the time needed from testing to diagnosis, counseling, and referral. Although this course of action would be obvious nowadays, blood sample testing was the usual approach at the time this study was designed. Similar issues were raised during vaccination. Although we chose a medium/short vaccination scheme (0, 4, and 16 weeks) as more appropriate for vulnerable populations, several eligible individuals, mainly migrants, failed to complete their vaccine scheme. Alternative schemes must be explored in future studies. Faster schemes (eg, 0, 1, and 3 weeks with the first dose given to all people irrespective of being susceptible), although they require a booster dose at 1 year to increase rates of immune coverage, may be preferable. In general, vaccination schemes must be adjusted to the specific characteristics of the target population.

Finally, the required sample size for the general population was estimated based on HCV prevalence, which is expected to be lower than HBV prevalence. However, HIV infection in the general population is expected to be much lower than that of HCV (around 0.13%), and thus, estimates of HIV prevalence are expected to be of low precision.

Conclusions

In conclusion, the Hprolipsis results will increase our understanding on health needs and burden of infectious diseases not only in the general population but also in Greek Roma people and migrants. Policy makers, NGOs, and Greek Roma and migrant communities can rely on the Hprolipsis results for planning population-targeted interventions. The implementation of this integrated program was a great experience, providing useful recommendations for future studies, particularly in vulnerable populations. However, to have a complete picture of the total burden of the investigated diseases in Greece, similar studies in other vulnerable populations such as homeless individuals, prisoners, and sex workers are needed.

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Conflicts of Interest

GT has received EU and national resources grants to support this study and grants unrelated to this study from Gilead Sciences Europe, UCL, ECDC, EU, and National funds. GP has been advisor/lecturer for AbbVie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, Roche, Spring Bank and has received research grants unrelated to this study from AbbVie, Bistrol-Myers Squibb, Gilead, Janssen, Roche. AH has received grants unrelated to this study from AbbVie, BMS, Gilead and MSD. VS has received grants unrelated to this study from Gilead Sciences and AbbVie and honoraria from Gilead Sciences, AbbVie and Janssen. The rest of the authors have no conflicts of interest to declare.

Multimedia Appendix 1
Detailed survey sections and questionnaire items.
[DOCX File , 14 KB - resprot_v9i1e13578_app1.docx]

Multimedia Appendix 2
Immunization card.
[DOCX File , 118 KB - resprot_v9i1e13578_app2.docx]

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Abbreviations

anti-HCV: Hepatitis C Antibody
ELSTAT: Hellenic Statistical Authority
EMENO: National Survey of Morbidity and Risk Factors
HBsAg: Hepatitis B surface Antigen
HBV: hepatitis B virus
HCDCP: Hellenic Centre for Disease Control and Prevention
HCV: hepatitis C virus
NGO: nongovernmental organization
NKUA: National and Kapodistrian University of Athens
PICF: participant information and consent form
SC: steering committee

SOP: standardized operating procedure

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Protocol

Early Signs Monitoring to Prevent Relapse in Psychosis and Promote Well-Being, Engagement, and Recovery: Protocol for a Feasibility Cluster Randomized Controlled Trial Harnessing Mobile Phone Technology Blended With Peer Support

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Abstract

Background: Relapse in schizophrenia is a major cause of distress and disability and is predicted by changes in symptoms such as anxiety, depression, and suspiciousness (early warning signs [EWSs]). These can be used as the basis for timely interventions to prevent relapse. However, there is considerable uncertainty regarding the implementation of EWS interventions.

Objective: This study was designed to establish the feasibility of conducting a definitive cluster randomized controlled trial comparing Early signs Monitoring to Prevent relapse in psychosis and prOmote Well-being, Engagement, and Recovery (EMPOWER) against treatment as usual (TAU). Our primary outcomes are establishing parameters of feasibility, acceptability, usability, safety, and outcome signals of a digital health intervention as an adjunct to usual care that is deliverable in the UK National Health Service and Australian community mental health service (CMHS) settings. We will assess the feasibility of candidate primary outcomes, candidate secondary outcomes, and candidate mechanisms for a definitive trial.

Methods: We will randomize CMHSs to EMPOWER or TAU. We aim to recruit up to 120 service user participants from 8 CMHSs and follow them for 12 months. Eligible service users will (1) be aged 16 years and above, (2) be in contact with local CMHSs, (3) have either been admitted to a psychiatric inpatient service or received crisis intervention at least once in the previous 2 years for a relapse, and (4) have an International Classification of Diseases-10 diagnosis of a schizophrenia-related disorder. Service users will also be invited to nominate a carer to participate. We will identify the feasibility of the main trial in terms of recruitment and retention to the study and the acceptability, usability, safety, and outcome signals of the EMPOWER intervention. EMPOWER is a mobile phone app that enables the monitoring of well-being and possible EWSs of relapse on a daily basis. An algorithm calculates changes in well-being based on participants' own baseline to enable tailoring of well-being messaging and clinical triage of possible EWSs. Use of the app is blended with ongoing peer support.

Results: Recruitment to the trial began September 2018, and follow-up of participants was completed in July 2019. Data collection is continuing. The database was locked in July 2019, followed by analysis and disclosing of group allocation.

Conclusions: The knowledge gained from the study will inform the design of a definitive trial including finalizing the delivery of our digital health intervention, sample size estimation, methods to ensure successful identification, consent, randomization, and follow-up of participants, and the primary and secondary outcomes. The trial will also inform the final health economic model to be applied in the main trial.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): 99559262; http://isrctn.com/ISRCTN99559262

International Registered Report Identifier (IRRID): DERR1-10.2196/15058

(JMIR Res Protoc 2020;9(1):e15058) doi:10.2196/15058

KEYWORDS

schizophrenia; psychosis; relapse; mHealth; randomized controlled trial

Introduction

Background

Relapse influences the long-term course of psychosis with rates identified as 28% (range 12%-47%), 43% (range 35%-54%), 54% (range 40%-63%) at 1, 1.5, 2, and 3 years follow-up, respectively [1], and more recent evidence shows similar relapse rates [2,3]. Relapse is also associated with poorer response to subsequent antipsychotic treatment [4]. Relapses can occur in up to 80% of participants at the 10-year follow-up [5] and can lead to higher inpatient and outpatient costs [6].

One important predictor of relapse is lack of acceptance of treatment and unplanned discontinuation of antipsychotic medication [1]. Poorer adherence often signals a lack of engagement with services and failure of services to build a collaborative working alliance [7]. Nonadherence to antipsychotic treatment is predicted by poorer insight, previous experience of involuntary treatment, poorer premorbid functioning, comorbid substance misuse, forensic history, poor relationship with the prescriber, greater deprivation, and transfer to secondary care [8-10]. Relapse itself is an important marker of the severity and complexity of illness and is predicted by previous suicide attempts [11]; depression, hostility, and embarrassment [12]; poorer premorbid functioning; family criticism; substance misuse; social isolation [1]; and negative interpersonal style (possibly linked to poorer utilization of social support) [13].

Birchwood et al [14] pioneered the development of systematic early signs monitoring for relapse and its integration into routine care. It is now known that relapse is the culmination of a process of changes that commence days and sometimes weeks before psychosis symptoms reemerge or are exacerbated. These early warning signs (EWSs) include affective changes and incipient psychosis. These EWSs can be detected as early as 8 weeks before rehospitalization [15]. A systematic review [16] found that the sensitivity of early signs to relapse (proportion of relapses correctly predicted) ranged from 10% to 80% (median 61%) and specificity (proportion of nonrelapses correctly identified) ranged from 38% to 100% (median 81%). Detection

of relapse was improved by more frequent monitoring (at least fortnightly) and by the inclusion of both psychotic and affective symptoms.

A significant barrier to relapse prevention is fear of help seeking arising from previous experiences of relapse [17]. For example, people may avoid calling their care coordinator in the context of an increase in EWSs for fear of being admitted to the hospital. Research has demonstrated that fear of relapse is linked to more traumatic experiences of psychosis and hospital admission and greater fear of symptoms, such as voices and paranoia [18]. In a randomized controlled trial (RCT) of relapse detection, fear of relapse contributed independently to the prediction of relapse (sensitivity=72%, 95% CI 52-86; specificity=46%, 95% CI 32-60) compared with EWSs (sensitivity=79%, 95% CI 62-89; specificity=35%, 95% CI 23-50). Fear of recurrence was also associated with greater depression, feelings of entrapment, self-blame, and shame [19]. Therefore, it is important to include fear of recurrence in the monitoring of EWSs.

Fear of illness and stigma are closely related to emotional distress [20] and to poorer insight into schizophrenia [8]. Feelings of fear, depression, and helplessness are common emotional experiences before full relapse [21]. In an effort to minimize the stigma of illness and prevent relapse, people can adopt avoidant coping styles that are associated with increased risk of relapse [20]. These coping styles are associated with greater insecurity in relationships, lower self-esteem, lower levels of adherence, and reluctance to seek help in a crisis. Reluctance to seek help may result from greater fear of relapse arising from experiences of involuntary admission. In this sense, avoidance of help seeking can be understood from the perspective that people with experience of psychosis are attempting to minimize or avert the adverse consequences of help seeking based on their lived experience. A recent systematic review [22] found that greater difficulties in forming relationships were associated with poorer engagement with services, more problematic relationships with staff, and more frequent and longer hospital admissions. In sum, the detection of and action following EWSs may be constrained by poor relationships between service providers and people using services, avoidance of help seeking, perceived stigma, fear of relapse, and reluctance to disclose EWSs.

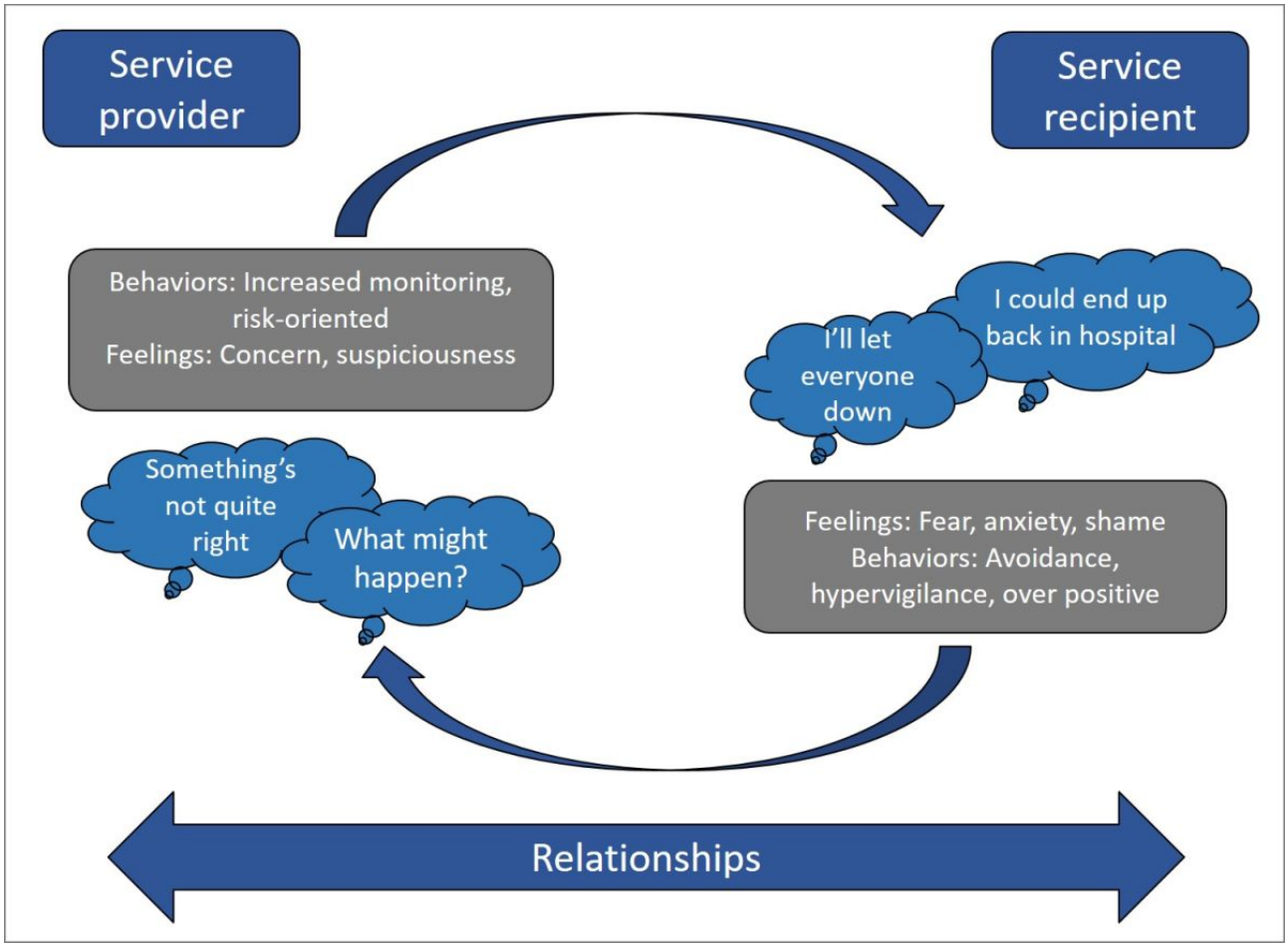
A Cochrane review focused on the effectiveness of interventions targeting recognition and management of EWSs of relapse in schizophrenia [23]. Significant effects in favor of EWS interventions were found for the number of participants relapsing (15 RCTs; n=1502; risk ratio [RR] 0.53, 95% CI 0.36-0.79) and the number of participants being rehospitalized (15 RCTs; n=1457; RR 0.48, 95% CI 0.35-0.66); however, the methodological quality of the trials was poor in terms of randomization, concealment, and blindness. Future EWS interventions need to address these methodological problems that limit their generalizability to usual care. Until this happens, EWS interventions cannot be recommended for routine implementation in health services [23].

An important aspect of service provision for those people at greatest risk of relapse is having access to an integrated mental health care system that enables clear shared planning for managing risk and relapse prevention. One example of this is the role of joint crisis plans (JCPs) in the United Kingdom. The CRIMSON study [24] was an individual-level RCT that compared the effectiveness of JCPs with treatment as usual (TAU) for people with a diagnosis of schizophrenia. There was no significant impact on the primary outcome (reduced coercion into hospital). It was noted that when faced with crisis, in spite of the considerable effort in developing the JCP with service users, the teams reverted to *custom and practice*. The staff did not consult JCPs in planning the team response to a crisis. Furthermore, people in receipt of services experienced an inability to influence clinicians' behaviors, and this was interpreted as signaling a lack of respect for their views and opinions. Consequently, they described their interactions with clinicians as *playing the game*, that is, appearing to comply with treatment decisions. Clinicians themselves experienced their interactions with people using services as ritualized, especially in the context of responding to increased risk [25].

Gumley and Park [17] highlighted that relapse prevention based on EWS monitoring relies on the person receiving services initiating help seeking in the context of feeling vulnerable and threatened. Many individuals find help seeking a challenge and may have had difficult or traumatic experiences of psychosis. Delay in help seeking narrows the window of opportunity for successful relapse prevention, which in turn increases reliance on coercive measures confirming pre-existing negative expectations. It is therefore essential to develop and evaluate an intervention that can facilitate safe and honest disclosure of possible EWSs while also reorienting the response of mental health teams and the actions of their staff in a crisis toward a more collaborative approach.

Our conceptual framework for improving relapse detection and prevention aims to understand how EWSs unfold in the context of important caring relationships. Figure 1 provides an illustration of our cognitive interpersonal model for EWSs. Fear of recurrence drives feelings of fear, anxiety, and shame. Coping strategies to regulate emotional distress (eg, increased hypervigilance, worrying, and avoidance) shape care providers' own cognitive and emotional responses to perceived increased risk of relapse. For example, care providers may interpret increased emotional distress or avoidance (eg, cancelling appointments) as evidence of increased risk prompting changes in clinical care and risk management. These changes may further confirm individuals' negative expectations of services and fear of recurrence. Therefore, interventions that can enhance positive emotional awareness (through self-monitoring), choice and autonomy (through self-management promotion), and improved communication (through increased understanding) could provide a means to disrupt and change negative interpersonal cycles.

Figure 1. Cognitive interpersonal framework for early warning signs.



Digital technology has the potential to offer a step change that can influence early signs monitoring both for people receiving and providing mental health services [26,27]. Mobile phones to support health care are promising for the delivery of interventions that are unconstrained by the limitations of existing treatment settings. Mobile phones are widely available and are continuously dropping in cost, and nearly 3 billion people are projected to own a mobile phone by 2020 [28]. Mobile phone ownership among people who experience psychosis is increasing with estimated rates of ownership from 66.4% (95% CI 54.1%-77.6%) rising to 81.4% (n=454) in more recent studies [29]. Furthermore, people with psychosis express an interest in the use of mobile phones to enhance contact with services and to support self-management [29,30]. Mobile phones, particularly *mobile phones*, offer opportunities for ecological momentary assessment (EMA) to collect data on repeated occasions, in real time, and in the context of daily life [31]. This enhances the ability to assess individuals in their usual context, temporally close to relevant events, and intensively and repeatedly as psychological processes unfold over time [32]. Bell et al [33] found that across 9 interventions (n=459), interventions for people with psychosis using EMA show satisfactory levels of feasibility and acceptability as well as preliminary evidence of improved clinical outcomes. Furthermore, studies that prospectively assess symptom course using mobile phone apps in people with psychosis show promise [34-45] in terms of feasibility of, acceptability of, and adherence to regular daily monitoring and also delivery of in-time interventions to support coping [36] or delivery of cognitive behavioral therapy [38].

However, studies employing mobile phones to promote relapse detection and intervention are not without their challenges. The Information Technology–Aided Relapse Prevention Program in Schizophrenia (ITAREPS) utilized a weekly text-based monitoring system to detect EWSs in people with psychosis. This system gathers data on early signs of psychosis using text messaging with clinicians notified by alerts where scores breach a specified threshold. Treating clinicians are expected to increase medication by 20% within 24 hours of an alert. In the initial studies [46,47], adherence by people using services and family members was problematic, in that only 47% were described as *high* users with 70% return rates. In the ITAREPS RCT [48], trial adherence improved; however, adherence to the treatment protocol was problematic at 39% largely owing to conflicts between protocol-indicated medication increases and psychiatrists' clinical judgment. Komatsu et al [49] found that adherence to the ITAREPS protocol was improved when mental health nurses were involved in triaging EWS assessments. More recently, Eisner et al [50] demonstrated that over 6 months, adherence to mobile phone-based assessments of EWSs was 65% and successfully predicted increased psychotic symptoms 3 weeks later.

In sum, mobile phone technology offers a significant opportunity to deliver EMA-based monitoring of changes in well-being that are ecologically valid and contextually sensitive. Preliminary

studies show encouraging levels of user acceptability and engagement, and thus, they offer the potential to recognize EWSs and activate timely assessment and intervention to promote self-management and relapse prevention. However, there are important implementation challenges to ensure that these technologies can enhance relationships and shared decision making, particularly during times of increased stress and crisis.

Objectives

The overall aim of this study is to establish the feasibility of conducting a definitive cluster randomized controlled trial (cRCT) comparing Early signs Monitoring to Prevent relapse in psychosis and prOmote Well-being, Engagement, and Recovery (EMPOWER) against TAU. We will establish the parameters of the feasibility, acceptability, usability, safety, and outcome signals of an intervention as an adjunct to usual care that is easily deliverable in the National Health Service (NHS) and Australian community mental health service (CMHS) settings. The EMPOWER intervention aims (1) to enhance the recognition of EWSs by people using services and their carers and (2) to provide a stepped-care pathway that is either self-activated or in liaison with a carer and/or community health care professional, which then (3) triggers a relapse prevention strategy that can be stepped up to a whole team response to reduce the likelihood of a psychotic relapse.

Specifically, we aim to do the following:

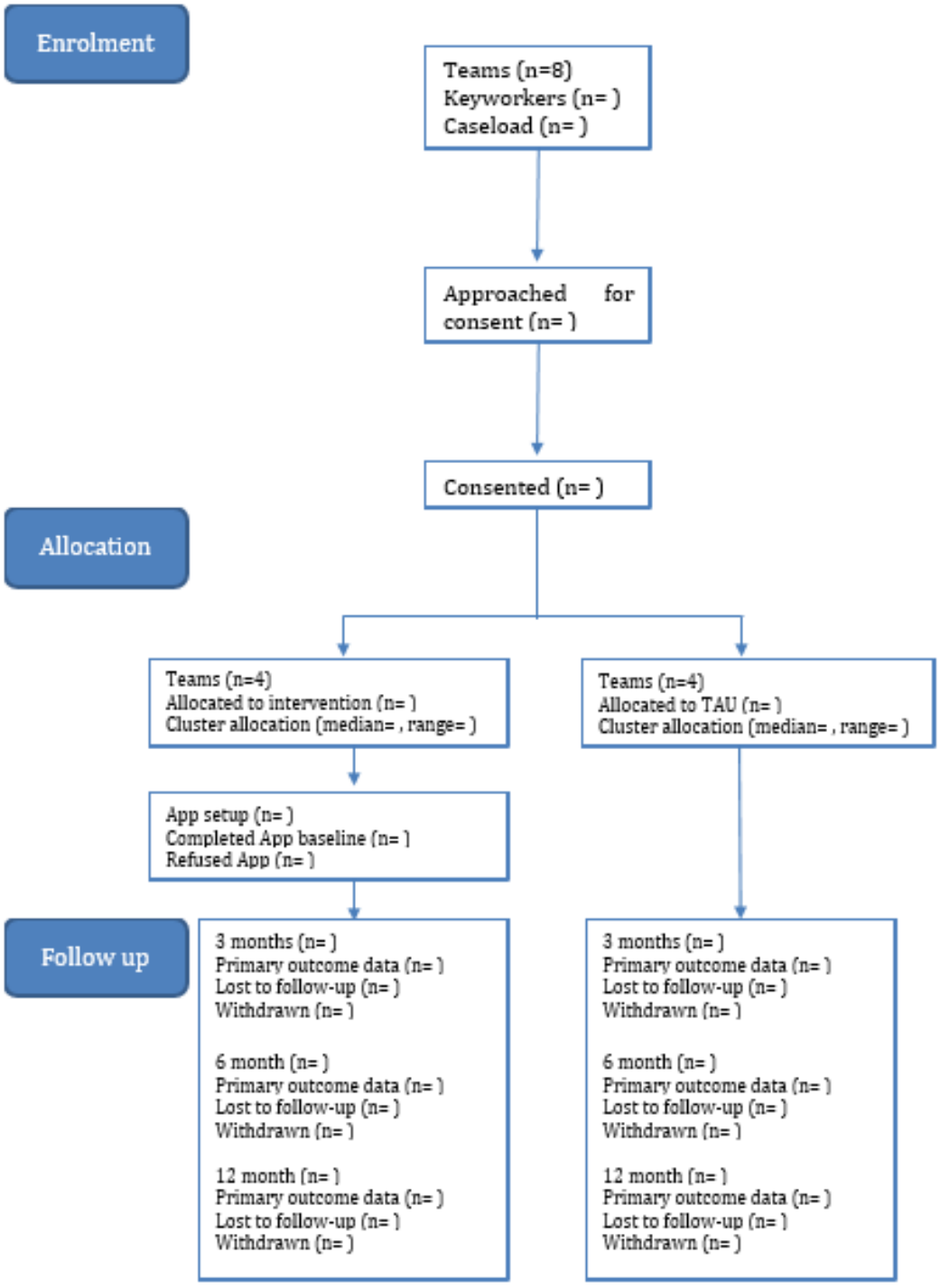
1. Enhance and tailor our mobile phone software app to deliver EWS monitoring, self-management interventions, and access to a relapse prevention pathway that is firmly embedded in whole team protocols and action.
2. Determine rates of eligibility, consent, and recruitment of potentially eligible participants (people using services, carers, and care coordinators) to the study.
3. Assess the performance and safety of the EMPOWER Class 1 Medical Device (CI/2017/0039).
4. Assess the feasibility, acceptability, and usability of the intervention including feedback on suggested enhancements from people receiving the intervention, peer support workers, and clinicians.
5. Assess primary and secondary outcomes to determine preliminary signals of efficacy of the EMPOWER Relapse Prevention Intervention as a basis for the estimation of sample size requirements of a future definitive trial.
6. Undertake a qualitative analysis of relapses to refine the intervention in the main trial.
7. Establish the study parameters and data-gathering frameworks required for a coordinated health economic evaluation of a full trial across the United Kingdom and Australia.

Methods

Trial Design

We will evaluate EMPOWER using a multicenter, 2-arm, parallel group cRCT involving 8 purposively selected CMHSs (2 in Melbourne, Australia, and 6 in Glasgow, Scotland) with 12-month follow-up. The CMHS will be the unit of randomization (the cluster), with the intervention delivered by the teams to people using services and with outcomes assessed within these clusters. The Standard Protocol Items: Recommendations for Interventional Trials checklist is provided as an additional file. The study is planned and implemented in concordance with the Consolidated Standards of Reporting Trials (CONSORT) cluster trial extension [51] and the extension to randomized pilot and feasibility trials [52]. We chose a cluster design as the EMPOWER intervention aims to enable a team-based response to people in receipt of services whose real-time EWS monitoring has activated a relapse prevention pathway. Our CONSORT diagram is detailed in Figure 2.

Figure 2. Consolidated Standards of Reporting Trials flow diagram. TAU: treatment as usual.



Ethics and Governance

The West of Scotland Research Ethics Service (GN16MH271 Ref: 16/WS/0225) and Melbourne Health Human Research Ethics Committee (HREC/15/MH/344) approved the study. The study sponsors are NHS Greater Glasgow & Clyde in the United Kingdom and North Western Mental Health in Australia. Approvals from the NHS Health Research Authority and a notice of no objection for a trial of a medical device (CI/2017/0039) from the United Kingdom's Medicines and Health care products Regulatory Agency (MHRA) was also received for the trial, and it has been prospectively registered (ISRCTN99559262). The basic trial methods of enrolment, interventions, and assessments are summarized in Table 1.

Table 1. Participant timeline.

Assessment timeline	Study period and time point				
	Enrolment (baseline)	Allocation (0 months)	Post allocation		Close-out (12 months)
			3 months	6 months	
Enrolment					
Eligibility screen	X[a]	—[b]	—	—	—
Informed consent	X	—	—	—	—
Allocation	—	X	—	—	—
Intervention					
EMPOWER[c]	—	—	X	X	X
Service u ser assessments					
Feasibility	X	—	X	X	X
Acceptability and usability		—	X	X	X
Remission status	X	—	X	X	X
Relapse		—	X	X	X
Positive and Negative Syndrome Scale	X	—	X	X	X
Personal and Social Performance Scale	X	—	X	X	X
Calgary Depression Scale for Schizophrenia	X	—	X	X	X
Time Line Follow Back	X	—	X	X	X
Hospital Anxiety and Depression Scale	X	—	X	X	X
Personal Beliefs about Illness Questionnaire	X	—	X	X	X
Service Attachment Scale	X	—	X	X	X
Medication Adherence Rating Scale	X	—	X	X	X
EuroQol 5 Dimension	X	—	X	X	X
Assessment of quality of life	X	—	X	X	X
RUQ[d]	X	—	X	X	X
Questionnaire for Personal Recovery	X	—	X	X	X
Generalized Self Efficacy Scale	X	—	X	X	X
Psychosis Attachment Measure	X	—	X	X	X
Perceived Criticism and Warmth Measure	X	—	X	X	X
Carer assessments					
Feasibility	X	—	X	X	X
Carer Quality of Life 7 Dimension	X	—	X	X	X
EuroQol 5 Domain 5 Level	X	—	X	X	X
Resource Use Questionnaire	X	—	X	X	X
Perceived Criticism and Warmth Measure	X	—	X	X	X
Involvement Evaluation Questionnaire	X	—	X	X	X
Care coordinator					
Feasibility	X	—	X	X	X
Service Engagement Scale	X	—	X	X	X

[a]Item was applicable at the relevant study time point.

[b]Item was not applicable at the relevant study time point.

[c]EMPOWER: Early signs Monitoring to Prevent relapse in psychosis and prOmote Well-being, Engagement, and Recovery.

Preliminary Work—Patient and Public Involvement

At the outset of the study, we conducted extensive consultation with key stakeholders including mental health staff (n=88), people with lived experience (n=21), and carers (n=40) in a series of 25-focus groups across Glasgow and Melbourne. The stakeholder consultation shaped the development of the EMPOWER intervention [53]. The Scottish Recovery Network also played a key role in shaping further consultation with people with lived experience in further refining the intervention development and planning.

Eligibility Criteria

Participation will be sought from CMHS in NHS Greater Glasgow & Clyde in the United Kingdom and North Western Mental Health Services in Melbourne, Australia. All participants (mental health staff, service users, and carers) will be approached for their informed and written consent before assessment and randomization. Research assistants (RAs) will be responsible for recruitment and written informed consent. Recruitment took place between September 2018 and July 2019. Final follow-up assessments were completed end of June 2019.

Community Mental Health Services

We will likely engage CMHSs to have 5 or more care coordinators willing to participate for a period of 12 months and where potential care coordinators having eligible service users on their caseload being likely to consider participation.

Service Users

Service users from participating CMHSs are eligible for inclusion if they are adults (aged 16 years and above); are in contact with a local CMHS; have either been admitted to a psychiatric inpatient service at least once in the previous 2 years for a relapse of psychosis or received crisis intervention (eg, via a crisis intervention service, reengaged with a CMHS) in the previous 2 years for a relapse of psychosis; have received a diagnosis of schizophrenia-related disorder, specifically 295.40 schizophreniform disorder (International Classification of Diseases-10 [ICD10]=F20.81), 295.70 schizoaffective disorder (ICD10=F25), 295.90 schizophrenia (ICD10=F20.9), 297.10 delusional disorder (ICD10=F22); and are able to provide informed consent as adjudged by the care coordinator, if in doubt, the responsible consultant.

Carers

Carers of people receiving support from participating CMHSs will be eligible for inclusion if they have been nominated by eligible participants; they are in regular contact with the person receiving services; and they provide informed consent to participate in the study.

Exclusion Criteria

Individuals will be ineligible for participation if they do not meet the inclusion criteria outlined above. In addition, participants will be excluded if they have experienced a recent relapse operationally defined as having been discharged from the care of a crisis team or psychiatric inpatient service within the previous 4 weeks.

Interventions

In describing the EMPOWER intervention in the following section, we have utilized the Template for Intervention Description and Replication Checklist [54].

Early Signs Monitoring to Prevent Relapse in Psychosis and Promote Well-being, Engagement, and Recovery Intervention

Rationale

The rationale for the EMPOWER intervention was informed by the cognitive interpersonal model outlined in Figure 1 and has been designed to enable participants to daily monitor changes in their well-being. In EMPOWER, we refer to changes in well-being as *ebb and flow* as a means of moving away from risk-orientated monitoring that can sensitize individuals to increased fear of relapse. The terminology also conveys a normalizing framework for understanding changes in emotions and psychotic experiences in daily life. The EMPOWER intervention is blended with peer support. A peer support worker (PSW) is involved in setting up and personalizing the daily questionnaire, alongside regular fortnightly follow-up. Clinical triage of changes in well-being that are suggestive of EWSs is enabled through an EMPOWER algorithm that triggers a check in prompt (ChIP). This enables prompt identification of EWSs and triggers a relapse prevention pathway.

The EMPOWER app was developed through consultation with people using services, their carers, and mental health professionals. Service user participants have access to the EMPOWER app for up to 12 months of the intervention period. EMPOWER was developed as a flexible user-led tool to (1) daily monitor the *ebb and flow* of changes in their well-being which incorporates, (2) personalized EWS items, (3) enables the delivery of EMPOWER (self-management) messages directly to service users and, (4) provides a mobile phone user interface to enable service users to review their own data and keep a diary of their experiences.

Materials

Daily monitoring of well-being is initiated by pseudorandom mobile phone notifications to complete the EMPOWER questionnaire. The questionnaire contains 22 items reflecting 13 domains (eg, mood, anxiety, coping, psychotic experiences, self-esteem, connectedness to others, fear of relapse, and personalized EWSs). Items include both positive (eg, “I’ve been feeling close to others”) and negative (eg, “I’ve been worrying about relapse”) content. Each item is completed using a simple screen swipe that enables quick and efficient completion by users. Each item is automatically scored on a scale of 1 to 7. Where particular items score >3, users are invited to complete supplementary questions to enable a more fine-grained assessment of that domain. This provides up to a maximum of 56 questionnaire items. The questionnaire was piloted among 7 participants for an average of 36.7 days (range 32-49), and the app was completed on an average of 24.5 days (range 16-35), giving an overall rate of engagement of 68.9%.

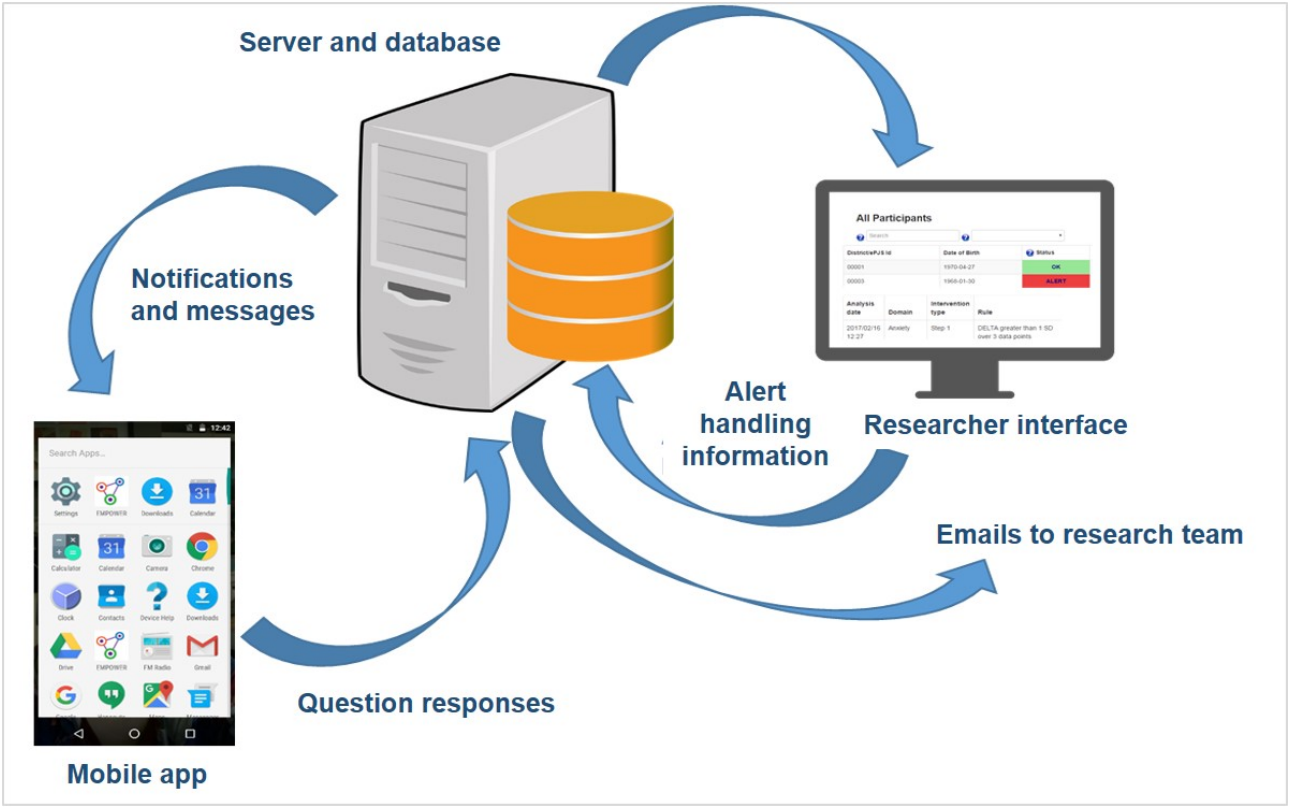
Procedures

A PSW meets with participants on an individual basis to introduce the rationale for using the app, collaboratively sets up the app on their own or a study mobile phone, and supports the individual's familiarization with the handset and app functions. Participants are invited to choose up to 3 personalized EWS items to be included in the EMPOWER questionnaire, and further personalization of delusion specific items can also be made. Where possible, an individual's care coordinator and nominated carer are invited to contribute to this meeting. Participants are invited to undertake daily monitoring for an initial 4-week baseline period to help establish their personal baseline of the *ebb and flow* of their well-being. During this period, additional support is provided by PSWs through weekly telephone follow-up. This provides an opportunity to encourage usage of the app, solve any technical problems, and identify any adverse effects. At the end of the 4 weeks, a further meeting is arranged with a PSW or mental health nurse to review monitoring, encourage engagement with EMPOWER messages, agree participants' preferences for actions in response to changes in well-being that are suggestive of EWSs and encourage continued utilization of local CMHSs for clinical care. All participants are offered ongoing fortnightly PSW support to encourage use of the app: to support their reflection on changes in well-being and their broader context including, for example, stressful life events, and to encourage use of self-management strategies prompted by EMPOWER messages.

Digital Procedures

The analysis and handling of questionnaire data is governed by the EMPOWER algorithm. The EMPOWER algorithm is a Class 1 Medical Device (ISO 14155:2011[E]), which is an algorithm that forms one part of a broader system that is designed to identify and respond to changes in well-being that are suggestive of EWSs. Figure 3 provides a graphical representation of the system's high-level components and data flow.

Figure 3. Early signs monitoring to prevent relapse in psychosis and promote well-being, engagement, and recovery system.



Participants use a mobile phone app that prompts them to answer a daily questionnaire about potential EWSs of psychosis. The data are then submitted to the EMPOWER server and analyzed by the EMPOWER algorithm. The algorithm compares a participant's latest data entry against their personal baseline. If changes exceed predefined thresholds, a ChIP is generated for the participant. The consequences of the ChIP are that the research team, which includes a registered mental health nurse (in the United Kingdom), clinical psychologists (United Kingdom and Australia), and general psychologist (Australia only), is emailed about the participant and that the participant's status is set to *alert* and is highly visible on a secure Web-based researcher interface. In addition to viewing and handling ChIPs, researchers can also view longitudinal graphs of their participants' well-being and possible EWSs, filtered by question or by domain (group of questions). In response to ChIPs, a member of the research team checks in with the participant and based on the outcome of this triage assessment, they can share an update with the participants' care coordinator who can, if indicated, escalate increased support to the participant from their local CMHS to reduce risk of relapse. These actions are agreed on a case-by-case basis, and we did not constrain the service user's treatment provider to respond within a specific timeframe or indeed in a specific way. We have undertaken the responsibility to update the individual on any ongoing actions.

The EMPOWER algorithm also runs a separate process scan for EWS changes against the baseline. On the basis of these changes, the logic selects a message from the most appropriate of several content-based message pools (ie, one message pool contains helpful messages about *mood* and another about *anxiety and coping*). This message is delivered back to, and displayed on, the participant's EMPOWER app. Messages are intended to help people have a greater sense of control over their mental health and well-being and to support self-management.

Training and Support to Community Mental Health Service Staff

Following randomization of CMHSs to EMPOWER, we will aim to provide training to mental health staff in those teams based on our model of relapse prevention, which emphasizes (1) therapeutic alliance, (2) barriers to help seeking, (3) familiarization with app, (4) developing an individualized formulation of risk of relapse, and (5) developing a collaborative relapse prevention plan. Following this, we aim to meet with care coordinators on a fortnightly basis to provide support in the implementation of EMPOWER. These meetings are aimed to clarify and encourage formulation of any changes and participants' responses within the model and support clinicians to consider EMPOWER-consistent intervention options.

Treatment as Usual Control

TAU was chosen as a control condition in both the Glasgow and Melbourne centers as this provides a fair comparison with routine clinical practice. In Glasgow and Melbourne, secondary care is delivered by adult CMHSs, which largely involve regular, fortnightly, or monthly follow-up with a care coordinator and regular review by a psychiatrist. TAU is the modal comparison for digital interventions in schizophrenia. However, recent trials [38] have included active monitoring control groups. Our comparison with TAU will be reviewed before submitting the main trial application.

Outcomes

All outcome measures will be administered at baseline and subsequently at 3, 6, and 12 months by RAs who will have been trained in the use of all the instruments and scales and who have achieved a satisfactory level of interrater reliability. RAs have as a minimum a strong honors degree in Psychology or a related discipline. Regular interrater reliability assessments will be conducted during the trial. RAs will enter anonymized participant data onto an electronic case record form hosted by the University of Aberdeen, with the exception of relapse data. Relapse data will be entered by the trial manager (SB). Data quality and error checking will be conducted at each time point including baseline, 3 months, 6 months, and 12 months post randomization.

Primary Outcomes

Feasibility

For all participants, outcome assessment will include the proportion of eligible and willing service users who then consent and the proportion continuing for 3, 6, and 12 months to the end of the study. We will report on the perspectives of service users, carers, and mental health staff in relation to the frequency of seeking help in relation to EWSs; the frequency in which a family member/carer has sought help in response to EWSs, and the frequency of clinical care that has changed in response to EWSs at 3, 6, and 12 months.

Acceptability and Usability

For those randomized to EMPOWER, we will report the length of time participants are willing to use the app and the number completing >33% of EWS datasets. We will also report the self-reported frequency of app use, frequency of sharing data with the keyworker, frequency of sharing data with the family member/carer, and frequency of accessing charts at 3, 6, and 12 months. We will also assess self-reported acceptability and usability using an adapted version of the Mobile App Rating Scale [55].

Safety—Adverse Events

Details of recording and reporting all adverse events is contained in our Standard Operating Procedure for Adverse Events that complies with Medical Devices Regulations 2002, ISO/FDIS 14155:2011 and Standards for Good Clinical Practice. An adverse event is defined as serious if it (1) results in death, (2) is a life-threatening illness or injury, (3) requires (voluntary or involuntary) hospitalization or prolongation of existing hospitalization, (4) results in persistent or significant disability or incapacity, or (5) is a medical or surgical intervention required to prevent any of the above, (6) leads to fetal distress, fetal death, or consists of a congenital anomaly or birth defect, or (7) is otherwise considered medically significant by the investigator. We will record any adverse device effects (serious or otherwise) arising from the EMPOWER algorithm. In addition, we will measure all adverse effects arising from study procedures including use of the EMPOWER app. We have prespecified (but not limited) these to (1) increased fear of relapse or paranoia associated with responding to questions in the EMPOWER app and (2) increased worries about surveillance by psychiatric services. We will also assess changes in fear of relapse using the Fear of Recurrence Scale [18].

The relationship between the investigational medical device and the occurrence of each adverse event will be assessed and categorized. In consultation with the RA and the trial manager, the chief investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the participant's underlying condition, concomitant therapy, and other risk factors, will be considered.

We also record medical device deficiencies, which is any inadequacy of the EMPOWER medical device. These can include malfunctions, end user errors, and inadequate labeling.

Performance

The following performance endpoints have been identified:

1. Each participant has the app successfully uploaded on a mobile phone.
2. Each participant has personalized EWSs included in the EMPOWER questionnaire.
3. Each participant receives a daily prompt to complete their questionnaire.

4. Participants receive an EMPOWER message each time they complete the questionnaire.
5. Following 4 weeks of usage, the EMPOWER algorithm calculates each of the participant's individualized baseline or variance of symptoms and experiences.
6. Participants can access charts of their symptoms and experiences covering 1-week and 1-month time intervals.
7. Following completion of the questionnaire, participants' data are transferred to the secure server.
8. Researchers access participants' questionnaire responses and generate charts to observe changes over time.
9. Researchers receive a record of alerts for each participant and can record actions in relation to these alerts.

Candidate Outcomes

Candidate Primary Outcome

Data related to symptom change and possible relapse will be extracted prospectively from electronic case notes by RAs. Relapse is defined as (1) a return or exacerbation in psychotic symptoms of at least moderate degree; (2) where symptoms have lasted at least one week in duration, and there is evidence of a decline in functioning or an increase in risk to self or others; and (3) there is evidence of a clinical response from services. Relapse criteria are summarized in Table 2.

Table 2. Early signs monitoring to prevent relapse in psychosis and promote well-being, engagement, and recovery relapse criteria.

Criteria	Notes and definitions
A return or exacerbation in psychotic symptoms of at least moderate degree; If present score=1	• These are defined as first rank psychotic symptoms including hallucinations, delusions, thought disorder and persecutory paranoia • In line with Positive and Negative Syndrome Scale assessments, moderate severity means that these occur at least occasionally or intrude on daily life to a moderate extent
AND Where symptoms have lasted *at least* 1 week in duration; If present score=1	• There was clear evidence that duration of psychotic symptoms occurred over at least 1 week
AND Where there is evidence of a decline in functioning; If present score=1	• Includes a decline in one or more of the role performance areas identified from the Personal and Social Performance Scale: • Socially useful activities, including work and study (this should include cooperation with household tasks, voluntary work, and *useful* hobbies, such as gardening) • Personal and social relationships (this includes relationships with a partner or relatives and broader social relationships) • Self-care (personal hygiene, personal appearance, and dressing) • General domains to consider are physical and psychological health care; lodging (area of residence and living space care); contribution to household activities; participation in family life or residential/day-center life; intimate and sexual relationships; childcare; social network, friends, and helpers; general interests; financial management; use of transport; coping skills in crisis; keeping social rules
OR An increase in risk to self or others; If present score=1	• Increase in risk to self includes deliberate self-injury and/or suicidal ideation that was clinically significant in the investigator's judgment. Evidence is required of either an increase in thoughts or an intent to act upon such thoughts. These must occur within the context of the episode and be accompanied by a service response. The service response can be reflected in that there is a statement of increased risk, there is a note of discussing safety plans, or staff have ensured that the participant has access to crisis contacts • Increase in risk to others includes significant violent and aggressive behavior. This also includes homicidal ideation, with evidence of intent to act upon this. Violent and aggressive behavior should only be recorded as an increase in risk where there is evidence of a service response to manage this behavior
AND There is evidence of a clinical response from services; If present score for each of these criteria=1 (Maximum=3)	• An increase or change in medication, increased home visits, or referral to crisis services • Any hospital admission or imposition of a Community Treatment Order in response to psychosis • Use of the mental health act to enforce an involuntary hospital admission

RAs who are not blinded to the treatment condition extracted data from electronic case records to document all recorded episodes of changes in psychotic symptoms, functioning, risk, and clinical management. These episodes will provide the basis for individual anonymized case vignettes that are submitted to our independent and blinded adjudication panel. All vignettes will be fully anonymized and any information relating to the EMPOWER intervention will be concealed. This panel will contain expert clinicians/researchers who will have the necessary knowledge, experience, and skills to make independent blinded judgments regarding relapse/exacerbation. The panel will determine that a relapse event has occurred and will also rate the severity of relapse on a 7-point scale based on the criteria included in Table 2. We will report time to first relapse, type of relapse (Relapse, Exacerbation, and Unspecified). We will also report number (%) with (1) return or exacerbation in psychotic symptoms, (2) duration of at least one week, (3) reduction in functioning, (4) increase in risk, (5) change in clinical management, (6) admission to hospital, and (7) use of mental health act. We will report details of all relapse outcomes across both groups. All participants will be assessed at each follow-up point for the presence of any of these criteria

described in Table 2, enabling us to calculate a mean severity score across participants and allocated groups at each follow-up point.

Candidate Secondary Outcomes

We will also assess changes in symptoms, substance use, emotional distress, carer burden, service engagement, and adherence and health-related quality of life.

1. Mental health status: The Positive and Negative Syndrome Scale [56], Personal and Social Performance Scale [57], and the Calgary Depression Scale for Schizophrenia [58] will be completed with service user participants.
2. Substance use measures: Time line follow back for drugs and alcohol [59]
3. Emotional distress: Hospital Anxiety and Depression Scale [60] and the Personal Beliefs about Illness Questionnaire-Revised [61].
4. Service engagement: The Service Attachment Scale [62] and the Medication Adherence Rating Scale [63] will be completed by service user participants.
5. Health Economics: EuroQol 5 Dimension 5 Level (EQ-5D-5L) [64] and the Assessment of Quality of Life—8 Dimension (AQoL-8D) [65], the CarerQoL [66], and a Resource Use Questionnaire (RUQ).

Candidate Mechanisms

Measures have been selected that map directly onto hypothesized mechanisms of change and known predictors of relapse. Mechanisms of service user benefit are operationalized as improvements in personal recovery, empowerment, and utilization of social support.

1. Recovery and self-efficacy: Questionnaire for Personal Recovery [67] and the General Self-Efficacy Scale [68] will be completed by service user participants.
2. Social and interpersonal context: Psychosis Attachment Measure [69] and Perceived Criticism and Warmth Measure adapted from the Perceived Criticism Measure (PCM) [70] will be completed by service user participants.

Carer Outcomes

The Involvement Evaluation Questionnaire [71] will be completed as a measure of carers worrying, tension, urging, and supervision. A carer PCM adapted from the PCM described above will be used as a measure of carers' perspectives on relationship quality.

We will also assess Carer Health Economic Outcomes using a purposively designed RUQ, time cost questionnaire, the EQ-5D-5L, and the CarerQol-7D.

Care Coordinator Outcomes

Participants care coordinators will complete the Service Engagement Scale [72].

Process Evaluation

In line with recent MRC Guidance on process evaluation of complex interventions [73], we will produce a logic model for the EMPOWER intervention and conduct a process evaluation. The process evaluation will be used to explore the ways in which EMPOWER may operate to produce outcomes. Specifically, it will focus on intervention fidelity, exposure, reach, context, recruitment, retention, and contamination, as well as the acceptability of study procedures. We will interview service users, carers, mental health staff, and research staff to ensure a multiperspective understanding of the intervention. We will publish the protocol for the process evaluation elsewhere.

Sample Size

No formal sample size calculation is appropriate for this pilot phase. The proposed sample size of up to 120 service users across 40 care coordinators in 8 CMHSs is deemed to be sufficient to establish feasibility and obtain parameters (including the relevant ICCs for the cluster design) to inform the design and size of a future definitive, pragmatic, multicenter, and multinational cRCT.

Recruitment and Randomization

The unit of randomization is the CMHS (the cluster). Participating CMHSs will be randomized within stratified pairs to the EMPOWER Relapse Prevention Intervention or to continue their usual approach to care. A statistician at the Centre for Healthcare Randomised Trials (CHaRT) at the University of Aberdeen will provide the allocation codes. The 2 clusters in Australia form a single stratum. The 6 clusters in Glasgow will be paired based on similarity of catchment area in terms of social deprivation or CMHS type (eg, early intervention service).

Researchers will approach each eligible care coordinator and seek their consent to participate in the trial. Before randomization, consenting care coordinators will provide an anonymized list of their current potentially eligible caseload of people using services. This list will then be randomly ordered by CHaRT. Researchers will then approach identified people sequentially in blocks of up to 5 potentially eligible participants and seek informed consent to participate in the study. If there are further participants eligible for inclusion at the end of this block, the researcher will move onto the next block of 5 (if applicable). Care coordinators will provide participants with an easy-to-read information leaflet about the study to enable potential participants to express interest in finding out more information. In Australia, information posters will be displayed within staff areas of participating sites to inform care coordinators of the study and provide contact details of RAs, should they wish to participate.

We aim to approach and consent on an average of 3 participants per care coordinator (giving a total of up to 120 potential participants). Following consultation with the independent Data Management and Ethics Committee (DMEC) and the Study Steering Committee (SSC) in May 2018, these recruitment objectives were amended to 86 participants. This was because of a number of challenges to recruitment including (1) temporary suspension of the study to apply for registration with the MHRA, which delayed start up to recruitment, (2) comprehensive and detailed screening of all potential trial participants, (3) delays arising from care coordinators approaching potential participants, and (4) high rates of turnover among care coordinators. Following independent methodological and statistical advice, there was clear guidance that the original

feasibility aims will be met by the trial, and this change to recruitment targets was approved by the funders. After completing baseline assessments on all consenting service users in care coordinators' and CMHSs' caseload, the Clinical Trials Unit (CTU) at CHaRT will conduct randomization of the CMHSs. For Australia, with just 2 clusters, this will be by simple randomization by the CTU. For Glasgow, with 6 clusters, the CTU will create 3 pairs of teams based on similarity of the catchment area in terms of social deprivation (Carstairs) score or CMHS type (eg, early intervention service). The CTU will randomly allocate one member of the pair to the intervention, and the remaining member will be allocated to control.

We will explore in this pilot phase the best method of randomly allocating the clusters in the full trial, specifically to establish what matching factors (if any, and/or if matching at all is appropriate, methodologically) are suitable. Any violations of the study protocol will be recorded and reported to the Research Ethics Committee, SSC, and the independent DMEC.

Statistical Analysis

A full statistical analysis plan will be written before (and published on the CHaRT website) any analysis is being undertaken. All analyses will be carried out using the intention-to-treat principle with data from all participants included in the analysis including those who do not complete the intervention. Every effort will be made to follow up all participants in both arms for research assessments. The analysis will follow the guidelines of the CONSORT statement for clustered randomized trials and recommendations for the analysis of clustered randomized trials when presenting and analyzing the data. Here, we have potentially repeated measures on individual patients nested within care coordinators who are nested within teams (the unit of randomization) who are in turn nested within region (Australia and the United Kingdom or possibly to be known as Scotland). The analysis will adjust for these factors using appropriate random (service user, if relevant; care coordinator; and team) and fixed (region) effects. The trial statistician will remain blind until the main analyses are complete. Baseline characteristics of the study population will be summarized separately within each randomized group. Baseline characteristics will also be presented for drop-outs and completers within each treatment group.

A full Health Economic Statistical Analysis Plan will be written before any analysis is being undertaken. As part of the within trial economic evaluation, we propose to test 2 health-related quality of life measures (which can be used to assess Quality-Adjusted Life Years), the EQ-5D-5L, and the AQoL-8D in the feasibility trial. Although the EQ-5D-5L is very commonly used in the United Kingdom and Australian context, its sensitivity and appropriateness in people with schizophrenia has been seriously questioned [74]. The AQoL-8D is a newer HRQoL measure and was developed to be sensitive to the domains of quality of life that are important to people with mental health problems. A RUQ to capture costs incurred will also be tested. This questionnaire will need to be appropriate to both the United Kingdom and Australian context but may require some system-specific modules for services, which differ between the 2 settings.

Data Sharing

Data generated by this research will be made available as soon as possible based upon reasonable request to the study chief investigator.

Ethics Approval

West of Scotland Research Ethics Service (GN16MH271 Ref: REC/16/WS/0042) and Melbourne Health (HREC/15/MH/344).

Results

Recruitment to the trial began in September 2017, and follow-up of participants was completed in July 2019. The database lock was in July 2019, followed by analysis and disclosing of group allocation.

Discussion

Relapse among people with a diagnosis of schizophrenia is a major contributor to poorer outcomes in terms of greater symptom severity, distress, and risk of a range of adverse outcomes including coercion into care, self-harm, and suicide [8-12]. People diagnosed with schizophrenia worry about relapse, and this is linked to feelings of anxiety, shame, depression, and shorter time to relapse [18]. Relapse contributes to carers' experiences of distress and worry and has been linked to greater needs for continuity of communication with mental health care professionals [75]. Mental health staff are concerned about the impact of relapse on service users and carers, but the impact on their roles are also considerable in terms of responding to crises and increased risk [24]. These sources of strain place relationships under significant pressure, which can break down communication, anticipatory care, and shared decision making especially in the context of EWSs of relapse. This can potentially result in loss of collaboration, increased risk of disengagement, and greater use of coercion, thus confirming many of the fearful and threat-based expectations held by service users, carers, and, arguably, the staff [25].

On the basis of our theoretical model outlined earlier, we have developed an intervention that blends a digital intervention with peer support, with triage of increased risk of relapse to prompt early interventions that are attuned to needs of service users. Our approach uses digital technology to enable service users to monitor the *ebb and flow* of emotional well-being in daily life and utilizes an algorithm to deliver messages to enhance attunement, awareness, curiosity, and self-management in response to changes in well-being. In our theory, the blending of digital with peer support is important to cultivate helpful conversations to promote greater autonomy, empowerment, and recovery. We anticipate that conversations focused around the *ebb and flow* of changes in well-being in daily life can also increase opportunities for earlier help seeking, collaboration, and shared decision making in the event of possible EWSs facilitated by clinician triage into a relapse prevention pathway embedded in mental health services.

The EMPOWER trial will deliver the protocol for a blended digital intervention and will establish the feasibility of running a definitive cRCT. We will establish the safety, acceptability,

usability, and performance parameters of the EMPOWER intervention. We will learn how to optimize the identification, consent, and follow-up of potentially eligible participants. We will establish the feasibility of measuring and collecting our candidate primary, secondary, and mechanistic outcomes. However, in its own right, our study has a number of important broader implications for digital health interventions for people diagnosed with schizophrenia and psychosis. Our mobile phone app will be available for people to use for up to 1 year on a daily basis. To our knowledge, this will be the longest RCT of a mobile phone app in psychosis to date. In addition, the algorithm that underpins the assessment of *ebb and flow* is, to our knowledge, the first mental health app to be registered as a medical device trial (CI/2017/0039) by the United Kingdom's Medicines and Healthcare products Regulatory Agency.

We will also establish and report the rater reliability of our a priori definition of relapse that has been informed by our theoretical model [18] that underpins the intervention. In studies of relapse in schizophrenia, there is a lack of consensus as to the definitions of relapse measurement [76], very often studies actually fail to report their definitions of relapse [77], and, to our knowledge, none have ever consulted people with lived experience of psychosis on how relapse is measured and defined. Our approach to relapse assessment aims to address these major shortcomings in the literature making the theory, rationale, measurement, and interrater reliability of our definition explicit. In addition, our approach will enable us to report time to relapse, severity of relapse, and mean severity scores across groups at each follow-up timepoint.

Acknowledgments

The authors are grateful to all the service users, carers, and mental health staff and CMHSs who gave their time and resources to contribute to the development of this study during the consultation phase. This was critical in shaping the refinement of the EMPOWER intervention and outcomes. The authors are grateful to all the service users, carers, and mental health staff and CMHSs who gave their time and resources to contribute to the cRCT. The authors also express their gratitude to their SSC members, Professor David Kingdon (Chair), Professor Daniel Freeman (independent member), Professor Fiona Lobban (independent member), David Kavanagh (independent member), Frances Simpson (independent public and patient involvement representative), and Graham Morgan (independent public and patient involvement representative). The authors express their gratitude to their Data Monitoring and Ethics Committee members, Professor Emmanuelle Peters (Chair), Dr Alison Brabban (independent clinician), Professor Rod Taylor (independent statistician), and Professor Greg Murray (independent statistician). This study was funded in the United Kingdom by the National Institute for Health Research Health Technology Assessment program (project number 13/154/04) and in Australia by the National Health and Medical Research Council (APP1095879). It will be published in full in the Health Technology Assessment. This study is supported by NHS Research Scotland, through the Chief Scientist Office and the NHS Scotland Mental Health Network. The Health Services Research Unit is funded by the Chief Scientist Office of the Scottish Government Health Directorate. MA-J is supported by a Career Development Fellowship (APP1082934) from the National Health and Medical Research Council. SA is supported by a Cremore Research Fellowship, bequested to the University of Glasgow. The study sponsors and funders were not involved in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Authors' Contributions

AG is a chief investigator who together with JG and JF developed the study protocol alongside the other coinvestigators (JA, MA-J, MB, AB, SB, SBu, SMC, PF, RL, SL, GMacL, CM, JN, SM, SS, SSu, AT, CW, and AY) and has overall responsibility for the management and delivery of the trial. AG, JF, JG, SB, and EM finalized the study protocol for implementation. SB is the trial manager and is responsible for coordinating the trial. EM is the trial coordinator in Australia and is responsible for coordinating the trial in Melbourne. EM, HW, AC, CMa, and IB are RAs on the trial and have responsibility for participant recruitment and data capture. HMcL, SB, and EM developed and implemented standard operating procedures for participant assessment and data collection. AG, SB, JF, and EM oversee the design and implementation of the intervention. AWK, EM, EC, DT, and JA contributed to the development and implement the intervention. AB, CM, LE, and NMcM lead the health economic evaluation and modeling. SA is the process evaluation researcher. LB has implemented the evaluation of data quality at each follow-up. The Scottish Recovery Network via JF and LS led public and patient involvement at the outset of the study. All authors commented on and approved the final version of the paper.

Conflicts of Interest

AG reports personal fees from the University of Manchester, personal fees from the University of Exeter, personal fees from BABCP, and other interests with NHS Education for Scotland outside the submitted work. JA and SB report other interests with Affigo CIC, outside the submitted work. AB reports personal fees from Bayer, Merck, Janssen, Novartis, Sword Health, Amgen, and Daiichi Sankyo outside the submitted work. JF reports grants from National Health & Medical Research Council (Australia) during the conduct of the study and other interests with Melbourne Health (NorthWestern Mental Health) outside the submitted work. SL reports grants from MRC, nonfinancial support from Affigo CIC, and personal fees from Xenzone PLC outside the submitted work. HMcL reports grants from NIHR HTA during the conduct of the study. CM reports grants from National Health & Medical Research Council (Australia) during the conduct of the study. JN reports grants from the University of Aberdeen and

the University of Edinburgh during the conduct of the study and declares membership of the following NIHR boards: CPR decision-making committee; HTA Commissioning Board; HTA Commissioning Sub-Board (EOI); HTA Funding Boards Policy Group; HTA General Board; HTA Post-Board funding teleconference; NIHR CTU Standing Advisory Committee; NIHR HTA & EME Editorial Board; and Pre-exposure Prophylaxis Impact Review Panel. CW reports grants from NIHR during the conduct of the study and other interests with Five Areas Ltd outside the submitted work. MA-J was supported by a Career Development Fellowship (APP1082934) from the National Health and Medical Research Council. SA, SBr, SS, MS, FR, MB, SSu, PF, SC, LE, EM, GMacL, NMcM, AT, MM, RL, DT, HW, IB, AW-K, and LB all declare no conflicts of interest outside the submitted work.

Multimedia Appendix 1
Peer-reviewer report from the National Institute for Health Research - Health Technology Assessment Programme (NIHR-HTA).
[PDF File (Adobe PDF File), 831 KB - resprot_v9i1e15058_app1.pdf]

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Abbreviations

AQoL-8D: Assessment of Quality of Life—8 Dimension
CHaRT: Centre for Healthcare Randomised Trials
ChIP: check in prompt
CMHS: community mental health service

CONSORT: Consolidated Standards of Reporting Trials
cRCT: cluster randomized controlled trial
CTU: Clinical Trials Unit
DMEC: Data Management and Ethics Committee
EMA: ecological momentary assessment
EMPOWER: Early signs Monitoring to Prevent relapse in psychosis and prOmote Well-being, Engagement, and Recovery
EQ-5D-5L: EuroQol 5 Dimension 5 Level
EWS: early warning sign
ICD10: International Classification of Diseases-10
ITAREPS: Information Technology–Aided Relapse Prevention Program in Schizophrenia
JCP: joint crisis plan
MHRA: Medicines and Healthcare products Regulatory Agency
NHS: National Health Service
PCM: perceived criticism measure
PSW: peer support worker
RA: research assistant
RCT: randomized controlled trial
RR: risk ratio
RUQ: Resource Use Questionnaire
SSC: Study Steering Committee
TAU: treatment as usual

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Protocol

Effects of Bluetooth-Enabled Desk Ellipticals on Office Work Performance: Rationale, Design, and Protocol for a Randomized Trial With Overweight and Obese Adults

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Abstract

Background: Workplaces that provide opportunities for physical activity without requiring extra time for activity could help counteract the obesity epidemic. Desk ellipticals can contribute to activity-supportive workplace environments; however, the feasibility of engaging employees in pedaling ellipticals during simultaneous office work has not been well evaluated.

Objective: We aim to present the rationale and methods from an ongoing randomized trial with overweight and obese employees that will evaluate (1) the effects of pedaling a compact desk elliptical on work performance and (2) the influence of different incentive types and schedules on desk pedaling quantity.

Methods: Overweight and obese medical center employees are being recruited in dyads for a 2 (gift card type: healthier food vs Amazon) by 3 (gift card schedule: immediate incentive contingent on individual pedaling quantity; immediate incentive partially contingent on dyads' joint pedaling quantity; and delayed noncontingent pedaling incentive) cluster randomized within-subjects factorial trial. All participants receive a Bluetooth-enabled desk elliptical for 4 weeks and access to a mobile app that provides real-time pedaling feedback. The primary aims are to assess (1) change in employee work performance from pre- to postelliptical installation via employee and supervisor ratings and (2) effects of gift card type and schedule on quantity of objectively measured desk pedaling completed.

Results: Data collection is ongoing. We expect to complete main outcome analyses in 2020.

Conclusions: This trial represents one of the earliest attempts to assess the effects of desk pedaling and pedaling-incentive types in real-world offices. It could help bridge the research-to-practice gap by providing evidence on whether desk pedaling can be sustained without compromising work performance.

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KEYWORDS

physical activity; obesity; reinforcement; environment design; built environment; occupational health; workplace; mHealth

Introduction

Background

Most working-aged US adults spend more than half of each day in sedentary behavior [1,2] and at least 60% do not meet recommended physical activity guidelines [3,4], which increases the risk for obesity and chronic disease [4-6]. Adults in the workforce identify lack of time as one of the most significant barriers to regular physical activity [7,8]. Fewer than 1 in 3 employed adults typically participate in workplace physical activity programs [9,10].

Desk ellipticals, which enable people to expend about 85 to 90 extra kilocalories per hour over sedentary sitting [11,12], can address the time barrier to physical activity in 2 unique ways. First, desk ellipticals reduce the opportunity cost of physical activity, as employees can pedal *while* working and are not required to commit extra time to complete physical activity [13]. Second, unlike typical workplace physical activity interventions which are conducted outside working hours [14], desk ellipticals can be placed in employees' immediate environment—near computers, telephones, and coworkers [11]. This feature is important because lack of time for physical activity often reflects a low density of immediate cues (prompts) and reinforcers (eg, economic, social, physical, or emotional benefits) for physical activity, coupled with a higher density of such cues and reinforcers for competing work and social demands [15,16]. Placing desk ellipticals in employees' workspaces, where they can generate immediate cues and reinforcement for activity (eg, visual prompts to pedal, coworker modeling of pedaling, or praise for pedaling), is consistent with ecological models and research supporting the importance of proximal environmental influences on physical activity and sedentary behavior [17,18].

Desk Pedaling and Work Performance

To disseminate desk ellipticals or similar devices on a large scale, employers will require evidence that pedaling such devices does not compromise work performance [19,20]. Most previous studies that assessed simultaneous work performance during desk pedaling were conducted in lab-based settings [21-26]. These lab-based studies supported the feasibility of completing specific work tasks during simultaneous desk pedaling, within controlled environments that maximized internal validity [27]. However, there has been limited research on work performance and simultaneous desk pedaling in field settings where employees perform their actual jobs. Conducting work performance evaluations in field settings is important for the external validity of study findings, as these settings may include unique social and built environment constraints or facilitators (eg, coworker criticism or praise, and office layout variations) that are difficult to engineer in a lab [27,28].

Among several studies that investigated the use of compact elliptical or pedaling devices in real-world offices, employee-administered surveys suggested that it was feasible to work productively while engaged in simultaneous pedaling [13,29,30]. However, these studies lacked input from supervisors about the effects of pedaling devices on employee performance—which is needed to ensure more widespread acceptance and dissemination of these devices. These studies also lacked assessment of employees' ability to perform specific common office work tasks (eg, emails and phone calls) while pedaling. Therefore, a more comprehensive assessment of work performance during office-based pedaling is warranted.

Incentives and Desk Pedaling Quantity

Previous office-based desk pedaling studies demonstrated small declines in employees' pedaling activity over time [13,29,31,32], suggesting a need for greater reinforcement of pedaling activity. Both primary food-based and generalized monetary reinforcers can help to sustain physical activity [33-39], but these types of incentives have not been explored in desk pedaling trials, or directly compared for their effects on sustaining physical activity or other health behaviors. Providing healthier food-based incentives may offer advantages over traditional monetary incentives or cash-equivalent gift cards, including the potential to address the obesity epidemic, increase cost-effectiveness via improved health, and build cultural norms for healthful eating [33]. In contrast with money or cash-equivalent gift cards which are obtained at a fixed price point, there may also be opportunities to secure volume discounts for food items to attain cost savings for population-wide interventions. Understanding the differential effects of healthier food versus monetary or cash-equivalent incentives could inform the design of popular workplace incentive plans for healthy lifestyle change [40].

In addition to the differential effects of incentive type, incentive delivery schedules may impact desk pedaling quantity. Food or monetary reinforcers delivered on an immediate reinforcement schedule close-in-time to achieving physical activity and other behavioral goals have been more effective in increasing physical activity or motivation than delayed reinforcers [34,41,42]. Some evidence also suggests increased likelihood of achieving behavioral health goals when the receipt of reinforcers is partially contingent on 2 or more people achieving a goal, rather than solely dependent on individual goal achievement [43,44]. The effects of varying these reinforcement schedules on desk pedaling quantity have not yet been investigated.

Purpose and Hypotheses

In sum, we aim to present the rationale and methods for a randomized trial among overweight and obese employees that will assess the effects of (1) desk pedaling on work performance using comprehensive employee- and supervisor-rated work performance measures and (2) healthier food versus monetary incentives with varied reinforcement schedules on pedaling quantity. We hypothesize that a 4-week desk pedaling intervention period, as compared with a 4-week preintervention period of standard office sitting, will not yield meaningful differences in employees' work performance. We also hypothesize that healthier food and monetary incentives delivered (1) on an immediate rather than a delayed schedule, and (2) partially contingent on dyadic- rather than solely individual-goal achievements, will yield greater pedaling quantity. Achieving these aims could help bridge the research-to-practice gap in translating desk ellipticals from laboratory settings to real-world office environments.

Methods

Design

We will use a 2 (gift card type: healthier food vs Amazon) by 3 (gift card schedule: immediate incentive contingent on individual pedaling quantity, immediate incentive partially contingent on dyads' joint pedaling quantity, and delayed noncontingent pedaling incentive) cluster randomized within-subjects factorial design. Employee dyads (n=60 or 30 two-person clusters) will be recruited on a rolling basis to join the program together and will be randomly assigned in clusters to 1 of the 6 study groups using computer-generated permuted block randomization (block size of 6 with equal allocation, determined by a statistician).

The intervention phase will last 4 weeks, with within-subject assessments (via pre- and postintervention questionnaires) used to capture changes in work performance and reported nonpedaling physical activity between a 4-week preintervention period with standard office sitting and a 4-week intervention period with desk pedaling. The primary outcomes are (1) changes in employee- and supervisor-reported work performance between the 4-week preintervention period and the 4-week intervention period and (2) objectively measured pedaling quantity during the 4-week intervention period based on data from the Bluetooth-enabled desk ellipticals. The secondary outcomes include employee-reported changes in nonpedaling physical activity, cost-effectiveness of incentive conditions (measured by the total dollar value of gift cards distributed and redeemed, and by work productivity and body weight changes), participant satisfaction, and built and social environment influences on employees' work performance and pedaling quantity.

The study was approved by the Pennsylvania State University College of Medicine Institutional Review Board, and the National Institutes of Health peer-review statements are included in Multimedia Appendices 1 and 2.

Inclusion and Exclusion Criteria

Inclusion criteria for participation are shown in Textbox 1. Exclusion criteria for participation are shown in Textbox 2.

Textbox 1. Inclusion criteria.

- Overweight or obese (body mass index between 25 and 55 kg/m^2)
- Employed full time at Penn State Hershey Medical Center and physically present in the office a minimum of 35 hours per week to ensure it is feasible to complete daily pedaling
- Work between 6 am and 6 pm, Monday through Friday, as this is the time frame during which study staff are available to oversee the program
- Desk-based office job involving sedentary work for ≥5 hours per day, 5 days per week
- Use a nonshared desk so the pedaling measured can be attributed to the study participant
- Aged between 18 and 70 years
- Able to read and speak English
- Own an Android or iPhone smartphone with internet or Wi-Fi access and willing to install the free Cubii cycling app (Fitness Cubed Inc) needed for all study conditions on their smartphone
- Work in a campus building that has at least one onsite Hershey-operated food vendor. On the basis of research showing the importance of resource proximity for resource use [45,46], the food-based rewards are more likely to be used if they are easily accessible
- Able to obtain their supervisor's approval to participate
- Able to identify a coworker to do the program together with, who also meets all eligibility criteria after separately completing the screening form, based on evidence that social environment support can promote physical activity [45,47,48]

Textbox 2. Exclusion criteria.

- Currently pregnant
- Health or personal condition (eg, planned surgery) that could prevent program completion
- Physical Activity Readiness Questionnaire [49] response indicating that participants (1) have been advised that they have a heart condition and should only do physical activity recommended by their doctor or (2) have chest pain during physical activity
- Planned travel or relocation that will lead participants to be unavailable for 3 or more days during the study and that cannot be accommodated by adjusting the program dates
- Already have a cycling device or treadmill workstation at their desk

Setting and Recruitment

The study is based at the Penn State Hershey Medical Center, a major teaching and research hospital with more than 12,000 employees in Central Pennsylvania [50]. Sedentary desk jobs at the medical center are diverse and include secretarial and administrative work, grant proposal preparation, budgetary administration, radiology and scan analysis, quality control initiatives, and faculty member and other research or clinical support positions. A brief study description was distributed via

electronic newsletter to all employees to publicize the study. The study description contained a link to the secure REDCap site [51] to complete a screening form to assess inclusion and exclusion criteria. The study description was additionally emailed to administrative staff who were given the option of forwarding this information to department employees. Study information was also posted on Penn State's research recruitment website.

Employees who remain eligible to participate after completing the screening form are asked to provide their supervisor's contact information. Supervisors then receive a brief study summary, together with a link to a secure Web-based REDCap form to enable them to document consent for their employee(s) to participate. Following receipt of the supervisor's permission form, an initial study meeting is scheduled at the participant's office. At this approximately 20-min meeting, the consent form and baseline questionnaire are administered, and the research team evaluates the participant's desk setup to determine if modifications are required to ergonomically place the elliptical under the participant's desk (eg, accessible electrical outlet to plug in the elliptical and relocation of underdesk items).

Intervention Procedures

Common Elements

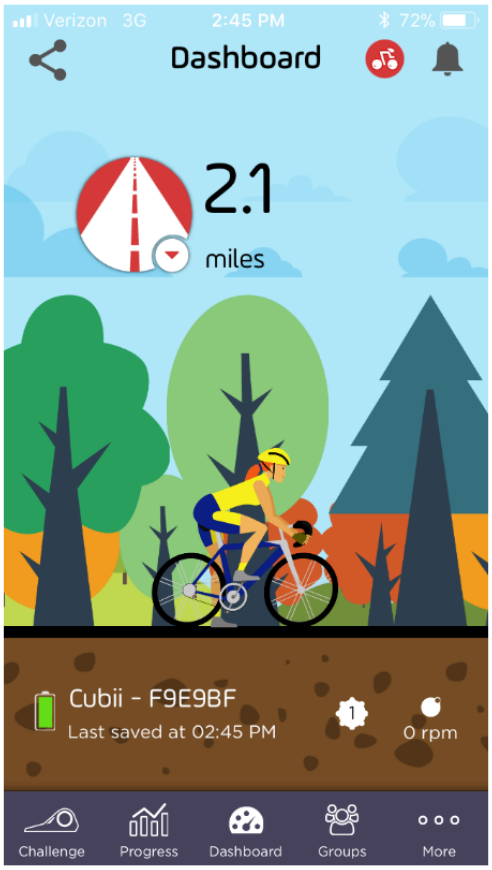
Participants in all 6 conditions are provided with the Cubii Pro elliptical (Fitness Cubed Inc) at no cost (Figure 1). During an approximately 1-hour elliptical setup meeting, research staff work with each participant to set up the desk elliptical ergonomically, including placing the elliptical at a comfortable distance and angle from the participant's chair and keyboard and equipping participants with rubber mats and chair anchors to prevent excess chair and elliptical motion while pedaling.

During the elliptical setup meeting, research staff also install the free Cubii elliptical app on each participant's Android or iPhone smartphone. This app provides participants with real-time automated feedback on both their own and their partner's pedaling volume (ie, miles, strides, minutes, and calories expended), and shows a bicyclist moving in real time in sync with each participant's pedaling (Figure 2). Research staff demonstrate key app features to participants and explain how to check the elliptical is connected to the app to prevent loss of pedaling data. Research staff also link each participant's pedaling data to a research-administered Cubii server account and Fitbit account to enable automatic uploading of each participant's pedaling data. Although the Cubii server data can only be obtained by the researchers on a delayed basis, participants' pedaling data on the Fitbit site are available continuously—enabling research staff to monitor pedaling adherence in real time.

All participants are asked to attempt to pedal the elliptical at least 2 miles daily (approximately 1 hour of daily pedaling) from Monday through Friday. The goal of 2 miles, or 1 hour, of daily pedaling was determined by prior studies, which suggested that this goal could have a clinically significant impact on weight gain prevention while being feasible for overweight and unfit participants [11,13]. Participants are informed that they can choose to pedal more or less than the 2-mile goal and are advised to self-select a comfortable pedaling pace, intensity, and duration. Participants are also advised that they can pedal the desk elliptical in short bouts of a few minutes at a time or in longer bouts. Although participants are asked to attempt to pedal on all 5 workdays, they are informed that it is understandable if they occasionally need to miss a day or reduce their pedaling.

Figure 1. Desk elliptical setup in standard office cubicle.

Figure 2. Screenshot of Cubii mobile app dashboard with real-time pedaling feedback.



Participants receive a verbal description and handout outlining their reward type and schedule that is tailored to the study group to which they and their partner have been randomly assigned. Participants are informed in the consent document that while all participants will receive incentives, the incentive type (ie, vendor) and delivery schedule may vary depending upon which group they are randomly assigned to. To prevent treatment contamination, participants are not given procedural details regarding the incentive type and schedule that other groups receive.

Features Specific to Each of the Intervention Groups

Figure 3 summarizes key details for each of the 6 intervention groups. More specific procedural details are provided below.

Individual Contingent Immediate Reward (ICIR) and Joint Contingent Immediate Reward (JCIR) participants receive daily reminder emails to notify research staff when they reach the 2-mile pedaling goal by using the single-click Cubii app notification feature to email staff an automatically generated summary of their pedaling mileage. Each daily reminder includes a brief tip (eg, “Desk cycling can help people deal with daily life hassles and stressors!”). Research staff typically send each participant a reward email with an e-gift card (Figure 4) within 2 hours after participants submit a notification that they reached or exceeded the 2-mile daily pedaling goal.

To redeem gift cards, Pedal4Food group participants are asked to print each gift card and hand it to the Penn State-Hershey food service cashier. Participants and cashiers are instructed that the food gift cards may only be used to redeem the specific beverage or food items displayed on each gift card. All food gift cards are stapled to each participant’s food receipt and held for weekly pickup by research staff, who then manually record each card’s ID number and the items purchased. The Pedal4Money group redeems gift cards by applying their Amazon gift card codes at the Amazon website toward any purchase; redemption is tracked via Amazon by research staff.

The value of compensation over the 4-week intervention period for both the ICIR and JCIR groups ranges from US $0 (if zero pedaling is done) to US $72 (if participants meet all pedaling goals: 5 workdays×US $2=US $10, plus US $8 bonus=US $18/week×4 weeks=US $72). The maximum weekly compensation rate of US $18 was based on systematic reviews which suggested that this amount is representative of average incentive sizes and is associated with increased physical activity [38,39]. Assuming the ICIR and JCIR groups attain typical physical activity adherence rates of approximately 65% to 70% that were observed in prior trials with financial incentives [41,52-54], we expect that most ICIR and JCIR participants will earn approximately US $50—equivalent to the US $50 compensation amount provided to the Usual Delayed Reward participants.

Figure 3. Randomized 2 (gift card type) by 3 (gift card schedule) factorial study design. a: In the Pedal4Food—Individual or Joint Contingent Immediate Reward groups, the $2 e-gift card covers a beverage (standard small coffee, tea, or bottled water), and the $8 e-gift card covers a meal (any combination of a salad, wrap, sandwich, soup, or bottled water) redeemable at the Hershey Medical Center-operated cafeterias, Au Bon Pain and Starbucks); the Usual Delayed Reward group receives $50 of combined beverage and food e-gift cards proportional in quantity to the other 2 groups; b: In the Pedal4Money—Individual or Joint Contingent Immediate Reward groups, the $2 and $8 e-gift cards can be applied toward any purchase on Amazon; the Usual Delayed Reward group receives incentives combined as a $50 Amazon e-gift card; c: The symbol "X" indicates that an intervention procedure was administered for the designated study group; d: This bonus is received if both partners meet pedaling goals on at least 4 workdays, or if one partner meets pedaling goals for 3 workdays and one meets goals for 5 workdays.

	Gift Card Type		
	Pedal4Food: Receives food e-gift cards[a]	Pedal4Money: Receives Amazon e-gift cards[b]	
	Gift Card Schedule		
Intervention Procedures	Usual Delayed Reward	Individual Contingent Immediate Reward	Joint Contingent Immediate Reward
Share pedaling data with partner via Cubii app.	X[c]	X	X
E-gift card ($50) given post-intervention; not contingent on pedaling quantity.	X		
Email prompt each workday to pedal for e-gift card.		X	X
Daily $2 e-gift card available each workday; receipt contingent on *individual* success in reaching 2-mile daily pedaling goal.		X	X
Bonus $8 e-gift card available each work week; receipt contingent on *individual* success in reaching 2-mile pedaling goal on at least 4 of 5 workdays.		X	
Bonus $8 e-gift card available each work week; receipt contingent on dyad's *joint* success in reaching 2-mile pedaling goal for *average* of at least 4 of 5 workdays.[d]			X

Figure 4. Sample e-gift card: Pedal4Food—Individual Contingent Immediate Reward condition.

Measures

The study's measures are shown in Table 1. The objective measures for pedaling volume are obtained from the Cubii company's server and provided by the Cubii company to our research team via password-protected files. Aside from the objective Cubii measures and the gift card redemption receipts and records, all other measures are administered via secure Web-based REDCap surveys [51]. Employee participants are compensated at the end of the study US $10 in cash for completing the preprogram survey and US $15 in cash for completing the postprogram survey. Employees' supervisors are not compensated for survey completion. Supervisors are asked to *not* share their ratings of each employee's work performance with employees.

Table 1. Measures and measurement schedule.

Measures	Schedule		
	M0[a]	M1[b]	M2[c]
Employee ratings of work performance			
1. The World Health Organization Health and Work Performance Questionnaire: Employees rate overall work performance in previous 4 weeks on a 10-point scale; lower employee-rated work performance associated with odds of lower performance in supervisor evaluations and records and experience sampling across multiple job types (odds ratios: 3.2-12.3, *P* values<.05) [55].	X[d]	—[e]	X
2. Employees rate work quantity, work quality, and interaction quality in previous 4 weeks on a 5-point scale; evidence of face validity [56]; higher work quantity associated with higher physical fitness (*P*=.045), higher work quality associated with higher moderate physical activity (*P*=.002), lower interaction quality associated with greater obesity (*P*=.02) [57].	X	—	X
3. Work performance by task type: Employees rate ability to perform common work tasks (eg, emails and phone calls) during elliptical use in previous 4 weeks, using a 5-point investigator-generated scale.	—	—	X
Supervisor ratings of employee work performance			
1. The World Health Organization Health and Work Performance Questionnaire: Slightly adapted for supervisor ratings from above employee version [55].	X	—	X
2. Supervisors rate employees' work quantity, work quality, and interaction quality: slightly adapted from above employee version [56,57].	X	—	X
Elliptical pedaling volume			
1. Objectively measured pedaling output from Cubii elliptical: total pedaling miles, strides, minutes, and calories expended.	—	X	—
2. Percentage achieving daily 2-mile pedaling goals.	—	X	—
Gift card distribution, redemption, and costs			
1. Number of gift cards distributed, by amount and type.	—	X	—
2. Percentage of food gift cards redeemed, via food service receipts.	—	X	X
3. Percentage of Amazon gift cards redeemed, via Amazon website.	—	X	X
Total nonpedaling physical activity			
1. Stanford Leisure-Time Activity Categorical Item: Participants select 1 of 6 categories to describe their physical activity in the previous month; test-retest Spearman ρ=0.80 [58], associated with accelerometer-measured moderate-vigorous activity min/week, Spearman ρ=0.40, *P*<.001 [59].	X	—	X
2. Global Physical Activity Questionnaire: Captures domain-specific physical activity in typical week; test-retest Spearman ρ=0.67-0.81 [60], associated with accelerometer-measured moderate-vigorous activity min/day (r=0.48; *P*<.005) [61].	X	—	X
Participant satisfaction			
1. Investigator-generated program evaluation measures [62].	—	—	X
2. Qualitative, open-ended user evaluation questions.	—	—	X
Built and social environment			
1. Office Spatial Layout: Employees rate office environment features (eg, office layout and coworker proximity) on a 5-point scale; test-retest intraclass correlation coefficient=0.70-0.87, associated with occupational sitting (*P*<.05) [63].	X	—	—
2. Employees rate reactions of coworkers, supervisor, family members, and friends to their elliptical use on a 5-point investigator-generated scale.	—	—	X
Demographic and health characteristics			
1. Employee demographics, self-rated health, height, and weight.	X	—	X
2. Supervisor demographics.	X	—	—

[a]M0=preintervention.

[b]M1=4-week intervention phase.

[c]M2=postintervention.

[d]The symbol "X" indicates that a measure was administered at this assessment point.

[e]A measure was not administered at this assessment point.

Statistical Analysis

We will perform descriptive analyses for all measured variables. We will examine data normality and skewness, along with missing data and address any identified issues using standard procedures [27].

Effects of Desk Pedaling on Work Performance

For the study's first goal, to test whether mean work performance scores during the 4-week desk pedaling intervention period are equivalent to performance during the 4-week preintervention period with standard office sitting, we will apply the equivalence test of means based on 2 one-sided *t* tests [64,65] with the significance level adjusted for multiple comparisons via the Bonferroni correction factor. We will also use the confidence interval approach for testing equivalence when regression models are considered [66].

We define equivalence based on 2 related standards: (1) the International Organization of Standardization ergonomic standard for computer keyboards indicates that average typing speeds obtained using a new keyboard must not exceed 0.75 standard deviations of average speeds for standard keyboards (in the direction of poorer performance) to be acceptable [67]; (2) in clinical research, a change of 0.50 standard deviations in health status sometimes is used as a basis for treatment modifications [68,69]. Using the approximate midpoint of these 2 standards, we define equivalence, or feasibility, for the desk elliptical as average work performance scores that do not exceed 0.60 standard deviations (in the direction of poorer performance) of average work performance scores obtained during standard office sitting.

We will also explore how work performance varies by tertiles of elliptical pedaling quantity. To evaluate changes in overall work performance, and work performance by task type, which are repeatedly measured, we will plot mean scores over time and conduct longitudinal analysis based on mixed effects models [70]. We will use random effects to account for measurement correlation within the same subject and clustering effects. The estimated time effect from mixed effects models will indicate whether performance increased, decreased, or remained stable over the preintervention and intervention periods.

For the qualitative assessment of participants' capacity to pedal and work simultaneously, NVivo software (QSR International) will be used to organize data from the qualitative open-ended questions. A codebook will be developed to classify major themes, and data will be coded by 2 independent coders. Coding discrepancies will be discussed and resolved, and interrater reliability will be calculated.

Effects of Incentive Condition on Desk Pedaling Quantity

For the study's second goal, to assess the effects of the 6 incentive conditions on pedaling quantity (miles and minutes) completed over 4 weeks, we will model elliptical miles and minutes per day as continuous outcomes using linear mixed effects models with repeated observations of each outcome variable (level 1) treated as nested within (n=60) individual participants (level 2), while accounting for clustering effects within each dyad (level 3). We will add to our models effect coded vectors for gift card type (food vs Amazon) and gift card schedule (Usual Delayed Reward vs ICIR vs JCIR) to test for main effects; along with gift card type×gift card schedule interaction terms to test for simple effects across cells.

Covariates will be included in all analyses to adjust for participants' demographic and health characteristics (eg, age, gender, race and ethnicity, education, body mass index, and nonpedaling physical activity). Finally, we will use multivariable mixed effects models to explore the association of employees' demographic and health characteristics, social and built-office environment factors, and supervisor characteristics with employees' work performance and pedaling quantity. All mixed effects models will follow an intention-to-treat principle, using all available data.

Other secondary analyses will depend on the specific research question and the most appropriate statistical or qualitative methods for the design.

Power and Sample Size

We assume that an equivalence margin standardized by the standard deviation is 0.60 for the primary outcome, based on clinical and industrial engineering standards [67-69]. We also assume an intracluster correlation of 0.05 and a significance level of 0.05. Therefore, a sample size of 50 (25 dyads) gives 80% power to detect equivalence when assessing the mean delta change in total work performance scores from the preintervention period to the intervention period. Anticipating 10% to 20% attrition, we expect to recruit up to 60 participants. The study was not powered to detect differences in pedaling volume by the 6 incentive conditions because of resource constraints and because a key exploratory goal was to assess feasibility and preliminary effects of different incentive strategies.

Results

Data collection will be completed by December 2019. We expect to complete main outcome analyses in 2020.

Discussion

Principal Considerations

Since 1960, increased computer automation in the workplace has led average work-related energy expenditure to drop by more than 100 calories per day [71]. This progressive decline in working adults' daily energy expenditure has contributed to rising obesity rates, with 40% of US adults currently obese [71-73]. Adults in small-to-medium size metropolitan statistical areas, such as Central Pennsylvania, are at even greater risk for obesity than adults in more urbanized regions [74], indicating a need for wider environmental support to promote employee health. Desk ellipticals, which are compact, relatively low-cost, and scalable across diverse workplaces, may contribute to creating healthier workplace environments—consistent with the goals of the National Institutes of Health Total Worker Health Initiative [75]. This study aimed to respond to the need to create healthier workplaces to prevent or reduce overweight

and obesity by conducting a randomized trial to assess the feasibility of engaging employees in pedaling desk ellipticals while simultaneously completing productive office work. The knowledge gained from this study may help guide efforts to create environments and policies that promote *active* office work as a standard feature of occupational health practice.

Strengths and Limitations

Strengths of this study include its use of supervisor ratings of employee work performance and objective measures of pedaling quantity and gift card redemption. Limitations of this study include its short duration and use of a small convenience sample of employees at a single worksite. An intervention period of 4 weeks was selected given resource constraints and to maximize the likelihood of supervisors agreeing to permit employees to participate in this novel intervention. Future studies should use a longer intervention duration to obtain more complete information about the effects of desk pedaling on work performance and the effects of different feedback and incentive strategies on employees' pedaling volume. Furthermore, our goal was to obtain estimates of the most effective incentive strategies before automation; however, future trials could increase efficiency by automating incentive delivery.

Comparison With Prior Work

Previous research indicates that employees can pedal desk pedaling devices without detrimental effects on objectively measured nonpedaling physical activity [30,76] and employee-rated work performance [13,29,30], and that there is interest in using these devices among adults with multiple health risk factors [77]. Our study adds to this early literature by including measures important for guiding wider dissemination of desk pedaling devices, including supervisor ratings of employee work performance, the differential effects of different incentive strategies on pedaling volume, social and built-office environment influences on desk pedaling, and qualitative assessment of user-encountered issues. Our study also allows enrollment of participants with greater health risks than most previous similar studies, which can inform the real-world generalizability of desk pedaling.

Conclusions

Demonstrating that people can simultaneously pedal compact devices and work productively, and that they are willing to sustain this pedaling, will set the stage for future trials to (1) track longer term effects of desk pedaling on health outcomes and work performance in diverse populations and (2) evaluate effects of automated real-time feedback and incentive systems to sustain desk pedaling. Ultimately, these initiatives will grow the evidence base needed to build workplaces that support active lifestyles as a normative occupational practice.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
First summary statement from National Institutes of Health peer review. Our proposal was funded to conduct two studies: a lab study and a field study. This manuscript describes the protocol for the field study.
[PDF File (Adobe PDF File), 175 KB - resprot_v9i1e16275_app1.pdf]

Multimedia Appendix 2
Second summary statement from National Institutes of Health peer review.
[PDF File (Adobe PDF File), 167 KB - resprot_v9i1e16275_app2.pdf]

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Abbreviations

ICIR: Individual Contingent Immediate Reward
JCIR: Joint Contingent Immediate Reward

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Protocol

The Use of Web-Based Support Groups Versus Usual Quit-Smoking Care for Men and Women Aged 21-59 Years: Protocol for a Randomized Controlled Trial

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Abstract

Background: Existing smoking cessation treatments are challenged by low engagement and high relapse rates, suggesting the need for more innovative, accessible, and interactive treatment strategies. Twitter is a Web-based platform that allows people to communicate with each other throughout the day using their phone.

Objective: This study aims to leverage the social media platform of Twitter for fostering peer-to-peer support to decrease relapse with quitting smoking. Furthermore, the study will compare the effects of coed versus women-only groups on women's success with quitting smoking.

Methods: The study design is a Web-based, three-arm randomized controlled trial with two treatment arms (a coed or women-only Twitter support group) and a control arm. Participants are recruited online and are randomized to one of the conditions. All participants will receive 8 weeks of combination nicotine replacement therapy (patches plus their choice of gum or lozenges), serial emails with links to Smokefree.gov quit guides, and instructions to record their quit date online (and to quit smoking on that date) on a date falling within a week of initiation of the study. Participants randomized to a treatment arm are placed in a fully automated Twitter support group (coed or women-only), paired with a buddy (matched on age, gender, location, and education), and encouraged to communicate with the group and buddy via daily tweeted discussion topics and daily automated feedback texts (a positive tweet if they tweet and an encouraging tweet if they miss tweeting). Recruited online from across the continental United States, the sample consists of 215 male and 745 female current cigarette smokers wanting to quit, aged between 21 and 59 years. Self-assessed follow-up surveys are completed online at 1, 3, and 6 months after the date they selected to quit smoking, with salivary cotinine validation at 3 and 6 months. The primary outcome is sustained biochemically confirmed abstinence at the 6-month follow-up.

Results: From November 2016 to September 2018, 960 participants in 36 groups were recruited for the randomized controlled trial, in addition to 20 participants in an initial pilot group. Data analysis will commence soon for the randomized controlled trial based on data from 896 of the 960 participants (93.3%), with 56 participants lost to follow-up and 8 dropouts.

Conclusions: This study combines the mobile platform of Twitter with a support group for quitting smoking. Findings will inform the efficacy of virtual peer-to-peer support groups for quitting smoking and potentially elucidate gender differences in quit rates found in prior research.

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KEYWORDS

smoking prevention; support group; cigarettes; tobacco

Introduction

Background

State tobacco quitlines have demonstrated efficacy but remain underutilized, reaching an average of only 1% of smokers annually [1]. Dozens of randomized controlled trials have examined websites with advanced features such as QuitNet [2,3], or one-way SMS text messaging or email messaging services such as txt2stop [4,5], but these interventions are limited by information exchanges that are largely unilateral, noninteractive, and nonpeer-based. Notably, although the initial results of one-way messaging services for smoking cessation looked promising [4,6-8], a recent review found that only 3 of 15 randomized trials showed significant benefits [9].

To increase utilization of quit-smoking programs, researchers and practitioners are seeking to harness the power of social media [10]. Very popular social media sites such as Facebook and Twitter allow users to stay connected to individuals and groups in real time and to share content at virtually no cost [11]. Social media is entrenched in the United States with 73% of online adults using social media sites, 42% using multiple sites, and the majority visiting them daily [12]. Twitter has a reported 326 million active users (100 million daily) posting 500 million tweets daily, with 80% using the platform on their phone in 2018 [13]. There are already over 140 reported medical and health care uses of Twitter [14]. Relative to Facebook, Twitter has a superior application programming interface, which makes it easier to create programs for research and intervention purposes [15]. In addition, Twitter does a much better job of ensuring that group member communications stay within the group only by readily allowing for private groups to be set up that are completely and permanently isolated from friends, family, and the public.

Objectives

Social media looks highly promising for delivering tobacco and other addiction treatment interventions as a result of its broad reach and appeal, real-time interactivity, and free cost. However, despite its apparent promise and observational evidence indicating that existing socially mediated forums may increase patient compliance [16], social media's potential for delivering health interventions and developing new treatment approaches has not yet been fully realized. The earliest forms of social media interventions tended to be large online health forums, and these generally did not yield significant benefits [17-21], although the people who were actively engaged did often benefit [22]. Thus, the main problem with prior social media interventions seems to be that engagement was too low [23]. Our Twitter-based intervention called Tweet2Quit tests and improves a socially mediated intervention that already has been shown to produce good engagement [24]. We believe that engagement happens because of the development of a sense of online community through extensive interpersonal and, especially, dyadic interactions [25,26]. In response to calls for the application of systems science to public health [27], we will apply network analysis to examine tie strength among buddies (paired people in the group based on similarity in age, gender, location, and education) [28] and to identify social brokers (people who facilitate communication between otherwise unconnected individuals) [29].

Our *first primary aim* is to test the 6-month efficacy of Tweet2Quit with biochemical verification of abstinence. We hypothesize that relative to control coed (male and female) groups (n=240), Tweet2Quit coed groups (n=480) will achieve significantly greater bioconfirmed sustained abstinence at 6-months follow-up. Our *second primary aim* is to test whether women do better in Tweet2Quit women-only versus coed groups. We hypothesize that women will achieve significantly greater bioconfirmed 6-month abstinence in Tweet2Quit woman-only groups (n=240) versus Tweet2Quit coed groups (n=240 women), as people tend to form stronger social connections with others who share their defining characteristics such as gender [30]. *Secondary aims* will test the same hypotheses but based on 3-month (end of treatment) sustained and bioconfirmed abstinence, and we will also test 7-day point prevalence abstinence at 1, 3, and 6 months.

Exploratory aims will study the Tweet2Quit groups' social network structures with a focus on the buddy pairs and the identification of social brokers (group members who facilitate interaction between otherwise unconnected individuals), using both baseline theoretically based measures and observed tweeting behaviors. We predict that active buddies in the group will enhance tie strength, among both buddy-partner ties and partner-group ties, which will increase smoking abstinence. We also predict that better social brokers will enhance tie strength, as they will encourage more people to engage in the intervention (tweet their group), which will increase smoking abstinence.

Methods

Study Setting

The study setting is virtual—hosted online via the study website and Twitter—but the study is conducted by the University of California, Irvine (UCI).

Trial Design

The study runs parallel groups, with treatment and control groups starting and stopping at the same time. Treatment group (n=20) and control group (n=10) allocation began once 30 participants passed screening, using a 2:1 ratio (see the Randomization section below).

Inclusion Criteria

Participants are considered eligible if they are aged between 21 and 59 years (21 years being the strictest minimum age to receive nicotine replacement therapy [NRT] products in the

United States); speak English, so they are able to communicate with their group; are current smokers (have smoked at least 100 cigarettes in their lifetime and are smoking at least five cigarettes a day) to meet the requirement for NRT products; have a mobile phone with an unlimited texting plan (unlimited data not required) and internet to receive intervention messages; have an active email account to receive quit-smoking guides; live in the continental United States, so that all participants are in a similar time zone to facilitate communication; can send/receive SMS text messages at least once a week; and have an active social media account to show they are familiar with and can communicate on this platform.

Exclusion Criteria

Due to use of NRT in this study, participants are ineligible if they have contraindications for NRT including irregular heartbeat, high blood pressure not controlled with medication, recent heart attack, pregnant or breast feeding, skin allergies to adhesive tape, or serious skin problems [31]. Consistent with other quit-smoking trials, those who do not want to set a quit date or are not intending to quit in the next 30 days are excluded [31]. As this social media intervention uses a peer-to-peer support model, without a formal group moderator, and because this is an initial demonstration trial, individuals taking medicine for depression, using an illicit drug, or regularly using marijuana are excluded [32]. For study retention, personal contact information is required as is email verification. Those who fail to provide these contact details, or who provide nonworking phone numbers or emails, are excluded [33]. As we want to conduct saliva tests using webcams, that is, cameras on mobile phones, participants must show us they have this. To prevent problems with misrepresentation, those who fail the screening survey in the past are, henceforth, excluded. To prevent problems with contamination, we exclude those who already take medication for quitting smoking, who have participated in the 2011-2014 Tweet2Quit study [34], or who live with someone or have an immediate relative who has already participated or will participate in the current Tweet2Quit study.

Electronic Cigarettes/Vaping

Electronic cigarettes (e-cigarettes)/vaping are discouraged during the course of the program but are not forbidden, and participants are not disqualified if these products are used. During the follow-up surveys, participants are asked about the use of e-cigarettes/vaping to include in the analyses.

Treatment (Twitter) Arms: Coed and Women-Only

The treatment participants are put into a private Twitter group of 20 participants as well as paired with another participant in the group for a buddy system. These participants are encouraged to tweet (message) each other daily for support by logging into a Twitter account that we provide to them free of charge, and they receive a daily discussion topic as a tweet to help start conversations. The discussion topics encourage participants to get to know each other, express their quitting goals, and share tips on how to stay smoke free. Participants are encouraged to send at least one tweet a day, and their participation is monitored automatically by the program.

In addition, treatment participants receive daily automated texts providing feedback on their prior-day tweeting behavior, which praises tweeters and encourages nontweeters to engage. If the number of tweets over consecutive days falls below the minimum expected (varies per week; decreases as the group goes on), an additional text is sent to get participants onto Twitter to respond to a new discussion topic. These extra tweets and texts are to encourage treatment participants to interact with other group members about quitting.

Coed treatment groups consist of 20 participants with a mixture of men and women. However, there are even numbers of men and women in each coed treatment group, so that buddies can be of the same gender. Women-only treatment groups have 20 participants consisting of only women. All treatment interventions (eg, discussion topics) for the coed and women-only groups are the same. All treatment participants receive 8 weeks of nicotine patches (1 per day) and their choice of gum or lozenges (12 per day while on the patch), and Smokefree.gov quit guides are emailed about every 5 days.

Control Arm

Control participants receive 8 weeks of nicotine patches (1 per day); their choice of nicotine gum or lozenges (12 per day while on the patch); and Smokefree.gov quit guides, which are emailed about every 5 days. Treatment and control groups run parallel to each other, ie, start at the same time.

Withdrawal

Participants can drop from the study, by request, at any time. If a participant stops sending tweets to their group, the team still follows up at the scheduled times unless otherwise requested, and the participants are still eligible for the gift cards for completing follow-up assessments.

Mode of Delivery/Communication

The NRT products are provided via mail, but all other components of the intervention are provided over the internet or email. Each participant receives log-in information, as well as all resource guides, automatically via email. Daily reminders are sent via SMS text messages. If the participant needs to interact with the study team, they can send an email (a contact form is available on the study website) or call the staff directly. The support group is virtually located on Twitter, and participants only have to log into their accounts to interact with their support group. Guides that clearly show participants how to log in and use Twitter are provided and also posted on the study website.

Outcomes

Primary Outcome

Participants report their use of tobacco products at 1, 3, and 6 months after the quit date (the date they selected to quit smoking) by answering the following questions: “How many cigarettes have you smoked,” “How many other tobacco products have you used,” and “How many times have you used e-cigarettes since the quit date.” If participants self-report no tobacco use and no use of NRT, this is confirmed biochemically using a salivary cotinine test at 3 and 6 months after the quit date. Participants will complete the salivary test while we

observe on a webcam (camera on their mobile phone), they take a picture of the test results, and they text us the picture. If webcam observation is unfeasible, participants will complete the salivary test on their own and text us a picture of the results. We will apply the Russell Standard for sustained abstinence, allowing five or fewer instances of tobacco use over 6 months. We will use online self-reported surveys to collect the tobacco use data.

In our primary (most rigorous) analysis, we will consider a cotinine-positive test, regardless of source, to be nonabstinent. In additional analyses, we will code as abstinent those who assert tobacco abstinence but continue use of US Food and Drug Administration–approved NRT. In other analyses, we will consider use of electronic nicotine delivery systems (ENDS; such as e-cigarettes or vaping), with ENDS users coded first as nonabstinent and then for comparison as abstinent. Secondary analyses will examine 3-month (end of treatment) sustained and bioconfirmed abstinence and 7-day point prevalence abstinence at 1, 3, and 6 months.

Time Schedule of Enrollment and Participation

Table 1 shows the study flow for each cohort. Enrollment and allocation to condition occurred first, followed by the 3-month intervention, with assessments occurring at 1 month, 3 months, and 6 months.

Table 1. Study flow.

Study activity	Study period and timepoint							
	Enrollment	Allocation	Post allocation					Close-out
	Month 0	Month 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Enrollment								
Eligibility screen	✓							
Informed consent	✓							
Verification of email, phone, and webcam	✓							
Randomization		✓						
Treatments								
Twitter mobile support group			✓	✓	✓			
Nicotine replacement therapy			✓	✓	✓			
Emails linked to Smokefree.gov			✓	✓	✓			
Assessments								
Follow-up surveys			✓		✓			✓
Saliva tests					✓			✓

Recruitment

All recruitment is done online through advertisements. Primarily, Facebook ads are purchased to recruit participants. Ads are designed to target people on Facebook who indicate interest in smoking or quitting smoking, with additional ZIP code targeting of black/African American participants and Hispanic/Latino participants living in high-smoking areas and some limited targeting of Spanish-English bilingual speakers to increase participant diversity. People see a study ad on Facebook, and if they click on the ad, they are brought to the study website, where they can fill out a brief form indicating interest. In addition, some free Google Ads (provided through the Google Grants program to assist nonprofits) appear for the study when quit-smoking keywords are entered into the Google search engine. Finally, an ad listed on Smokefree.gov directs traffic to the study website.

Randomization

Randomization occurs once the targeted number of participants for a cohort is reached based on the online eligibility screen and the verification of email, phone, and webcam (camera on mobile phone) for saliva testing. Participants are randomized to the treatment or control condition by statistician KD using deidentifiable ID numbers. The allocation is fully random, with each person having an equal chance of ending up in the treatment or control condition. Whether the cohort treatment is coed or women only is also randomly determined by KD. After the treatment commences, the condition assignment is not blinded to participants and the research team; however, during data collection, the staff members that contact participants (if participants do not complete follow-up surveys on their own) are not told the study condition of participants to ensure equal effort in gathering data. The process of starting a new treatment/control cohort is repeated every few weeks to a month until 960 participants are attained (36 treatment/control cohorts beyond the 20-person pilot).

Consent

As the study is conducted via internet across the continental United States, rather than in person, a waiver of signed consent has been obtained. At the beginning of screening, potential participants receive an information sheet that contains study information, and they must consent (by clicking yes or no) to continue with screening.

Institutional Review Board

The study is under the oversight of the UCI's and the Stanford University's institutional review boards (IRBs). Any requested changes to the protocol are submitted through these IRBs.

Study History

During 2011 to 2014, we ran an initial evaluation of Tweet2Quit that tested this mobile support group platform for quitting smoking, and we observed a self-reported abstinence rate of 40% at 60 days compared with 20% in the control group [34]. This study extends follow-up to 6 months to document sustained abstinence, uses bio-confirmation to validate self-report, and incorporates a women-only Tweet2Quit treatment arm. We also introduce demographically matched buddy pairs for extra support within the group, tweet streaks to encourage daily dyadic interactions (daily text messages to participants, showing the number of days in a row they tweeted other participants without missing), and low tweet messaging that supplies extra topics when the number of group tweets is low. We added these features to the Tweet2Quit intervention because we observed that tweeting about relevant topics, such as using nicotine patches and countering roadblocks to quitting, increased the participants' chance of achieving abstinence [24].

Revisions

This study is based on the most recent protocol version, September 2018. During the course of the study, there were no major study revisions, but we increased the monetary incentives for completing the outcome assessments to improve response rates.

Data Collection, Management, and Analysis

Self-assessment follow-up surveys are automatically emailed to participants by the software program Qualtrics (Provo, Utah) at 1, 3, and 6 months after a participant's quit date (the date they set to quit smoking). These surveys are compliant with the Checklist for Reporting Results of Internet E-Surveys. Participants' responses to the online survey questions are kept on the Qualtrics server until they are downloaded by the study team for analysis. When participants do not complete a survey themselves, the research team reaches out to them via phone to complete the survey with them, and the research team enters the data for them into the online Qualtrics survey. The survey questions assess the effectiveness of the intervention at promoting abstinence based on participants' self-reports, and they also track participants' self-reported use of NRT and ENDS products. All participants receive these surveys, along with a monetary gift card for completion, regardless of condition and even if the participant does not actively participate in (tweet) their treatment group.

Statistical Analyses

Dropout rates are examined by condition. Every effort is made to limit the amount of missing data from survey attrition by doing persistent follow-up with participants and contacting their preidentified collaterals (family members and friends) to urge survey completion. Before analysis, we will examine baseline predictors of attrition. If it appears that attrition is related to measured aspects of the participants, we will include those measures as covariates in the models. Sensitivity analyses will check that the methods of dealing with missing data do not have a major impact on the results. We will repeat the attrition analyses under two different models, one in which the missing data are assumed to be positive for smoking and one using only the respondents who did not have missing data. We expect to find that although estimates may change some, the conclusions generated by the modeling should not change.

For primary hypothesis testing of sustained abstinence at 6 months, we will use the 6-month postquit date survey (based on the quit date selected by the participant at the beginning of the study) and biochemical salivary cotinine verification. To test the *primary aim 1 hypothesis*, analyses will compare sustained abstinence for participants randomized to coed Tweet2Quit treatment versus control. Sustained abstinence will be modeled as a function of study arm (coed Tweet2Quit or control), gender, cohort, and individual using a logistic model and generalized estimating equations (Proc Genmod in SAS; SAS Institute Inc, Cary, North Carolina) to account for the clustering of individuals within cohort. Our statistical methods will use all the data in parameter estimation. We will test the coefficient of the study arm or treatment condition parameter by gender, if there is a treatment condition by gender interaction.

The same type of generalized logistic model, but focusing on women, will be used to test the *primary aim 2 hypothesis*, on whether women will achieve greater 6-month sustained, bioconfirmed abstinence if randomized to a women-only versus coed Tweet2Quit treatment group. Secondary hypotheses concerning sustained abstinence at 3 months (ie, at treatment end) and point prevalence (prior 7 days) abstinence at 1, 3, and 6 months will be tested using the same modeling approaches.

Exploratory aims will be met by testing our mediational models of predictors of abstinence. Regression models of each individual path will be tested. Subsequently, using a structural equation modeling approach, we will test whether the relationships between buddy pairs and abstinence, and social brokers and abstinence, can be accounted for by tie strength or other network characteristics, with direct paths modeled as well.

Smokefree.gov Collaboration

Whenever treatment or control participants receive our email with a link to a Smokefree.gov quit guide and click on the link, their behavior on the Smokefree.gov website, including the number of page views and time spent, is automatically logged. Smokefree.gov provides us with these data on usage of their quit-smoking guides so that we can determine if guide usage improves abstinence and if the Tweet2Quit treatment affects guide usage.

Data and Safety Monitoring Board

As the interventions are fairly standard and low-risk, a data safety monitoring board is not used.

Confidentiality

All collected data are kept on secure online databases that are password protected with access limited to the study team. Subject-identifiable data will be retained until publication, at which point it will be destroyed. At the end of each group,

Twitter profile pictures (pictures of participants' faces that we use to create their study accounts on Twitter) will be destroyed. Pictures of saliva test results, which do not show subject-identifiable data, will be kept indefinitely as proof of abstinence.

Privacy

Privacy is a concern with any study that is conducted online, especially in a support group that encourages participants to be open with each other. Although social media is a public platform, there are Twitter settings that quickly ensure groups are permanently and completely private. All these privacy features are turned on to prevent participants from being easily searched on Twitter or have their tweets seen by their family, friends, or other people outside the treatment group. Their tweets are even hidden from other treatment groups in the study. Participants are further taught how to interact on the Twitter platform to keep themselves and others safe and the group private.

Access to Data

UCI will be working with personnel from both the University of California, San Francisco (UCSF), and Stanford University in the analysis portion of this study, sharing both the survey data and the bioconfirmed abstinence data. UCI personnel will remove all identifiable data from the files before sharing with the other sites. JP has secured IRB approval from Stanford University and will be working in collaboration with UCI. No subject enrollment or data collection has been conducted at Stanford. Data will be shared between Stanford and UCI primarily in a deidentifiable fashion, but some datasets may include minimal identifiable data (eg, Twitter usernames). JP receives subject-identifiable data from UCI in the event of a serious adverse event but does not receive identifiable data at any other time. In sum, both deidentifiable data and identifiable data will be seen by JP while working from Stanford.

KD will conduct his portion of the study from UCSF; however, he will not have access to identifiable data. KD assists in randomizing participants to groups, but he only uses deidentifiable subject IDs for randomization and data analysis. KD has no interaction with human subjects. Both JP and KD will assist in analysis of deidentifiable data.

Dissemination of Data

The study team plans to present the findings at academic conferences and publish them in peer-reviewed academic journals. In addition, the team plans to discuss the findings with government officials such as those affiliated with Smokefree.gov. Only research team members will be authors of any papers written, and participant identifiers will be removed.

Results

Results for Recruitment and Retention

IRB approval of the study began in March 2016, with National Institutes of Health funding running from March 2016 to March 2021. Recruitment has taken place from November 2016 to September 2018, and 980 participants have been enrolled. However, 20 of these participants were part of a pilot group to pretest the intervention and will not be used in the main analyses. As part of the randomized controlled trial (n=960), 480 participants have been allocated to the coed treatment condition, 240 participants have been allocated to the women-only treatment condition, and 240 participants have been allocated to the control condition. Table 2 provides the demographics of these participants.

Table 2. Demographics of participants in the randomized controlled trial by condition.

Intervention	Coed treatment (n=480)	Women-only treatment (n=240)	Control (n=240)
Mean age, years (SD)	39.0 (9.52)	39.8 (9.45)	40.4 (9.69)
Gender, n (%)			
Male	142 (29.58)	0 (0)	73 (30.42)
Female	338 (70.42)	240 (100)	167 (69.58)
Ethnicity, n (%)			
White	376 (78.33)	204 (85.0)	197 (82.08)
African American/black	55 (11.46)	22 (9.17)	21 (8.75)
Hispanic/Latino	21 (4.38)	6 (2.50)	10 (4.17)
Other	28 (5.83)	8 (3.33)	12 (5.0)

Only 8 (<1%) participants withdrew from the study, that is, they requested removal from all intervention emails and texts (eg, the Smokefree.gov quit guides) and all assessments, and if in a treatment condition, they dropped out of their Twitter support group. At 6-month follow-up (the primary outcome measure), we have collected 896 surveys or 93.3% (896/960), with 56 of the participants or 5.8% (56/960) lost to follow-up and 8 or <1% (8/960) who discontinued the intervention (see Multimedia Appendix 1 for the breakdown at each follow-up). The primary analysis will compare the focal conditions to assess the percentages of participants with biometrically verified sustained abstinence. For this primary analysis, we have collected data from 437 of the 480 participants (91.0%) in the coed treatment condition, 226 of the 240 participants (94.2%) in the women-only treatment condition, and 233 of the 240 participants (97.1%) in the control condition.

No serious adverse events have occurred. There have been no security breaches, but there was a technical error that caused

the feedback texts and tweet streaks to be inaccurate for a few days in one group. Participants were told about the technical error and continued to interact normally.

Power Analysis

Sample sizes were selected to have sufficient power to test both primary hypotheses. For testing the aim 1 hypothesis, a logistic regression to assess power, based on sustained abstinence estimates of 20.0% for Tweet2Quit-coed (n=480) versus 8.0% for usual care-coed (n=240), estimated 98% power at *P*=.05 and 97% power with 13% (94/720) expected survey attrition. For testing the aim 2 hypothesis, a logistic regression to assess power, based on sustained abstinence estimates of 26.0% for Tweet2Quit-women-only (n=240) versus 14.0% for women in Tweet2Quit-coed (n=240), estimated 88% power at *P*=.05 and 83% power with 13% (62/480) expected survey attrition.

Regarding the structural equations models we will use to test for process effects, the standard fit statistics will be evaluated. We will not rely on the Chi-square statistic as it is sensitive to sample size. If we find poor fit in this exploratory analysis, we will examine the individual parts of the model to determine what aspects indicate poor measurement or relationships and revise the model accordingly.

Discussion

Principal Findings

This study builds on the encouraging effects found with the Tweet2Quit quit-smoking platform, which was developed and tested from 2011 to 2014. Current extensions include an analysis of 6-month sustained bioconfirmed abstinence and a comparison of women-only and coed treatment groups. Existing quit-smoking programs utilize Twitter groups or daily texts, but our program combines these ideas and creates private Web-based groups that connect people across the United States to receive peer support and daily messages for quitting smoking. We will test if after 6 months the participants attain sustained abstinence. Participants in the coed control condition and the coed Tweet2Quit condition will be compared. In addition, women participants in the coed Tweet2Quit condition and the women-only Tweet2Quit condition will be compared.

Strengths and Limitations

As only those who regularly use social media can participate in our Tweet2Quit program, a concern could be raised about reaching the relevant US population. However, this concern is mitigated by the fact that 73% of US adults who are online use social media, so we feel that we can reach the majority of the online population [12].

In our study, there is also the concern that, because participants know which condition they are in, if placed into the control rather than a treatment condition, they may withdraw from the study or its assessments. However, less than 1% of participants withdrew from the study. In addition, we have a team follow-up with all the participants who do not complete a survey on their own to gather the data. As a result, we have attained similar response rates across the study conditions and 90% or higher response rates overall.

Conclusions

If the Tweet2Quit treatment is found to be efficacious, it will provide an easily accessible program for anyone nationwide to help them quit smoking and stay smoke free. Furthermore, the intervention can be easily replicated in other health contexts because the Twitter platform can be used free of charge in nearly the entire world.

Acknowledgments

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Authors' Contributions

CAP and JP designed the Tweet2Quit interventions and assessments. CAP oversees the project staff that handles participant recruitment and survey assessments. JP provides ongoing advice on this and also assists UCI in the event that a Tweet2Quit participant is in need of mental health assistance. KD, a statistician, assisted with the study design and power analyses, randomizes the participants to condition, and will conduct the main statistical analyses. DC, a project coordinator, is responsible for managing the team that collects survey data. CP recruits participants by deploying Facebook advertisements.

Conflicts of Interest

Unrelated to this project, JP has provided consultation to pharmaceutical and technology companies that make medications and other treatments for quitting smoking. JP and CAP have served as expert witnesses in lawsuits against tobacco companies.

Multimedia Appendix 1
CONSORT diagram for the randomized controlled trial.
[DOCX File , 62 KB - resprot_v9i1e16417_app1.docx]

Multimedia Appendix 2
Peer-reviewer report from the NIH.
[PDF File (Adobe PDF File), 163 KB - resprot_v9i1e16417_app2.pdf]

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Abbreviations

e-cigarette: electronic cigarette
ENDS: electronic nicotine delivery systems
IRB: institutional review board
NRT: nicotine replacement therapy
UCI: University of California, Irvine
UCSF: University of California, San Francisco

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Protocol

A Mobile Phone–Based Telemonitoring Program for Heart Failure Patients After an Incidence of Acute Decompensation (Medly-AID): Protocol for a Randomized Controlled Trial

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Abstract

Background: Patients with heart failure (HF) are at the highest risk for hospital readmissions during the first few weeks after discharge when patients are transitioning from hospital to home. Telemonitoring (TM) for HF management has been found to reduce mortality risk and hospital readmissions if implemented appropriately; however, the impact of TM targeted for patients recently discharged from hospital, for whom TM might have the biggest benefit, is still unknown. Medly, a mobile phone–based TM system that is currently being used as a standard of care for HF at a large Canadian hospital, may be an effective tool for the management of HF in patients recently discharged from hospital.

Objective: The objective of the *Medly-After an Incidence of acute Decompensation* (Medly-AID) trial is to determine the effect of Medly on the self-care and quality of life of patients with HF who have been recently discharged from hospital after an HF-related decompensation.

Methods: A multisite multimethod randomized controlled trial (RCT) will be conducted at 2 academic hospitals and at least one community hospital to evaluate the impact of Medly-enabled HF management on the outcomes of patients with HF who had been hospitalized for HF-related decompensation and discharged during the 2 weeks before recruitment. The trial will include 144 participants with HF (74 in each control and intervention groups). Control patients will receive standard of care, whereas patients in the intervention group will receive standard of care and Medly. Specifically, patients in the intervention group will record daily weight, blood pressure, and heart rate and answer symptom-related questions via the Medly app. Medly will generate automated patient self-care messages such as to adjust diuretic medications, based on the rules-based algorithm personalized to the individual patient, and send real-time alerts to their health care providers as necessary. All patients will be followed for 3 months. Primary outcome measures are self-care and quality of life as measured through the validated questionnaires Self-Care

of Heart Failure Index, EQ-5D-5L, and the Kansas City Cardiomyopathy Questionnaire-12. Secondary outcome measures for this study include cost of health care services used and health outcomes.

Results: Patient recruitment began in November 2018 at the Sunnybrook Health Sciences Centre, with a total of 35 participants recruited by July 30, 2019 (17 in the intervention group and 18 in the control group). The final analysis is expected to occur in the fall of 2020.

Conclusions: This RCT will be the first to assess the effectiveness of the Medly TM system for use following discharge from hospital after a HF-related decompensation.

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KEYWORDS

heart failure; telemedicine; mobile phone; patient monitoring; randomized controlled trial

Introduction

Background

Over 670,000 Canadians live with a diagnosis of heart failure (HF) [1,2] and the prevalence is increasing [3]. HF is associated with a high mortality rate of 30% at 1 year [4] and high health care costs largely attributed to repeated hospital admissions [3]. The highest risk for rehospitalization is during the first few weeks after discharge when patients are transitioning from hospital to home [5]. Among all patient groups, patients with HF have the highest readmission rate within 30 days, at approximately 20% [5,6]. The 2019 Report on the Health of Canadians by the Heart and Stroke Foundation found that HF costs Can $2.8 billion per year and is the third most common reason for hospitalization (after respiratory disease and heart attack, which are both associated with HF) [1].

Up to 40% of readmissions have been found to be preventable [7] and related to suboptimal transitional care because of the lack of coordination and continuity of care as patients transfer between health care settings and providers [8]. To address the issue of frequent readmissions, quality improvement initiatives have included increasing education during vulnerable transition periods, such as just before discharge; rapid 7-day clinical reassessment; and improved discharge summaries [9-12]. Telemonitoring (TM) has also emerged as a potential approach to improve HF management during the transition from hospital to home, by enabling providers to closely monitor relevant physiological parameters and symptoms in real time.

Recent systematic reviews have found that TM for HF management reduces mortality risk and hospital readmissions, and more frequent transmission of patient data increases its effectiveness [13,14]. A large-scale randomized controlled trial (RCT) by Koehler et al [15] found reductions in all-cause mortality and length of hospital admissions. However, 3 previous large-scale trials have failed to show the benefits of TM [16-18]. This inconsistency in the findings of HF TM can be attributed to the heterogeneity of the trials with variations in the characteristics of the interventions, patients, providers, organizations, and structural characteristics (eg, policies and incentives). A review by Ware et al hypothesized that inconsistencies among the results of different TM studies may also be largely because of the lack of tailoring the TM program to the population and context for successful implementation [19].

Medly is a highly automated and user-centered mobile phone–based TM system developed at the University Health Network, Toronto, Canada. Medly has been evaluated through an RCT with outpatients with HF at the Ted Rogers and Family Centre of Excellence in Heart Function, University Health Network, a tertiary academic hospital. The RCT found improvements in quality of life and self-care management, a reduction in brain natriuretic peptide (BNP) levels, and an increase in left ventricular ejection fraction over a 6-month period [20,21].

Objectives

The main objective of the *Medly-After an Incidence of acute Decompensation* (Medly-AID) trial is to determine the effect of Medly on the self-care and quality of life (primary outcome measures) of patients with HF who have been recently discharged from hospital after a HF-related acute decompensation. Acute decompensation is when there is a sudden worsening of signs and symptoms of HF, which often leads to a visit to the emergency department (ED) or hospitalization. Secondary outcome measures include the cost of health care services used and health outcomes. A main difference between the Medly-AID trial and the previous Medly RCT is that the Medly-AID trial will be restricted to patients who have been discharged from hospital during the 2 weeks before recruitment, thus targeting the patients at the highest risk for rehospitalization.

Methods

Study Overview

Medly-AID is a multisite multimethod RCT with 144 patients with HF. Patients are enrolled in the study for 3 months. The Medly TM system will be implemented at 2 academic hospitals, namely, Sunnybrook Health Sciences Centre and Mount Sinai Hospital, both in Toronto, Canada. A third site, a community hospital, will also be included in the trial. This study has received approval from the research ethics boards at the Sunnybrook Health Sciences Centre (research ethics board number 143-2017) and the University Health Network (research ethics board number 17-5887), where the patient data will be

stored, and the submission to Mount Sinai Hospital is in review. The trial has also been registered at ClinicalTrials.gov (NCT03358303) since November 30, 2017.

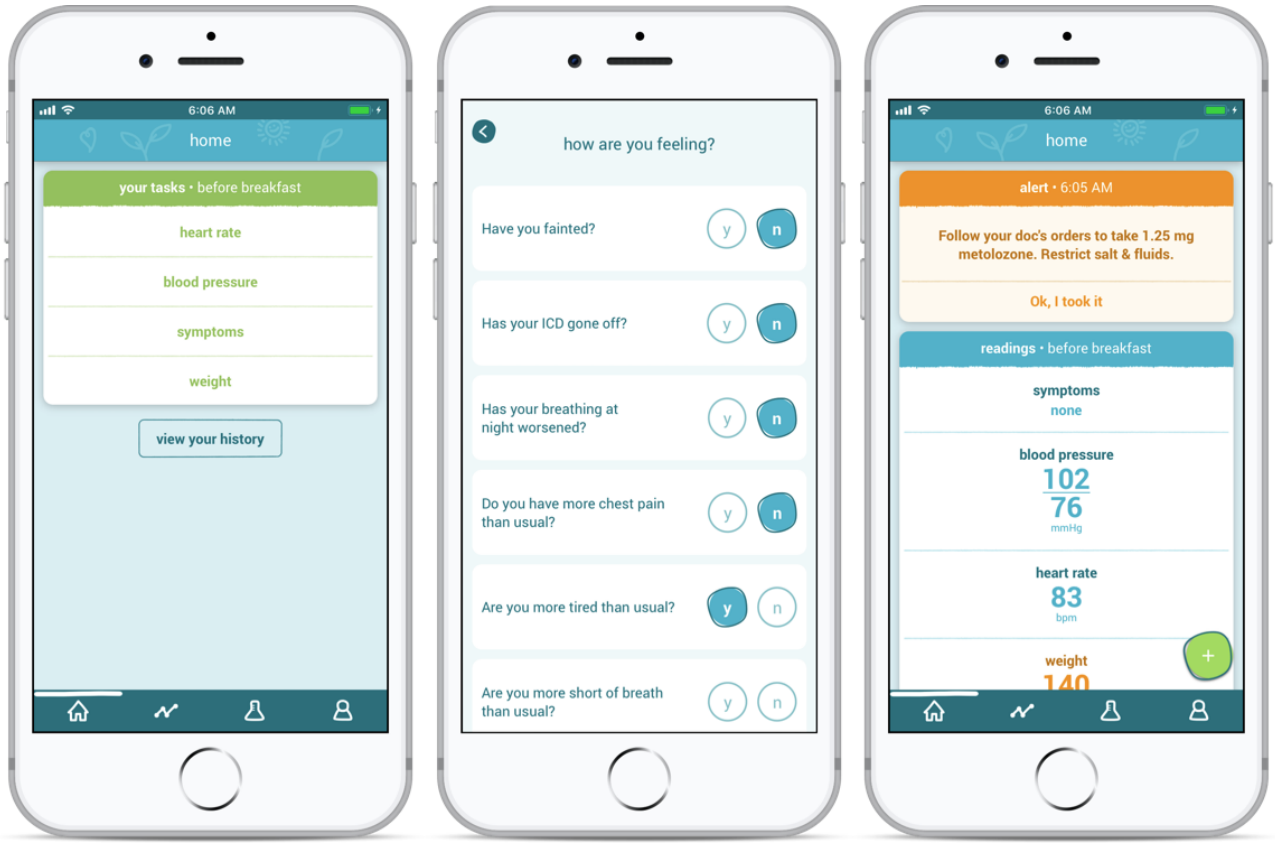
Sample Size Calculation

A sample size calculation was based on the Self-Care of Heart Failure Index (SCHFI), using a population standard deviation of 20 and an effect size of 10 as determined in previous studies (alpha=.05; power=0.8) [22]. The required sample size was calculated to be 63 per group. To compensate for patients who will be lost to follow-up during the course of the study, 72 patients will be recruited for the intervention group and 72 patients for the control group.

Medly Telemonitoring System

The mobile phone–based TM system, Medly, enables patients with HF to monitor their weight (A&D Medical Bluetooth weighing scales), blood pressure, and heart rate (A&D Medical Bluetooth blood pressure monitors) using wireless home medical devices. Medly was developed using a user-centered design approach that included iterative rounds of usability testing. See Figure 1 for screenshots of the Medly app. Patients are instructed to measure their weight and blood pressure (systolic and diastolic values) with the provided medical devices and to answer simple questions regarding their symptoms first thing each morning after the patient relieves themselves in the washroom and before eating or drinking. Heart rate values are also recorded simultaneously as they are taking their blood pressure values. Automated reminder phone calls are sent to the patient's own phone if they do not take their measurements by 10 am, but patients can opt out of this feature. If the patient is exhibiting HF-related symptoms such as increased shortness of breath or chest pain during the rest of the day, they are instructed to measure their blood pressure and to record their symptoms through the Medly app. The measurements are automatically and wirelessly transmitted via Bluetooth to the mobile phone with the Medly app and then relayed to a secure data server. On the basis of their readings and reported symptoms, automated and individualized self-care messages, such as to adjust diuretic medication and restrict fluid and sodium consumption, are sent to the patients [20]. If there are signs of clinical deterioration, an alert is sent to the clinician responsible for the care of the patient. Clinicians can access all relevant patient information through a secure Web portal, which allows them to access trends and historical data for each individual. These data enable clinicians to identify health deteriorations early and to address any issues remotely (eg, providing further self-care guidance or altering the patient's care plan in such a way that stabilizes the patient and ideally avoids a rehospitalization). The patient information on the mobile phone provided to patients can be remotely deleted if the phone is reported stolen or lost.

Figure 1. Sample screenshots of the Medly app.



Study Protocol

Patient Recruitment and Randomization

Patients are recruited within approximately 2 weeks post discharge, often during their regularly scheduled clinician visits for postdischarge care at the participating sites. After clinicians determine if the patient is eligible (inclusion and exclusion criteria can be found in Textboxes 1 and 2, respectively), the patient is asked if they are willing to speak to the study coordinator about enrollment. Informed written consent is obtained from patients by the research coordinator. Each patient is randomized to either the TM intervention or standard care control group. Block randomization is used with random block sizes of 2, 4, or 6 for each site. A Web-based computer-generated randomization tool, Sealed Envelope (Sealed Envelope Ltd.) [23], is used to determine the randomization order. Sequentially numbered envelopes are used to determine if the patient is in the intervention or control arm. The envelopes are prepared by a researcher outside of the study team. The study coordinator and patient are blinded to which group the patient is assigned until the patient has consented to participate in the study. Each participant in the control and intervention group receives a Can $25 Shoppers Drug Mart gift card to compensate them for their time in participating in the study.

Textbox 1. Patient inclusion criteria.

- Adults (18 years or older)
- Hospitalization duration for decompensated heart failure >24 hours
- Patient speaks and reads English adequately to provide informed consent and understand the text prompts in the app (or has an informal caregiver who can translate the prompts for them)
- Ability to comply with using Medly (eg, able to stand on the weight scale and able to answer symptom questions)

Textbox 2. Patient exclusion criteria.

- Dementia or uncontrolled psychiatric illness
- Patients who will require inpatient rehabilitation after discharge
- Participating in another clinical trial that may confound the results
- Residents of long-term care facilities
- Terminal diagnosis of any health condition with a life expectancy of <1 year
- Unable to provide informed consent
- Unable to speak or read English

Intervention Versus Control Groups

Patients in the intervention group will receive standard of care and also Medly, whereas the patients in the control group will receive standard of care. Standard of care will comprise the usual follow-up and routine management performed by each participating institution for patients with HF. Patients in the intervention group will receive the Medly kit to take home after being trained on how to use Medly. The Medly kit includes a mobile phone, with the Medly app, provided to the patient as well as a Bluetooth-enabled weighing scale and blood pressure monitor. Each patient will be followed for 3 months post discharge.

Study Outcome Measures

The primary outcome measures will be self-care as measured through the SCHFI [22] and quality of life as measured through the Kansas City Cardiomyopathy Questionnaire-12 [24] and the EQ-5D-5L [25]. Additional measures will include compliance with Medly utilization determined through the data on the Medly-AID servers regarding the frequency that patients took measurements; shortness of breath as measured using a visual analog scale for dyspnea in the patient questionnaires; and clinical status as measured by the New York Heart Association class, left ventricular ejection fraction, and BNP/N-terminal proBNP (NT-proBNP) levels (obtained via the electronic medical records). Health service utilization will be assessed by 30-day HF readmission rates, HF length of stay, and number of visits to the ED. The cost of the intervention will be determined by tracking the equipment costs and staff resources for clinical, technical, and administrative support and will be compared with the cost of health services. Creatinine, sodium, and potassium levels will also be assessed through routine blood tests from the patients, usually conducted at the participating institution's laboratories. These values will be obtained through the patients' electronic medical records. The schedule for data acquisition is depicted in Table 1.

Table 1. Schedule for data acquisition indicated by checkmarks at the specified time point.

Data Collected	Baseline	2 weeks	1 month	3 months
Questionnaires				
Demographics	✓	__[a]	—	—
EQ-5D-5L	✓	—	—	✓
Self-Care of Heart Failure Index	✓	—	—	✓
Kansas City Cardiomyopathy Questionnaire-12	✓	—	—	✓
Visual analog scale for dyspnea	✓	—	—	✓
Perceptions of Medly program (intervention group only)	—	—	—	✓
Health service utilization				
Number of hospitalizations in the previous 3 months	✓	—	—	✓
Number of days in the hospital in the previous 3 months	✓	—	—	✓
Number of emergency department visits in the previous 3 months	✓	—	—	✓
Number of clinic visits in the previous 3 months	✓	—	—	✓
Number of readmissions to hospital since recruitment	—	—	✓	—
Blood test outcomes				
N-terminal proBNP[b]/BNP levels	✓	✓	✓	✓
Creatinine	✓	✓	✓	✓
Sodium	✓	✓	✓	✓
Potassium	✓	✓	✓	✓

[a]Not applicable.

[b]BNP: brain natriuretic peptide.

Data Collection

Prestudy and poststudy questionnaires will comprise the aforementioned validated survey tools, whereas the poststudy questionnaire for the patients in the intervention group will have additional questions related to their perceptions of Medly. Prestudy and poststudy questionnaires will be administered to both control and intervention groups, which may be completed in the clinic or at home. Participants choosing to complete the questionnaires at home will be provided with prestamped envelopes addressed to the research team. The prestudy questionnaire will be provided to the participants at the time of enrollment, whereas the poststudy questionnaire will be provided after a follow-up appointment with the participant's clinician at the time of study completion (3 months after enrollment). Data on the 30-day HF readmission rates; HF length of stay; number of visits to the ED; and clinical measures, including creatinine, sodium, potassium, left ventricular ejection fraction, and BNP/NT-proBNP levels, will be determined through the hospital's electronic medical records and manual chart reviews.

Semistructured Interviews

Using purposive sampling, semistructured interviews at the end of the study will also be conducted with a subset of patients in the intervention group to receive feedback from patients with different experiences using Medly-AID. Participants for the interviews will be selected based on varying adherence to taking measurements, number of readmissions to hospital, difficulties in using Medly, etc. Interviews will be conducted until data saturation is reached (ie, interviewer determines no new relevant information is being collected), which is typically 15 to 20 participants. The interviews are expected to last for 20 min to 30 min and will be conducted in a quiet and private space within the clinic (eg, consultation room) during a regular clinic visit or over the telephone. All interviews will be audiotaped and transcribed for later analysis. Clinicians providing care for patients using Medly-AID will also undergo a semistructured interview post study to determine their perceptions of the use and impact of Medly-AID. It is anticipated that the clinician interviews will last for 15 min to 45 min.

Data Analysis

For each outcome measure, normality of the data will be verified using the Kolmogorov-Smirnov and Shapiro-Wilk tests of normality. Between-group analyses using independent Student *t* tests and Mann-Whitney tests (for normally and nonnormally distributed data, respectively) will be performed. Paired Student *t* tests and Wilcoxon signed rank tests will also be performed to compare baseline and poststudy data for both the intervention and control groups as appropriate. The statistical analyses will be performed using the statistical software SPSS 17.0 (IBM Corporation). Statistical significance will be considered at $P<.05$, unless otherwise specified. All reported test results will be 2-tailed.

The transcribed interview data will be analyzed using conventional content analysis, whereby 2 researchers will analyze the transcripts for themes independently [26]. The 2 researchers will then discuss the themes and issues that emerge until a consensus is reached. Triangulation, which is validation of the findings through the collection of data from different sources or methods, will be used for this study. Specifically, the interview findings will be used to try to confirm and explain the results of the quantitative data, including health services utilization and Medly usage.

Results

Patient recruitment began in November 2018 in the Sunnybrook Health Sciences Centre. The study is currently ongoing, with a total of 35 participants (17 in the intervention group and 18 in the control group) as of July 30, 2019. The anticipated date for final analysis of the data is fall of 2020.

Discussion

Strengths and Limitations of the Study

This RCT aims to investigate the impact of a mobile phone–based HF TM system on patients with HF recently discharged from hospital for decompensated HF. Previous studies on HF TM have yielded contradictory findings, with some showing benefits to patient outcomes, including reductions in hospitalizations, whereas other trials have found no benefits [16-18]. Factors influencing the benefits include the features of the TM system, patient population, study design, and the implementation plan [27,28]. A study by Ware et al [29] summarizes the available evidence on HF TM effectiveness and discusses the complexity in accounting for these factors. This was followed by a literature review and white paper from the Heart Failure Society of America, which concluded that HF remote monitoring was most beneficial for patients at most risk for decompensation and hospitalization, suggesting that null findings from previous studies might be attributed to including patient participants with HF who were already stable [30]. In this trial, we are employing a TM system, Medly, that is currently being used as a standard of care in an outpatient heart function clinic at a large academic hospital, with proven beneficial features in a mixed population of stable and unstable patients [20,21]. Therefore, this study is intended to test the impact of the same system with a target population that is hypothesized to benefit the most (ie, patients who have been discharged from hospital and are at the highest risk for readmissions).

In terms of the study design, a multimethod approach will be used, which will enable triangulation of data from questionnaires, patient data from home monitoring, Medly usage data, patient medical records, costing information, and interviews. This will allow for a comprehensive understanding of the impact of Medly on the end users, clinical workflows, cost savings, and perceptions of TM by clinicians and patients. For example, the interview data may help to understand the features of Medly that are useful and those that are not useful, as well as to understand how patients with HF recently discharged from hospital might differ in their perceptions and adherence to TM compared with other patients with HF. Finally, the extensive expertise from careful TM program implementation planning will be leveraged for the planning of this RCT [19,27,31].

A limitation of this study includes the relatively small patient sample size. It is expected that this trial will be underpowered to detect the impact of Medly on hospital readmission rates. Benefits of Medly on the primary outcomes would provide evidence to support a future larger clinical trial to determine the effectiveness of Medly on hospital readmission rates. The intent of the study is to deploy Medly within representative academic and community hospitals within Ontario. However, the number of deployment sites will be relatively small (3 to 4 sites), which is another limitation as it may impact the generalizability of the findings.

Significance of the Research

The rising incidence of HF [32,33] highlights the importance of developing and validating novel technologies or management strategies. This trial will be one of the few studies that will provide evidence of the impact of HF TM specifically for patients recently discharged from hospital. The trial will investigate the impact through various lenses, including patient self-care and quality of life, clinician experience and impact to their workflow, costs to the health care system, and patient health outcomes. It is anticipated that this study will help inform how to optimize the future scale and spread of TM to support patients and clinicians in the management of HF.

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Conflicts of Interest

Members of the research team (ES and HJR) have intellectual property rights of the Medly system.

Multimedia Appendix 1
Peer-reviewer report from the Sunnybrook Alternative Funding Plan.
[PDF File (Adobe PDF File), 258 KB - resprot_v9i1e15753_app1.pdf]

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Abbreviations

BNP: brain natriuretic peptide
ED: emergency department
HF: heart failure
Medly-AID: Medly-After an Incidence of acute Decompensation
NT-proBNP: N-terminal probrain natriuretic peptide
RCT: randomized controlled trial
SCHFI: Self-Care of Heart Failure Index
TM: telemonitoring

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Protocol

Self-Management Characterization for Families of Children With Medical Complexity and Their Social Networks: Protocol for a Qualitative Assessment

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Abstract

Background: Children with medical complexity (CMC) present rewarding but complex challenges for the health care system. Transforming high-quality care practices for this population requires multiple stakeholders and development of innovative models of care. Importantly, care coordination requires significant self-management by families in home- and community-based settings. Self-management often requires that families of CMC rely on vast and diverse social networks, encompassing both online and offline social relationships with individuals and groups. The result is a support network surrounding the family to help accomplish self-management of medical tasks and care coordination.

Objective: The goal of this study is to use a theoretically driven perspective to systematically elucidate the range of self-management experiences across families of CMC embedded in diverse social networks and contextual environments. This approach will allow for characterization of the structure and process of self-management of CMC with respect to social networks, both in person and digitally. This research proposal aims to address the significant gaps in the self-management literature surrounding CMC, including the following: (1) how self-management responsibilities are distributed and negotiated among the social network and (2) how individual-, family-, and system-level factors influence self-management approaches for CMC from a theoretically driven perspective.

Methods: This study will encompass a qualitative descriptive approach to understand self-management practices among CMC and their social networks. Data collection and analysis will be guided by a theoretical and methodological framework, which synthesizes perspectives from nursing, human factors engineering, public health, and family counseling. Data collection will consist of semistructured interviews with children, parents, and social network members, inclusive of individuals such as friends, neighbors, and community members, as well as online communities and individuals. Data analysis will consist of a combination of inductive and deductive methods of qualitative content analysis, which will be analyzed at both individual and multiadic levels, where interview data from two or more individuals, focused on the same experience, will be comparatively analyzed.

Results: This study will take approximately 18 months to complete. Our long-term goals are to translate the qualitative analysis into (1) health IT design guidance for innovative approaches to self-management and (2) direct policy guidance for families of CMC enrolled in Medicaid and private insurance.

Conclusions: Multiple innovative components of this study will enable us to gain a comprehensive and nuanced understanding of the lived experience of self-management of CMC. In particular, by synthesizing and applying theoretical and methodological approaches from multiple disciplines, we plan to create novel informatics and policy solutions to support their care within home and community settings.

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KEYWORDS

children with medical complexity; care coordination; social network; qualitative description; health care self-management; family management; multiadic analysis; contextual environment

Introduction

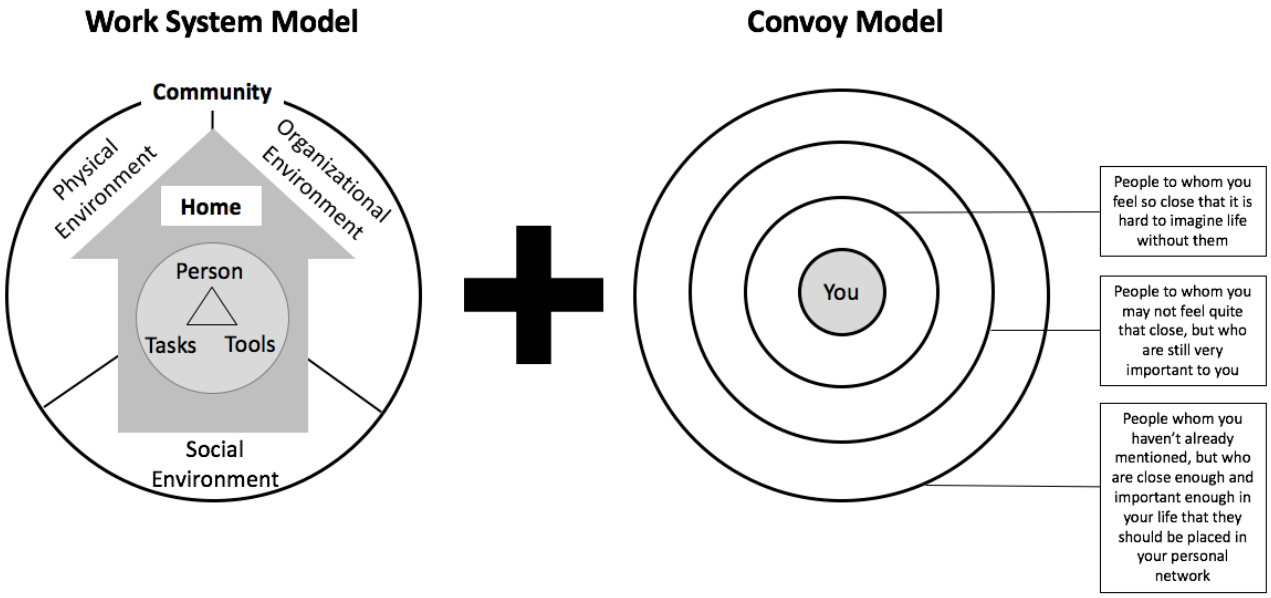
Children with medical complexity (CMC) are a growing population of medically fragile children with complex, multisystem disease states, technology dependence, severe functional limitations, complicated treatment regimens and therapies, and surgical interventions that require comprehensive self-management [1-3]. Advancements in neonatal and pediatric critical care, nutrition therapies, and emerging technologies have resulted in improved survival rates among medically fragile children [2]. These children are often left with life-threatening complex systemic health problems, including neurodevelopmental disabilities, gastrointestinal limitations, pulmonary and cardiac complications, and musculoskeletal abnormalities, among other issues [2]. CMC often require 24-hour-a-day monitoring and care, frequently occurring in home- and community-based settings and relying on immense caregiving efforts [4].

In the context of CMC, self-management can be conceptualized as family management, or care where the family —along with the child in some cases—is actively participating in the child's health management. Such self-management requires coordinating and implementing the instructions of numerous providers, which may include medications, therapies, home monitoring, technologic dependence, and complex care plans [5]. Beyond medical aspects, families of CMC must also engage in emotional management and role navigation management [6,7]. This range of activities occurs within variously configured contextual environments (eg, technological, community, and physical) that contribute to or act as barriers to high-quality self-management [8]. For example, patient portals from electronic health records and other digital tools present ample opportunities for improved care coordination. Yet, to date, implementation of such tools has not been robust, perhaps due to practice variations, regional restrictions, and reimbursement obstacles [9]. The current fragmented nature of care coordination and family-centered navigation suggests that the development of consumer health IT to enable these practices is in early stages, and the various technologies that do exist for this purpose are often not aligned with the realities of families' lives [10].

Despite CMC encompassing several diagnoses, the self-management needs and practices among all CMC and their families are shared, so it is critically important to contextualize CMC as a whole [11]. Moreover, to meet self-management challenges, families of CMC likely rely on vast and diverse social networks [11], defined as the web of social relationships surrounding an individual [12]. Involving social network members in self-management requires ongoing engagement and communication or sharing content through various media with multiple individuals [10]. Since these social relationships can exist either offline or online, there may be additional opportunities for innovative digital care coordination interventions.

The theoretical framework guiding this study is synthesized from literature in human factors engineering, nursing, and public health. The foundation of the theoretical framework is drawn from the public health structure-process-outcome model proposed by Donabedian [13]. It asserts that the home and community settings in which self-management of CMC occurs (ie, structure) impact the ways in which self-management is enacted (ie, process). These self-management processes, in turn, affect the health status of CMC (ie, outcome) [13-15]. The structure of home and community settings is grounded in work system theory, drawn from human factors engineering, which specifies that such settings are characterized by individual (ie, patient and others involved in his or her care) attributes (eg, literacy and age), tasks (eg, complexity and frequency), tools and technology (eg, access and usability), physical environment (eg, clutter and noise), social environment (eg, social support), and organizational environment (eg, routines and policies) [16-19]. The theoretical framework further emphasizes the primacy of the social environment, explicitly accounting for the structure of the affective social networks and the roles played by each social network member (see Figure 1). We draw on the convoy model from the nursing literature to explicate the structure of the social environment [10]. This model has been adopted and adapted for use in other similar studies seeking to understand the role of the social environment in health [10].

Figure 1. Theoretical underpinnings of the study involving the work system model and convoy model.



Self-management processes shaped by these structural components, and drawn from the nursing literature, include learning about the condition and health needs, recognizing and managing body responses, identifying and benefiting from psychological resources, processing and sharing emotions, and obtaining and managing social support, among others. Proximal and distal outcomes impacted by these self-management processes include those that are related to health status, quality of life, relationship dynamics, and cost of care [20].

This study focuses on structure and process, while follow-up studies will be extended to focus on outcomes. We view this study as a critical step in understanding family and social engagement surrounding self-management of patients with medical complexity. As consumer health information technologies are created to support family engagement in the self-management process, there is a critical need to ensure that the technologies, which are intended to support families, function in ways that families are working and communicating [10]. Thus, we will first focus on connecting all aspects of the work system to the experiences of self-management processes, while we will subsequently focus on more deeply connecting the social environmental component of the work system to self-management processes through a social network lens.

In summary, this research proposal aims to address the significant gaps in the self-management literature surrounding CMC, including the following: (1) how self-management responsibilities are distributed and negotiated among the social network and (2) how individual-, family-, and system-level factors influence self-management approaches for CMC from a newly synthesized theoretical perspective. This view includes individual and family factors within the context of people's social, technical, and environmental lives, while also systematically exploring perspectives from members of the CMC's network.

Methods

Overview

This study takes a qualitative descriptive approach [21,22] to understand self-management practices among CMC. The qualitative descriptive approach focuses on generating a comprehensive summary of events with presentation of interpretive categories in everyday language [22]. Given that qualitative descriptive studies may begin with an overarching framework [21], data collection and analysis will be guided by the combined theoretical framework described above. However, both data collection and analysis will remain open to the data; in other words, it is possible that the concepts of interest will change over time [21,22]. Data collection will consist of semistructured interviews with children, parents, and social network members. Data analysis will consist of a combination of inductive and deductive methods of qualitative thematic analysis [23], which will use data generated by interviews and application of line-by-line codes; relevant categories to generate final themes will then be used describe the phenomena of interest. Relevant categories and themes will be analyzed at both individual and multiadic levels (ie, intragroup) [21,22] to understand similarities and differences within each case (ie, child) in terms of the various facets of the family and social networks and across cases regarding the same. Further, multiadic analysis means that relevant comparisons and contrasts will be made across similar thematic domains within each case. We expect there to be a diversity in disease representations but a shared experience in self-management burdens and difficulty in navigation between a multitude of settings.

Eligible families will initially be approached to participate in this study from an academic children's hospital that provides specialist inpatient and outpatient services, including a pediatric complex care clinic. Each family will be comprised of a child between 0 and 21 years of age with diagnoses and/or a clinical presentation consistent with the definition of medical complexity, as well as the child's parents. Operationalization

of CMC will follow the Center of Excellence on Quality of Care Measures for Children with Complex Needs (COE4CCN) definition of the highest level of medical complexity of children with complex chronic disease [24]. This definition includes any of the following scenarios: significant chronic conditions in two or more body systems where the physical, mental, or developmental conditions have lasted at least a year; use of health care resources are above the level for a healthy child; and treatment is required for control of the condition. In addition, the conditions are expected to meet one of the three following descriptions: episodic or continuously debilitating, a progressive condition that is associated with deteriorating health with a decreased life expectancy in adulthood, child requires continuous dependence on technology for at least 6 months, or a progressive or metastatic malignancy that impacts life function. Maximum variance sampling [25] will be used to recruit participants; this will be based on condition as well as demographic characteristics shown to impact child self-management, including parent and child gender, age, race or ethnicity, geographic location, health literacy, educational background, and health status. This sampling strategy will enable us to gain insight into a wide range of established approaches to self-management in children with medical complexity.

If a child is unable to provide assent or consent, only the parents will be included. Furthermore, if only one parent is present or willing to participate, only this individual will be included. Thus, a family is eligible to participate in this study in any of the following combinations of individuals: a child and two parents, a child and one parent, two parents, or one parent. In this study, we refer to a social network set as the individual social networks of each family member. Thus, a social network set could be comprised of only one social network (ie, one parent's network), two social networks (ie, both parents' networks or one parental and one child network), or three social networks (ie, both parental networks and one child network). Together, a family and their social network set comprise a case. Social network members will be selected by participants based on prompts associated with the convoy model instrument [10] and may include individuals such as neighbors, friends, members of the community, and members of online social networks, in addition to family members [10]. During the consent process, it will be explained that the investigators are interested in contacting members of the participants' social network for potential inclusion in the self-management study. Following completion of the parent interviews, participants will be asked for contact information for potential social network recruitment.

Measures

Semistructured interviews (see Table 1) will be conducted and will consist of four overarching domains. Part 1 of the interview will involve opening questions where both parents and children will answer open-ended questions about their daily routines. Part 2 of the interview process will elicit questions surrounding how self-management responsibilities are distributed and negotiated among the social network. This section of the interview will provide an exploration of participants' social networks and the ways in which the network is engaged in self-management processes. Participants will be guided through a structured process of explicating their affective social networks [26]. They will be asked a series of open-ended questions to understand the characteristics of each social network member and their general relationship with the social network member. The interview will then transition to self-management. Participants will be asked about their own roles in specific self-management processes and the role of each social network member. Self-management processes include health-related domains of the following: therapeutics (ie, medications, technology dependence, and therapies), care coordination (ie, appointments, information exchange, logistics like transportation, and home activities of daily living), and management of unexpected health events (ie, side effects, unexpected illnesses, and unexpected hospitalizations).

Once each social network member has been discussed, participants will be asked if there is anyone else who helps with their own or their child's self-management whom they did not place in their social network. Participants will be asked whether or not these individuals should be placed in the social network and asked questions about each person similar to those above. Finally, participants will be asked to reflect on their network as a whole and the ways in which they engaged this network in specific self-management processes.

Part 3 of the interview will provide an exploration of participants' work systems and the ways in which work system elements shape self-management. Participants will be asked to think of times in the past when they were engaged in specific self-management processes. Participants will then be asked to reflect on how different aspects of their work system contributed to these experiences; these aspects include the following: personal attributes (eg, literacy, health literacy, education, socioeconomic status, and age), tasks (eg, complexity and frequency), technology (eg, access to and usability of personal health records, automated reminders, and health-related apps), physical environment (eg, clutter and noise), social environment (eg, support from social networks inclusive of individuals such as family members, friends, home care aides, and health care providers), community environment (eg, public transportation), and health policy environment (eg, insurance, characteristics of the health care delivery system such as financial assistance, and care coordination practices) [16]. A similar structure will be used to understand the challenges that participants have faced when engaging in the same self-management processes.

Table 1. Interview domains and sample questions for self-management of children with medical complexity (CMC).

Domain	Details	Sample questions for interviews with CMC and their parents or legal guardians
General		What does a typical day look like?
		What makes some days easier than others?
Social network member characteristics	Identification, characteristics, and stability	Can you tell me about your relationship with [social network member]?
		How has your relationship with [social network member] changed over time?
		What do you think makes [social network member] a part of your social network?
Self-management	Domains include therapeutics, care coordination, and management of unexpected health event	Now we are going to talk about taking care of your/your child's medication needs. This includes everything from getting a prescription from your provider, filling the prescription, and taking the medication as directed.
	Aim 1: How self-management responsibilities are distributed and negotiated among the social network	What do you do to take care of your/your child's medication needs?
		Please tell me about a time when you were taking care of your/your child's medication needs/treatment and felt things went well?
		Please tell me about a time when you were taking care of your/your child's medication needs and felt things went poorly?
Social network member self-management involvement	Corresponding with self-management domains	How does [social network member] help take care of your/your child's medication needs?
	Aim 1: How self-management responsibilities are distributed and negotiated among the social network	Why are they involved in that way?
		How do you feel about their involvement?
Reflection on social network as a whole	Aim 1: How self-management responsibilities are distributed and negotiated among the social network	How do you decide who to ask for help about [your child's] management?
		Who are the first people you reach out to?
		Why do you reach out to them first?
Work system	Demographics, social determinants, modifications, and financial toxicity	Now we want to know about how things in your environment (house and community) impact the care of your child.
	Aim 2: How individual-, family-, and system-level factors influence self-management approaches for CMC from a theoretically driven perspective	Have there been any modifications to the home that help you/your child accomplish activities of daily living?
		What kind of access to you have to the Internet?
		Have you moved around a lot from your current home?

Interviews with social network members will also consist of four parts. In addition to opening and concluding questions that mirror those above and include demographic questions, the following questions related to the two aims will be asked. Questions will be oriented to the individuals that placed the social network member in their network (eg, child only or both parents and child). Social network members will be asked general questions about their relationship with the child and/or parents. They will also be asked where in their social network they would place the parent or child. Social network members will then be asked about their role in managing the child's health, how they assumed that role, and how they feel about that role. Social network members will be asked about times in the past when they were involved in managing specific aspects of the child's health and felt that things went well. They will then be asked to reflect on how different aspects of the parent or child's work system (as described in Table 1) contributed to these experiences. Similar questions will be asked for when things were not perceived to go well. Follow-up questions will be skipped if a social network member does not engage in a specific aspect of managing the child's health.

Outcomes and Data Analysis

Analyses for both aims will begin with cross-sectional analysis, will move to within-case comparisons, and will end with across-case comparisons. These analyses will build on one another. That is, the cross-sectional analysis will be used to generate prevalent analytical categories and themes within the data. Within-case analysis will then be used to determine how these themes manifest and interact within each case. Finally, across-case analysis will be used as a higher order cross-sectional analysis that will allow for a meta-analysis of how these categories and themes manifest and interact across families and social networks.

Two types of cross-sectional views will be created: one drawn from all parent and child data and one drawn from all social network member data. In addition, analyses will be conducted both by self-management process and in aggregate across all self-management processes. Regarding the *parent and child view*, we will begin by describing parent and child social network structure and composition. Descriptive statistics (eg, demographics of social network members) and conventional qualitative content analysis [23], in which themes are derived

from data (eg, relationship with social network members), will be used to develop cross-sectional views of these social networks. This latter method will also be used to analyze open-ended questions about the nature of self-management responsibilities and how they are distributed and negotiated among social network members. We will then use directed qualitative thematic analysis [23], in which operational definitions for initial categories and subcategories are determined using theory. The work system model and relevant empirical studies will be used to develop initial categories of barriers and facilitators. Regarding the *social network view*, analysis will parallel that described for the *parent and child view*, resulting in an aggregate view and views by self-management process. As described above, conventional qualitative content analysis will be used to analyze open-ended questions.

Methods of multiadic analysis will be used to create two types of within-case comparisons [27,28]. The first type of within-case comparison will occur at the level of the family. When two or three individuals participate from one family (ie, both parents, both parents and child, or one parent and child), multiadic methods will be used to compare the responses provided by each individual. In particular, points of overlap and difference between viewpoints will be explicitly coded using a combination of directed and conventional qualitative content analysis (ie, deductive and inductive methods). Drawing on Eisikovits and Koren's framework [28], we will first code into four themes: (1) overlap on open and hidden reality, (2) contrast on open and hidden reality, (3) contrast on open reality and overlap on hidden reality, and (4) overlap on open reality and contrast on hidden reality. Open reality refers to what is described by individuals (eg, the event that occurred), whereas hidden reality refers to the ascribed meaning (eg, how the event was interpreted). This four-dimensional framework will be extended in the case of the participation of three family members. Within this framework, categories drawn from the data will be created to account for types of open and hidden realities. The second type of within-case comparison will occur at the level of the social network. A dyadic analysis will take place comparing the narratives of the family member with the narratives of each of their social network members (eg, What does the mother say about her own role and her sister's role, and what does her sister say about her own role and the mother's role?). This analysis will occur as described above. Another iteration of analysis will then be conducted to reduce the dyadic analyses into a synthesized view for each family member. For example, for each of 10 individuals in a child's social network, a dyadic analysis will be conducted that will result in material under each of the four themes. The next round of analysis would consist of a qualitative content analysis of all of the material within each theme. Thus, the final analysis for each social network set would consist of an aggregate view of the four themes in Eisikovits and Koren's framework across all social network members. One aggregate analysis will be created for each family member.

A final structural layer of analysis will be added with across-case comparisons. To create comparable analytic instruments that further reduce the data, we will create individual case reports [29,30]. These reports will be narrative in nature and will highlight key characteristics of each case (eg, number of family members involved, family demographics, and key themes from cross-sectional, dyadic, and multiadic analyses). Case reports will be comparatively analyzed using conventional qualitative content analyses. Guiding questions relevant to this analysis will include the following: (1) Which approaches to distributing and negotiating self-management responsibilities are common and distinct across families and their social networks? and (2) How do families and social networks with apparently similar characteristics differentially engage in distributing and negotiating self-management practices? Analyses guided by these questions will enable a nuanced understanding of mechanisms driving specific self-management experiences within and across various social networks. For all analysis steps, all investigators will individually analyze 20% of the data before reaching a consensus. Consensus guidelines will be documented for use in subsequent analyses. The remaining analyses will be divided between the principal investigators, who have in-depth experience with both forms of qualitative content analysis to be used in the study. Analysis will be discussed at regular full-team meetings. All analyses will be conducted using NVivo 11 (QSR International). Reflective journal entries will be maintained by the lead investigators during the research process. Methods to ensure rigor and trustworthiness [31] of the data analysis will include aspects of demonstrating (1) credibility (ie, direct observation of online communication, iterative questioning, and frequent debriefing), (2) transferability (ie, contextual review), (3) dependability (ie, maintaining an audit trail), and (4) confirmability (ie, bracketing, investigator triangulation, and member checking through the stakeholder advisory board). The key decision points for the qualitative research analysis will also be assessed and recorded in an online platform through the Center for Open Science to ensure rigor and reproducibility. Anticipated limitations of this study design include the following: lack of generalizability based on recruitment from a single-site study and potential for recall bias with self-reported data. Additionally, we lack the ability to triangulate self-management experiences within the school or other immersive environments.

Results

We anticipate that this project will take nearly 18 months, including recruitment, interviewing, and completion of data analysis. Challenges to the protocol may involve study recruitment challenges; feasibility of the completion of long parent interviews, while caring for CMC; and analytic integration of multiadic components. To offset these potential challenges, we will consider opening the recruitment to online methods, offering participants the ability to complete the interviews in more than one session, and developing network mapping approaches to be applied to data analysis to offset the sheer quantity of data and analytics lenses. Findings from this study will be disseminated to academics, clinicians, and policy makers. Our long-term goal is to translate the qualitative analysis into (1) health IT design guidance for innovative approaches to self-management and (2) direct policy guidance for families of CMC enrolled in Medicaid and private insurance.

Discussion

This study is theoretically, conceptually, and methodologically innovative. First, the theoretical framework is innovative in nature, in that it synthesizes nursing, human factors engineering, and public health perspectives. In doing so, it elaborates upon existing theoretical frameworks used to guide the study of self-management. Our model is grounded in Donabedian's structure-process-outcome assessment model [13-15]. Key concepts and relationships derived from this public health sciences model are present in general models of self-management [32,33] and those that are specific to children with chronic conditions [34,35], demonstrating the relevance of Donabedian's model for conceptualizing self-management. Previous models, however, are not explicitly grounded in additional theoretical perspectives. We address these limitations by integrating nursing and human factors engineering theories into Donabedian's model. Integration of the convoy model [26] from nursing enables explicit consideration of the social network. Integration of a synthesized work system model from human factors engineering [16] enables explicit consideration of all structural elements in previous self-management models, in addition to elements empirically shown to impact self-management [8] but not included in these previous models. This integration of the work system model with another model is consistent with a novel approach within human factors engineering [36].

Second, this study is innovative in extending the conceptualization of the "who" in self-management. A traditional definition of self-management focuses on an individual's solitary actions or actions that require interacting with members of the formal health care delivery system [37]. More recently, the definition of self-management has been extended by many, including the National Institutes of Health (NIH) [38], to encompass the actions of the individual's family members. This study augments this conceptualization in two ways. First, it explicitly accounts for the extended social network of the individual with a chronic condition, enabling systematic understanding of the ways in which individuals beyond family members are engaged in health management. Such an approach will allow us to understand the potentially limited but essential roles played by a broader range of actors. Second, this study explicitly includes the extended social network not only of the individual with a chronic condition, but also of the primary caregivers. This expanded approach will foster a more holistic understanding of how self-management relies not only on a patient's social network, but also on the social networks of the primary informal caregivers.

Methodologically, this study is innovative in adopting an analytic approach from counseling psychology and family communication. To our knowledge, such an approach has not been applied to studies of self-management nor of CMC. Namely, this study leverages methods of dyadic and multiadic analysis—in which interview data from two or more individuals, focused on the same experience, is comparatively analyzed—to explicitly account for multiple perspectives on CMC self-management. These methods of qualitative analysis [27] have the potential to reveal points of agreement, disagreement, and differential understanding among individuals [28]. Points of misunderstanding and disagreement may then be conceptualized as points of intervention. It is important to underscore that such an approach is distinct from approaches that comparatively analyze all patient data with all family caregiver data. Such an approach compares narratives only at the aggregate level. The approach of this study is comparative, both at the dyad level as well as at the aggregate level. In conclusion, multiple innovative components of this study will enable us to gain a comprehensive and nuanced understanding of the lived experience of self-management of CMC and an understanding of the spillover impacts experienced by families of CMC and members of their social networks. In particular, by synthesizing and applying theoretical and methodological approaches from multiple disciplines, we plan to create novel informatics and policy solutions to support care within home and community settings. Subsequent studies will (1) enable us to further investigate how diverse lived experiences are tied to health outcomes and (2) enable us to determine how innovative health IT and policy solutions may alter these lived experiences to positively affect health outcomes.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports from the University of Virginia.
[PDF File (Adobe PDF File), 150 KB - resprot_v9i1e14810_app1.pdf]

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Abbreviations

CMC: children with medical complexity
COE4CCN: Center of Excellence on Quality of Care Measures for Children with Complex Needs
NIH: National Institutes of Health
NINR: National Institute of Nursing Research

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Protocol

Smartphone Cardiac Rehabilitation, Assisted Self-Management Versus Usual Care: Protocol for a Multicenter Randomized Controlled Trial to Compare Effects and Costs Among People With Coronary Heart Disease

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Abstract

Background: Alternative evidence-based cardiac rehabilitation (CR) delivery models that overcome significant barriers to access and delivery are needed to address persistent low utilization. Models utilizing contemporary digital technologies could significantly improve reach and fidelity as complementary alternatives to traditional center-based programs.

Objective: The aim of this study is to compare the effects and costs of the innovative *Smartphone Cardiac Rehabilitation, Assisted self-Management* (SCRAM) intervention with usual care CR.

Methods: In this investigator-, assessor-, and statistician-blinded parallel 2-arm randomized controlled trial, 220 adults (18+ years) with coronary heart disease are being recruited from 3 hospitals in metropolitan and regional Victoria, Australia. Participants are randomized (1:1) to receive advice to engage with usual care CR or the SCRAM intervention. SCRAM is a 24-week dual-phase intervention that includes 12 weeks of real-time remote exercise supervision and coaching from exercise physiologists, which is followed by 12 weeks of data-driven nonreal-time remote coaching via telephone. Both intervention phases include evidence- and theory-based multifactorial behavior change support delivered via smartphone push notifications. Outcomes assessed at baseline, 12 weeks, and 24 weeks include maximal aerobic exercise capacity (primary outcome at 24 weeks), modifiable cardiovascular risk factors, exercise adherence, secondary prevention self-management behaviors, health-related quality of life, and adverse events. Economic and process evaluations will determine cost-effectiveness and participant perceptions of the treatment arms, respectively.

Results: The trial was funded in November 2017 and received ethical approval in June 2018. Recruitment began in November 2018. As of September 2019, 54 participants have been randomized into the trial.

Conclusions: The innovative multiphase SCRAM intervention delivers real-time remote exercise supervision and evidence-based self-management behavioral support to participants, regardless of their geographic proximity to traditional center-based CR

facilities. Our trial will provide unique and valuable information about effects of SCRAM on outcomes associated with cardiac and all-cause mortality, as well as acceptability and cost-effectiveness. These findings will be important to inform health care providers about the potential for innovative program delivery models, such as SCRAM, to be implemented at scale, as a complement to existing CR programs. The inclusion of a cohort comprising metropolitan-, regional-, and rural-dwelling participants will help to understand the role of this delivery model across health care contexts with diverse needs.

Trial Registration: Australian New Zealand Clinical Trials Registry (ACTRN): 12618001458224; anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374508.

International Registered Report Identifier (IRRID): DERR1-10.2196/15022

(JMIR Res Protoc 2020;9(1):e15022) doi:10.2196/15022

KEYWORDS

telemedicine; telerehabilitation; mHealth; myocardial ischemia; coronary artery disease; exercise; behavioral medicine; health services accessibility; costs and cost analysis

Introduction

Background

Cardiac rehabilitation (CR) is a cost-effective multifactorial intervention that plays a critical role in the secondary prevention of coronary heart disease (CHD) [1-4]; however, low rates of participation in traditional center-based programs (ie, face-to-face delivery) [5] continue to limit impact on individual, clinical, and economic outcomes. Uptake and adherence to center-based CR are influenced by diverse factors, but access barriers such as limited program availability, transport restrictions, conflicting domestic/occupational responsibilities, and geographic isolation are key contributors [6-9]. Establishing new programs in diverse locations could improve accessibility, but this may not be feasible, given the high infrastructure costs associated with center-based facilities [10,11]. The traditional CR paradigm cannot meet the needs of many eligible individuals, and complementary alternatives that deliver evidence-based support outside of face-to-face settings are urgently needed to complement current services.

Home-based delivery overcomes many access barriers and can have comparable short-term effects on mortality, exercise capacity, and health-related quality of life [12], but it often lacks oversight and guidance from CR professionals, which are central to best-practice center-based programs.

Rapid advances in mobile communications and wearable sensor technologies could bridge the gap between home- and center-based delivery models by combining near-universal accessibility with responsive individualized clinical oversight. CR delivered via landline telephone, SMS, and Web-based mechanisms has demonstrated promising potential [13]. However, few interventions have incorporated emerging digital technologies that can support more comprehensive, responsive, and interactive intervention delivery that emulates center-based support [14]. We previously developed a 12-week exercise-based mobile health (mHealth) intervention, named Remote Exercise MOnitoring Trial for Exercise-based Cardiac Rehabilitation (REMOTE-CR), to address this unmet need [15]. Using mobile, Web, and wearable sensor technologies, our bespoke intervention remotely connected participants with exercise physiologists to receive real-time individualized supervision and coaching during exercise training from any geographic location with a local or mobile internet connection. In a noninferiority randomized controlled trial (RCT), we showed that the effect of REMOTE-CR on functional capacity was as good as traditional center-based programs. The trial also demonstrated comparable effects on modifiable cardiovascular risk factors and motivational outcomes, substantial program delivery cost savings via reduced infrastructure requirements, as well as high usability, acceptability, and end-user demand for REMOTE-CR as a usual care service [10,16]. Collectively, these findings suggest complementing existing center-based programs with effective mHealth delivery models could increase overall engagement with CR by allowing more individuals to access individualized intervention support.

However, REMOTE-CR trial findings also identified opportunities for further development. First, REMOTE-CR focused primarily on exercise training, whereas comprehensive CR should also incorporate health behavior change and education, management of other lifestyle risk factors—including healthy diet and tobacco smoking—and adherence to prescribed medications [2,3]. Second, the advantages of mHealth CR are likely to be greatest in regional and rural areas where access to existing services is lowest [17]; however, the predominantly urban sample in our trial meant we could not determine impact in regional or rural areas. Third, long-term maintenance of self-management behaviors is a key component of CR [2,3], and—in combination with substantial cost-efficiencies [10,18,19]—near-universal accessibility makes mHealth CR well suited for supporting long-term self-management. However, our REMOTE-CR intervention provided only 12 weeks of support. Fourth, our previous trial actively facilitated referral and priority enrollment into center-based rehabilitation for participants randomized to the control group. This differs from usual care practice as referral rates are far from optimal [20,21], and individuals are typically required to self-initiate engagement with usual care services.

We have subsequently developed a 24-week multifactorial intervention (*Smartphone Cardiac Rehabilitation, Assisted self-Management* [SCRAM]) that addresses previous participant feedback [16], includes more comprehensive multifactorial behavior change support, and integrates an additional 12-week maintenance phase to assist participants' transition toward self-determined long-term adherence to self-management behaviors.

Objectives

This protocol describes the rationale and design of a multicenter RCT that aims to compare the effects and costs of SCRAM on modifiable cardiovascular risk factors with usual care CR among urban-, regional-, and rural-dwelling individuals with CHD. Usual care CR was chosen as the comparator as it is the standard of care. We hypothesize that the effects of SCRAM on primary and secondary outcomes will be superior to usual care CR alone and that SCRAM will be cost-effective.

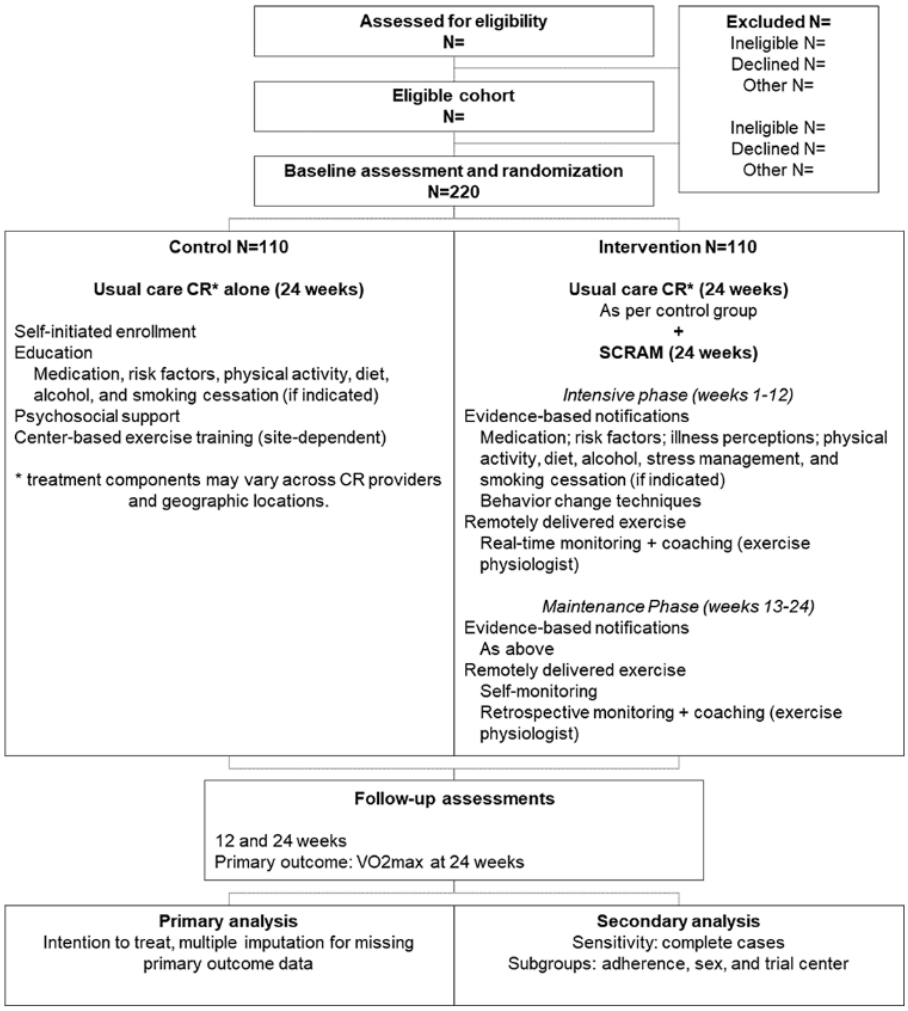
Methods

Design

A multicenter investigator- and assessor-, and statistician-blinded parallel 2-arm RCT is being conducted to compare effects of SCRAM and usual care CR on maximal aerobic exercise capacity, modifiable cardiovascular risk factors, and self-management behaviors (Figure 1). Process and economic evaluations aim to determine participants' perceptions of the SCRAM and usual care programs and the cost-effectiveness of SCRAM, respectively.

The trial protocol was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618001458224) on August 30, 2018, and it adheres to the Standard Protocol Items: Recommendations for Interventional Trials 2013 statement [22]. The intervention has been described according to recommendations in the Template for Intervention Description and Replication and Consolidated Standards of Reporting Trials (CONSORT; electronic health [eHealth] extension) statements (Multimedia Appendices 1-3). Reporting of trial outcomes will adhere to the CONSORT statement and its eHealth extension [23-25].

Figure 1. Consolidated Standards of Reporting Trials design schematic. CR: cardiac rehabilitation; SCRAM: Smartphone Cardiac Rehabilitation, Assisted self-Management.



Setting

The trial is being conducted at 1 metropolitan (Sunshine Hospital, Western Health) and 2 regional (University Hospital Geelong, Barwon Health; Bendigo Hospital, Bendigo Health) health care providers in Victoria, Australia. These trial centers collectively serve approximately 1.5 million individuals and provide acute coronary care services to individuals living in large regional and rural catchment areas across Northern and Western Victoria. This enables sampling of a geographically diverse cohort that includes metropolitan-, regional-, and rural-dwelling participants, which is particularly important as age-standardized rates of CHD hospitalizations and access to

traditional center-based CR are worse outside metropolitan areas in Australia [26,27].

We anticipate recruiting equal numbers of participants via each trial center; a priori prediction of the ratio of metropolitan, regional, and rural participants is not possible, but it will be reported together with trial outcomes.

Recruitment

Recruitment began at all trial centers on November 12, 2018, and it is monitored via monthly reporting to the trial steering group, comprising the trial investigators. Research nurses identify eligible individuals before hospital discharge and via outpatient cardiac clinics, provide potential participants with trial information and consent forms, obtain consent to refer interested individuals to the research team, and document reasons for declining participation. A researcher subsequently confirms individuals' interest in the trial, answers unresolved questions, and schedules baseline assessment appointments for those who volunteer to participate.

Eligibility

Eligible participants are adults (18+ years) with recently diagnosed CHD (angina, myocardial infarction, and coronary revascularization within the previous 6 months), who are clinically stable outpatients (no CHD-related hospitalization within 6 weeks of baseline assessment) and can understand and write English. Participants are excluded if they have New York Heart Association class III/IV heart failure, terminal disease, significant non-CHD exercise limitations, or contraindications for maximal exercise testing. Participants with an implanted pacemaker or automated defibrillator are excluded because of wearable sensor manufacturer recommendations. Smartphone ownership is not required; participants are lent a smartphone for the duration of the intervention period if required. Participants who cannot complete baseline primary outcome assessment are ineligible for randomization, and participants who experience exercise-induced medical complications may be ineligible, pending referral for medical assessment and approval.

Randomization

Upon completion of baseline data collection, participants are randomized at a 1:1 ratio to receive 24 weeks of usual care CR alone (control) or the 24-week SCRAM program (intervention). Treatment allocation follows a computer-generated schedule prepared by a biostatistician who is not involved in recruitment, treatment allocation, or outcome assessment; the randomization schedule is stratified by sex and trial center and uses random permuted blocks (n=2 and 4). A centralized Web-based randomization system (Research Electronic Data Capture [REDCap]; Vanderbilt University) ensures allocation concealment until the time of randomization. Access to the randomization schedule is restricted to the blinded trial biostatistician. The trial steering group is permitted access to summarized allocation progress data to monitor recruitment. Researchers undertaking data collection have no access to the randomization schedule other than to retrieve participants' concealed treatment allocation at baseline assessments.

Blinding

Primary outcome assessment will be blinded; participants are blinded at baseline (ie, prerandomization) but cannot be blinded thereafter because of the nature of the treatments. A trial investigator who is not involved with data collection may be unblinded to participants' treatment allocation if it is medically necessary. The biostatistician will remain blinded to treatment allocation throughout the analysis of trial outcomes.

Treatments

Usual Care Cardiac Rehabilitation

All participants retain access to standard outpatient CR (ie, usual care), regardless of treatment allocation. Usual care CR typically includes face-to-face delivery of support and education to adhere to medical treatment and health-promoting lifestyle behaviors, as well as supervised exercise training. Specific program components, content, frequency, and duration vary substantially across health care providers; however, the large majority of health care providers in Australia offer education and exercise components [28].

Usual care CR is not delivered as part of this trial; as per standard clinical practice, participants are required to self-initiate engagement by requesting referral from their local health care provider.

Varied usual care CR provision is expected because of the multisite trial design. Participants who receive acute treatment at the large recruiting hospitals but live in outlying regional and rural areas will receive usual care CR via smaller regional and rural health services. Given the number of CR programs across the collective trial catchment area, it is not possible to describe all candidate programs in detail, but stratification of the treatment allocation sequence by trial center will help to balance variation across treatment groups. Participants continue to take prescribed medications and medical treatments throughout the trial period.

Control

Participants randomized to the control arm are advised to seek referral to usual care CR—as described above—if they wish to participate. No additional support is provided (Figure 1).

Intervention

Participants randomized to the intervention arm receive the 24-week SCRAM intervention. SCRAM is a multicomponent dual-phase intervention that provides participants with a comprehensive, individualized, evidence-based program of exercise training and modular behavioral self-management support via a bespoke mHealth platform. An initial 12-week intensive phase supports the uptake of exercise and CHD self-management behaviors. A subsequent 12-week maintenance phase provides lower-intensity support to help participants transition toward autonomous, long-term adherence beyond the intervention period (Figure 1). The 24-week duration is considered appropriate to observe sustained behavior change [29].

The bespoke SCRAM mHealth platform builds on our previous research [15] and includes a wearable sensor (BioHarness 3,

Zephyr Performance Systems), a participant-facing app that is compatible with the Android mobile operating system (≥v5.0), and a CR professional-facing Web app that is compatible with mobile and desktop Web browsers (Figure 2). Participants access the smartphone app via a Google Play Store beta test program. Both apps have been redeveloped to ensure compatibility with recent updates to the Android mobile operating system, include improvements arising from our previous research [16], and integrate additional behavior support features.

Participants are familiarized with wearable sensor and smartphone app operation during bespoke intervention training immediately after randomization and receive an illustrated user guide. Participants also receive an induction phone call before their first scheduled exercise training session to build rapport with SCRAM exercise physiologists and reinforce operation of the technology platform. Additional technical support is provided as required throughout the trial via email and telephone.

As it is unethical to withhold evidence-based standard care, participants in the intervention arm can also self-initiate access to usual care CR, as described above. It is unclear how many participants will choose to access SCRAM and usual care CR; however, widespread low uptake of center-based CR suggests few will electively complete both programs. Self-reported usual care CR utilization will be assessed to explore the impact on trial outcomes.

Figure 2. *Smartphone Cardiac Rehabilitation, Assisted self-Management* mobile health platform components.

Intensive Phase (Weeks 1-12)

Exercise Training

During the initial intensive phase, real-time exercise monitoring and coaching are available during predefined operating hours (3 mornings, 06:00-10:00, plus 2 evenings 17:30-19:30 per week). At preferred times within these periods, participants self-fit the wearable sensor and activate the smartphone app to connect with remotely located exercise physiologists. Physiological (heart and respiratory rates, 1-lead electrocardiogram), geospatial (location, distance, speed—measured via Android location services), and self-reported symptom data (if any) are transmitted to a cloud server and visualized in the Web app for review by exercise physiologists, all in real time. Participants receive real-time individualized coaching, feedback, and support from exercise physiologists—based on exercise performance data—throughout exercise training via smartphone app text-to-voice audio notifications. Outside of predefined operating hours, participants use the smartphone app to self-monitor their exercise performance (in real time during exercise and retrospectively after exercise—using automated graphing elements); set exercise goals and review goal achievement feedback (via automated graphing elements); and receive evidence- and theory-based behavioral support via push notifications (see below).

During operating hours, exercise physiologists use the Web app to monitor participants' location, distance, speed, heart and respiratory rates, electrocardiogram, and self-reported cardiac symptoms (if any), as well as provide participants with regular real-time coaching instruction, feedback, and support during exercise. Coaching interactions are delivered to participants via a text-to-voice protocol. Exercise physiologists also

retrospectively review participants' exercise performance and goal achievement data via the Web app to inform individualized and progressive exercise prescription, and they may contact participants via telephone and email to discuss program progression if required. Collectively, these features enable optimal individualization and progression of participants' exercise prescription throughout the 12-week intensive phase.

Exercise physiologists received initial training to apply their expertise via the SCRAM platform, and they receive ad hoc support to maintain intervention fidelity and quality throughout the trial.

The SCRAM platform supports simultaneous monitoring of multiple participants, and the use of mobile and Web apps allows participants and exercise physiologists to operate in any environment with an active Wi-Fi or third/fourth generation cellular broadband connection; data use is typically less than 5 MB per participant, per hour of exercise training [15]. This level of oversight is similar to center-based programs and a significant improvement on existing home-based CR.

Following American College of Sports Medicine guidelines [30], exercise physiologists provide individualized exercise prescription based on participants' clinical status, exercise capacity, exercise-induced cardiac signs and symptoms (if any), age, sex, and personal preferences. Exercise frequency, duration, and intensity-level targets are delivered to participants via the smartphone app. Initial prescription targets 3 sessions per week of 30 to 40-min duration at 40% to 50% heart rate reserve (HRR). Exercise prescription parameters are progressively increased according to participants' exercise tolerance, signs and symptoms, and clinical status, targeting 3 to 5 weekly sessions of 60 min at 65% to 85% HRR by the end of the 12-week intensive phase. Prescribed exercise intensity levels are sufficient to induce physiological adaptation without inducing abnormal clinical signs or symptoms. All exercise training sessions include warm-up and cooldown periods to enable appropriate cardiovascular and musculoskeletal preparation and recovery. Walking is the preferred exercise mode, as it does not require specific equipment; however, participants can choose other land-based modes if preferred.

Self-Management Behavioral Strategies

Participants receive modular evidence- and theory-based smartphone push notifications that are designed to facilitate uptake and maintenance of chronic disease self-management behaviors. Behavioral content includes information (ie, education) and strategies (ie, behavior change techniques) to support heart health, physical activity and sedentary behavior, healthy eating and alcohol consumption, stress management, and—when indicated—smoking cessation (Table 1). Educational and behavioral content progresses over the intervention period to promote uptake, short-term adherence, relapse prevention/reuptake, and long-term self-determined maintenance. Participants are encouraged to activate all modules to facilitate multifactorial behavioral support, but they can activate/deactivate individual modules via the SCRAM app to meet their individual needs and preferences. Notification frequency depends on the number of active modules (Table 1). Activation (or reactivation) of modules after the start of the intervention period triggers a single-batch receipt of content that was scheduled for delivery before the (re)activation date. For example, if a module is activated 2 weeks after starting the intervention, all messages scheduled for receipt during the first 2 weeks are delivered in a single batch. Subsequent messages are received as per the normal delivery schedule. This approach maximizes behavioral support and preserves the progressive nature of education and behavior content over the intervention period, while also enabling participants to tailor the types of support they receive to meet their individual needs.

Table 1. Outline of self-management behavioral support modules.

Notification content		Weekly frequency (n)	
Module	Topics	Intensive phase	Maintenance phase
Heart health	Information about CHD[a] risk factors, medication beliefs, illness perceptions, and medical checkups; behavioral strategies to facilitate uptake and maintenance.	4	3
Physical activity and sedentary behavior	Information about the physical activity, sedentary behavior; activity suggestions; behavioral strategies to facilitate uptake and maintenance.	2	1
Healthy eating	Dietary recommendations for vegetables, fruit, wholegrains, legumes, fat, salt, and alcohol; emphases on variety, recipes, meal planning and preparation methods, cooking techniques, and mindfulness; behavioral strategies to facilitate uptake and maintenance.	2	1
Stress management	Information about emotional strain and negative affect, as well as strategies to facilitate uptake and maintenance of stress management behaviors.	2	1
Smoking cessation (if indicated)	Information about the impact of tobacco smoking on health and sources of smoking cessation support, as well as strategies to facilitate the reduction and cessation of tobacco smoking.	2	1

[a]CHD: coronary heart disease.

Maintenance Phase (Weeks 13-24)

Exercise Training

Participants continue to receive individualized and progressive exercise prescription during the maintenance phase; however, the format of supervision and coaching changes. Participants quantify their exercise performance using the SCRAM smartphone app and wearable sensor as per the intensive phase, but they no longer receive real-time supervision or coaching throughout training sessions. Instead, exercise physiologists provide individualized coaching feedback and update exercise prescription parameters during weekly telephone calls, based on assessment of participants' exercise performance and goal achievement using retrospective review features of the Web app. Nonadherence (ie, absence of recorded data) initiates prompts from exercise physiologists to promote reengagement.

As per the intensive phase, participants use the smartphone app to self-monitor exercise performance (in real time during exercise and retrospectively afterward using automated graphing elements); set exercise goals and review goal achievement feedback (using automated graphing elements); and receive evidence- and theory-based behavioral support push notifications.

Self-Management Behavioral Support

Self-management behavioral support—as described above—is delivered at a reduced frequency during the maintenance phase; notification frequency depends on the number of active modules (Table 1). Content emphasizes behavioral strategies that promote long-term adherence, including autonomy, self-directed motivation, and relapse prevention.

Theoretical Framework

Features and content of the SCRAM intervention are informed by Social Cognitive Theory, Self-Determination Theory, the Common Sense Model, and the Taxonomy of Behavior Change Techniques [31-34]. Theory-based platform components are designed to enhance task and barrier self-efficacy; perceptions of competence, autonomy, and relatedness; and perceptions of control over health and well-being, as these constructs influence the uptake and adherence of self-management behaviors [35-38].

Real-time biofeedback and exercise coaching during the intensive phase have been designed to support task self-efficacy and perceived competence by providing information about participants' exercise performance and progress toward prescribed exercise targets (ie, reinforcing mastery experiences via verbal persuasion). Delivery of exercise coaching by real accredited exercise physiologists—rather than automated processes—was chosen to enhance participants' perceived relatedness by providing a sense of connection and social support.

The remote intervention delivery model has been designed to support participants' perceived autonomy by enabling them to choose preferred aerobic exercise modes, exercise locations/routes, and exercise times (within predefined operating hours during the intensive phase). Enabling participants to develop exercise task and barrier self-efficacy in their own environment may also support long-term behavior change by overcoming barriers associated with transitioning away from the specialized facilities and equipment provided in center-based settings.

The smartphone app dashboard has been designed to support perceived competence and task self-efficacy by enabling participants to set individualized exercise goals, view automated goal achievement feedback, and self-monitor their exercise performance and progression throughout the intervention. Self-monitoring features provide access to brief summary data, as well as full-resolution data, to cater to varying participant engagement and preferences.

Behavioral support content builds on our previous CR SMS interventions that have been shown to improve self-management behaviors [10,39,40]; the larger character allowance of push notifications has been used to integrate more natural language than is typically possible with a 160-character SMS.

Table 2 summarizes the integration of 24 separate behavior change techniques into the exercise training and behavior change support components of the SCRAM intervention. Two techniques are implicit in the dual-phase design (7.3 Reduce prompts/cues) and inclusion of accredited exercise physiologists for exercise program delivery, as well as behavioral scientists for push notification content creation (9.1 Credible source). The remaining 22 techniques are collectively used 622 times across all push notification modules. Instances of behavior change techniques cannot be prospectively quantified for the exercise monitoring/coaching and goal setting/self-monitoring intervention components, as they are dependent on exercise physiologist interactions and participants' app usage, respectively.

Table 2. Integration of behavior change techniques into *Smartphone Cardiac Rehabilitation, Assisted self-Management* exercise training and behavioral support intervention components.

Behavior change technique	Exercise training		Push notification modules (n)					
	Monitoring+coaching	Goals+self-monitoring	Heart health	Physical activity	Healthy eating	Stress management	Smoking cessation	Total
1.1 Goal setting (behavior)	Yes	Yes	22	9	12	10	6	59
1.2 Problem solving	N/A[a]	N/A	17	18	6	3	10	54
1.4 Action planning	N/A	N/A	31	12	17	15	15	90
1.5 Review behavior goal(s)	Yes	Yes	6	4	0	N/A	4	14
1.6 Discrepancy between current behavior and goal	Yes	Yes	10	5	2	N/A	N/A	17
2.3 Self-monitoring of behavior	Yes	Yes	42	19	24	20	15	120
3.1 Social support (unspecified)	Yes	N/A	7	0	1	2	0	10
3.3 Social support (emotional)	Yes	N/A	15	9	1	9	8	42
4.1 Instruction on how to perform behavior	Yes	N/A	17	16	14	12	3	62
5.1 Information about health consequences	N/A	N/A	9	4	12	9	10	44
7.1 Prompts/cues	N/A	N/A	3	0	0	0	2	5
7.3 Reduce prompts/cues	Yes[c]	N/A	Yes[b]	Yes[b]	Yes[b]	Yes[b]	Yes[b]	Yes[b]
8.2 Behavior substitution	N/A	N/A	2	2	8	0	0	12
8.3 Habit formation	N/A	N/A	3	2	0	0	0	5
8.4 Habit reversal	N/A	N/A	0	1	0	0	1	2
8.7 Graded tasks	Yes	N/A	5	4	3	0	3	15
9.1 Credible source	Yes[c]	N/A	Yes[c]	Yes[c]	Yes[c]	Yes[c]	Yes[c]	Yes[c]
10.4 Social reward	Yes	N/A	16	13	5	2	5	41
10.9 Self-reward	N/A	N/A	2	0	0	0	0	2
11.1 Pharmacological support	N/A	N/A	1	0	0	0	3	4
12.1 Restructuring the physical environment	N/A	N/A	2	0	0	0	1	3
12.3 Avoidance/reducing exposure to cues for the behavior	N/A	N/A	0	0	0	0	3	3
15.1 Verbal persuasion about capability	Yes	N/A	5	1	1	2	3	12
15.3 Focus on past success	Yes	Yes	11	0	1	2	0	14
Number of discrete behavior change technique within intervention components	11	5	20	15	14	11	16	24
Total instances of behavior change technique use within intervention components	__[d]	__[d]	226	119	107	86	92	630

[a]Not applicable.

[b]Implicit in the dual-phase intervention design.

[c]Implicit in inclusion of accredited exercise physiologists and behavioral scientists in intervention design and delivery.

[d]Instances of behavior change technique use cannot be prospectively quantified for these features.

Outcomes

Outcome measures and the assessment schedule are summarized in Table 3.

Baseline and 24-week assessments are conducted at trial centers; 12-week assessments are conducted via telephone and internet survey. Furthermore, 12- and 24-week assessments are permitted ±2 weeks of the scheduled date to meet participant scheduling commitments. Participants who do not attend assessments are rescheduled for a second appointment; those who do not complete the 12-week assessment but do not withdraw their participation are contacted to complete the 24-week assessment. If participants cannot attend the 24-week assessment in person, self-report data may be collected via telephone and internet survey to minimize missing data.

Demographic and eHealth literacy data are collected at baseline to describe sample characteristics. Clinical data (diagnosis and treatment, hospitalization, and medication) are obtained with consent from hospital records, where possible. Self-reported adverse events are recorded and/or updated throughout the participation period as required.

Table 3. Schedule of enrollment, treatments, and assessments.

Activity	Description	Weeks −4 to 0	Week 0	Week 12	Week 24
Enrollment	Contact details, eligibility criteria, verbal consent for trial referral	Yes	N/A[a]	N/A	N/A
Consent	Trial procedures, health care/medication utilization data release	N/A	Yes	N/A	N/A
Allocation	Concealed centralized computer-based randomization	N/A	Yes	N/A	N/A
Treatments					
Control	Usual cardiac rehabilitation care alone	N/A	Start	Ongoing	Finish
Intervention	*Smartphone Cardiac Rehabilitation, Assisted self-Management*	N/A	Start intensive phase	Start maintenance phase	Finish
Characteristics					
Sociodemographic	Age, sex, ethnicity, income, education, and occupation	N/A	Yes	N/A	N/A
Clinical	Diagnostic, smoking and alcohol history, and medication	N/A	Yes	N/A	N/A
Electronic health literacy	Electronic Health Literacy Questionnaire [41]	N/A	Yes	N/A	N/A
Primary outcome					
VO_2max[b]	Maximal treadmill cardiopulmonary exercise test	N/A	Yes	N/A	Yes
Secondary outcomes					
Anthropometry	Body mass, body mass index, and waist and hip circumferences	N/A	Yes	N/A	Yes
Blood lipid concentrations[c,d]	Total/high-density lipoprotein/low-density lipoprotein cholesterol, and triglyceride	N/A	Yes	N/A	Yes
Blood glucose concentration[c,d]	≥3 hours fasted	N/A	Yes	N/A	Yes
Blood pressure[c,d,e]	Automated sphygmomanometer	N/A	Yes	N/A	Yes
Physical activity	Godin Leisure Time Physical Activity Questionnaire, % reporting leisure score index ≥ 14 units [42]	N/A	Yes	Yes	Yes
Dietary intake	Automated self-administered 24-hour dietary assessment tool-Australia, dietary guideline index, and vegetable and discretionary food consumption [43-46]	N/A	Yes	Yes	Yes
Alcohol consumption	3-item Alcohol Use Disorders Identification Test-C Questionnaire, % reporting ≤2 drinks/day [47]	N/A	Yes	Yes	Yes
Medication adherence	4-item Medication Adherence Scale, % adherent (score=4) [48]	N/A	Yes	Yes	Yes
Health-related quality of life	Assessment of Quality of Life 8-dimension, multiattribute utility score [49]	N/A	Yes	Yes	Yes
Adverse events[f]	Self-reported changes to health status	N/A	Yes	Yes	Yes
Economic evaluation	Delivery, health care/medication use, and participant costs	N/A	N/A	N/A	Yes
Process evaluation	Semistructured interviews; utilization data	N/A	N/A	N/A	Yes

[a]Not applicable.

[b]VO_2max: maximal aerobic exercise capacity.

[c]Measured after ≥3 hour fast.

[d]Measured before cardiopulmonary exercise test.

[e]Measured after ≥10 min of seated rest.

[f]Documented as required throughout the participation period.

Primary Outcome

The primary outcome is maximal oxygen uptake (VO_2max, $mL \cdot kg^{-1} \cdot min^{-1}$) measured at 24 weeks. VO_2max is the criterion measure of maximal cardiorespiratory fitness [30], and an important clinical surrogate outcome as a 1 $mL \cdot kg^{-1} \cdot min^{-1}$ improvement has been associated with a 10% reduction in cardiovascular mortality among both men and women [50,51].

After a 5-min warm-up, an individualized treadmill cardiopulmonary exercise test is initiated at a self-selected velocity and 0% gradient. Thereafter, gradient is increased by 1% every 60 seconds until volitional exhaustion or indications for test termination [30]. A 5-min cooldown is completed at or below the self-selected velocity and 0% gradient. Cardiorespiratory responses are measured using a calibrated online metabolic cart; VO_2max is defined as the mean value across 15 consecutive breaths before fatigue or symptom-limited test termination. Modification of treadmill velocity is permitted during the protocol if physiological responses indicate the self-selected velocity is insufficient to achieve an 8 to 12-min target test duration.

The individualized protocol is replicated at 24-week follow-up assessment; further modification of treadmill velocity is permitted after surpassing the baseline test duration, if required, to achieve a maximal performance.

Test procedures follow clinical guidelines, including continuous monitoring of 12-lead electrocardiogram, frequent assessment of blood pressure and patient-reported cardiovascular signs and symptoms, and medical support to administer treatment in the event of exercise-induced complications [30].

Secondary Outcomes

Secondary outcomes are outlined in Table 3. Resting systolic and diastolic blood pressure are measured after ≥10-min seated rest, in duplicate, to the nearest 1 mmHg, using a calibrated automated sphygmomanometer. A third measure is taken if duplicates differ by >10 mmHg; outcomes are recorded as the mean of the closest 2 measures.

Anthropometry outcomes are measured in duplicate with calibrated tools. Stature and body mass are measured to the nearest 0.1 cm and 0.1 kg, respectively. Third measures are taken if duplicates differ by >0.5 cm or >0.2 kg, respectively. Waist and hip circumferences are measured in duplicate to the nearest 0.1 cm at the levels of the umbilicus and the furthest posterior protrusion of the buttocks, respectively. Third measurements are taken if duplicates differ by >0.5 cm; all anthropometric outcomes are recorded as the mean of the closest 2 measures. Body mass index is calculated as weight (kg)/height $(m)^2$. Waist-hip ratio is calculated as waist circumference (cm)/hip circumference (cm).

Blood lipid and glucose concentrations are measured via peripheral capillary blood samples using a calibrated point-of-care analyzer (Cholestech LDX, Abbott). Participants are asked to fast (no food or nonwater beverages) for at least 3 hours before the appointments and blood samples are drawn before the cardiopulmonary exercise test.

Self-management behaviors are measured using validated self-report instruments (Table 3), including physical activity (Godin Leisure-time Physical Activity Questionnaire) [42], dietary intake (automated self-administered 24-hour dietary assessment tool [ASA24]-Australia) [43-46], alcohol consumption (Alcohol Use Disorders Identification Test-C) [47], medication adherence (Medication Adherence Scale) [48], and health-related quality of life (Assessment of Quality of Life 8-dimension) [49]. The ASA24-Australia is a Web-based diet recall tool. Participants complete a Web-based recall for 1 calendar weekday within 3 days of assessment appointments; those who require help complete the recall with a researcher at assessment appointments or via telephone. Recalls are audited to identify possible misreporting and participants are asked to complete a new recall if misreporting is confirmed.

Economic Evaluation

Detailed methods for the economic evaluation will be described separately but, briefly, the evaluation will adopt a health care system and a limited societal perspective incorporating all health care costs subsidized by state and Commonwealth governments in Australia. Types and costs of inpatient and outpatient health care as well as dispensed medications will be estimated from self-reported adverse events, the Australian Government Medicare Benefits Schedule, and the Australian Government Pharmaceutical Benefits Schedule, respectively. Productivity loss will be measured by self-reported work absenteeism.

A preference index for the calculation of quality-adjusted life years (QALYs) will be derived from the 8-dimension Assessment of Quality of Life to assess cost per QALY for comparison with other programs. Incremental costs per unit increase in the primary (VO_2max) and secondary outcomes will also be calculated. Extensive probabilistic uncertainty analysis will be undertaken in addition to the base case analysis.

Process Evaluation

Semistructured exit interviews are conducted to understand usability, acceptability, engagement, and satisfaction with the SCRAM and usual care CR treatments, respectively. SCRAM treatment fidelity is assessed via exercise session completion (determined from recorded exercise training data), self-reported compliance with behavioral notifications, and SCRAM platform usage metrics. Usual care treatment fidelity is assessed via self-reported uptake of standard CR services. Process data will be summarized using descriptive statistics (quantitative questions and analytics) and general inductive thematic analyses (open-ended questions). Interview data will be transcribed verbatim and analyzed using a general inductive thematic approach [52].

Data Collection and Analysis

Data Collection and Management

Primary outcome assessors have previous experience with cardiopulmonary exercise testing, and all outcome assessors completed standardized training for required data collection protocols/methods to ensure consistency across all 3 trial centers.

Trial data are collected and managed using REDCap tools hosted at Deakin University [53,54]. REDCap is a secure, Web-based

software platform designed to support data capture for research studies. Trial data are recorded directly into REDCap case record forms or, if required, on hard copy case record forms and transcribed into REDCap as soon as possible. Data entry is conducted by outcome assessors to maintain blinding. Validation rules (eg, range and completion checks) are prespecified in REDCap to identify inaccuracies and missing data; outcome assessors respond to queries as required. Hard copy corrections (if required) are initialed and dated by outcome assessors and transcribed into REDCap as soon as possible; REDCap data logging maintains an auditable record of all electronic data entries and corrections.

Electronic data are stored on a secure password-protected server; hard copy data are stored in secure filing cabinets at trial centers until they can be transferred to the coordinating trial center. Access to trial data is restricted to members of the research team. A data manager and individuals approved by the trial steering group retain access to data from all trial centers; however, outcome assessors can only access data for their individual trial center. Unique reidentifiable codes are used to anonymize trial data. Access to identifiable data is permitted for the purposes of contacting participants, verifying data entry, analysis, auditing, or other purposes approved by the Steering Group. There are no significant or uncertain risks of harm associated with the SCRAM intervention or usual care CR, and no interim analyses are planned. Accordingly, no data safety monitoring board has been established [55].

Statistical Analysis

Baseline characteristics will be summarized descriptively for the full sample and by treatment group. A linear regression model—adjusted for baseline values and stratification variables—will be fitted to assess the primary outcome. Primary analyses will be performed on the principle of intention to treat. Assuming there is a reasonable amount (>5%) of missing data, primary analyses will be conducted using multiple imputation, imputing all outcomes using a single (joint) imputation model. Imputation models will include participant age, sex, type of diagnosis (eg, angina, myocardial infarction, and coronary revascularization), in addition to any other covariates that appear to predict missingness. A per-protocol analysis will be conducted with complete cases to test the robustness of treatment effects under different assumptions. Preplanned subgroup analyses will be conducted to determine treatment effects by levels of treatment adherence, sex, and trial center (Figure 1). Secondary analyses will adjust the regression model for baseline prognostic factors, including age, sex, and employment status.

A similar approach will be used to assess continuous secondary outcomes (Table 3); logistic regression will be used for binary outcomes. Model-adjusted estimates and group differences will be reported with 95% CIs and probability values. All statistical tests will be 2-sided at α=.05. The biostatistician will remain blinded throughout the analysis of treatment effects. A detailed statistical analysis plan will be developed before the completion of data collection to guide analyses.

Sample Size

Our previous noninferiority trial [10] indicates that 174 participants are required to detect a clinically meaningful between-group difference of 2.0 $mL \cdot kg^{-1} \cdot min^{-1}$ in VO_2max (SD 6.75 $mL \cdot kg^{-1} \cdot min^{-1}$, r=0.80 between repeated measures, β=.9, and 2-sided α=.05). Allowing for 20% loss to follow-up (17% in our previous trial), a total of 220 participants are required to ensure equal numbers per treatment arm (ie, 110 per arm). Minimum detectable between-group differences in secondary outcomes at 24-week follow-up are summarized in Table 4.

Table 4. Minimum detectable differences in secondary outcomes (assuming a total sample size of 220 participants [110 per treatment arm] and beta=.8).

Secondary outcome	Group difference	Data source
Total cholesterol concentration	0.24 $mmol \cdot L^{-1}$	Maddison et al [10]
Low-density lipoprotein cholesterol concentration	0.16 $mmol \cdot L^{-1}$	Maddison et al [10]
High-density lipoprotein cholesterol concentration	0.10 $mmol \cdot L^{-1}$	Maddison et al [10]
Triglyceride concentration	0.29 $mmol \cdot L^{-1}$	Maddison et al [10]
Glucose concentration	0.60 $mmol \cdot L^{-1}$	Maddison et al [10]
Physical activity leisure score index	17%	Dale et al [40]
Health-related quality of life	0.06 units	Richardson et al [56]
Medication adherence	19%	Thornley et al [57]
Systolic blood pressure	4.70 mmHg	Maddison et al [10]
Diastolic blood pressure	2.76 mmHg	Maddison et al [10]
Body mass	3.80 kg	Maddison et al [10]
Body mass Index	0.90 kg/m^2	Maddison et al [10]
Waist circumference	2.60 cm	Maddison et al [10]
Hip circumference	1.80 cm	Maddison et al [10]
Alcohol consumption	21%	Dale et al [40]
Dietary guideline index	3.70 units	Livingstone and Mc-Naughton [45]

Protocol Amendments

The medication adherence self-report instrument was changed to the 4-item Morisky, Green, and Levine Medication Adherence Scale [48]—before prospective clinical trial registration—to comply with trademark restrictions on the 8-item Morisky Medication Adherence Scale.

Amendments will be formally documented in the version-controlled trial protocol. Changes will be disseminated to the approving ethics committees and participants as required, and the trial registration will be updated as required.

Availability of Data

Following trial completion and publication, requests for deidentified individual participant data or trial documents will be considered where the proposed use complies with trial ethical approval, does not conflict with planned use by the trial steering committee or other external data requests, and aligns with public good purposes, as well as where the requestor is willing to sign a data access agreement.

Dissemination

The trial will be disseminated via scientific conferences, peer-reviewed scientific journals, and other channels approved by the steering group. No identifiable data will be included in any outputs. Authorship for trial publications will be determined in accordance with International Committee of Medical Journal Editors authorship recommendations [58].

Trial Status

This manuscript describes version 2 (11/30/2018) of the full trial protocol. Recruitment began on November 12, 2018, and is anticipated to be completed by March 31, 2020.

Ethics Approval and Consent to Participate

The trial protocol has been approved under Australia's National Mutual Acceptance agreement by the Melbourne Health Human Research Ethics Committee (HREC/18/MH/119). Ethical approval has been ratified by the Deakin University Human Research Ethics Committee (2018-251). All participants provide written informed consent before undertaking baseline assessments. Separate consent is sought to extract health care and medication utilization data for the purpose of this trial and for participation in substudies, as required.

Results

The trial was funded in November 2017 and received ethical approval in June 2018, and recruitment began in November 2018. As of September 2019, 54 participants have been randomized into the trial.

Discussion

CR delivery has remained largely unchanged for several decades, and despite proven effectiveness [12,59], persistent low participation rates mean its potential to improve individual, clinical, and economic outcomes has not been fully realized. Accessibility barriers are important limitations of current CR delivery, and overcoming those challenges is a priority as people

with lower access to center-based CR have more adverse risk factor profiles [60].

This trial is among the first to evaluate an evidence- and theory-based multiphase mHealth CR intervention that can deliver real-time exercise supervision plus modular self-management support to participants in almost any geographic location. SCRAM combines key elements of our previous research into a single mHealth platform to address key accessibility barriers while preserving individualized oversight from CR professionals. As mobile broadband services cover 95% of the Australian population, the near-universal accessibility of the SCRAM program may (1) help to reduce geographic and socioeconomic inequalities in CR utilization, particularly in regional and rural areas where accessibility barriers are exacerbated [17], and (2) facilitate large-scale implementation in clinical practice.

Trial outcomes are associated with cardiac and all-cause mortality, and the inclusion of a geographically diverse cohort (metropolitan-, regional-, and rural-dwelling participants) will help to understand the role of mHealth CR across multiple health care settings with differing needs.

Our trial will also provide unique and valuable information about costs and cost-effectiveness, which are critical to inform health care providers about the potential for SCRAM to be implemented at scale in clinical practice—as a complement to existing CR services. Finally, direct involvement of clinicians and CR professionals in this research improves the prospect for timely translation of findings into clinical practice if the intervention is proven to be effective and cost-effective.

Acknowledgments

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Authors' Contributions

RM and JCR conceived of the trial. KB, BO, CKC, and SAM contributed to the design. KEL provided statistical expertise and will conduct the primary analysis. LG and MM provided health economics expertise and will conduct the economic analysis. CN, JA, and VN provided clinical expertise and oversee the respective trial centers. SC developed the SCRAM smartphone and Web apps. JCR drafted the manuscript. All authors critically revised and approved the final version.

Conflicts of Interest

The SCRAM platform and intervention content build on work initiated at the University of Auckland's National Institute for Health Innovation. The software and intervention content were developed by Deakin University's Institute for Physical Activity and Nutrition—led by RM, JCR, and SC—in conjunction with cardiac rehabilitation specialists and exercise scientists. We declare no further financial or competing interests.

Multimedia Appendix 1
Standard Protocol Items: Recommendations for Interventional Trials Checklist (2013).
[DOCX File , 23 KB - resprot_v9i1e15022_app1.docx]

Multimedia Appendix 2
Template for Intervention Description and Replication Checklist.
[DOCX File , 17 KB - resprot_v9i1e15022_app2.docx]

Multimedia Appendix 3
Consolidated Standards of Reporting Trials Checklist–electronic health extension.
[DOCX File , 25 KB - resprot_v9i1e15022_app3.docx]

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Abbreviations

ASA24: automated self-administered 24-hour dietary assessment tool
CHD: coronary heart disease
CONSORT: Consolidated Standards of Reporting Trials
CR: cardiac rehabilitation
eHealth: electronic health
HRR: heart rate reserve
mHealth: mobile health
QALY: quality-adjusted life year
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

REMOTE-CR: Remote Exercise MOnitoring Trial for Exercise-based Cardiac Rehabilitation
SCRAM: *Smartphone Cardiac Rehabilitation, Assisted self-Management*

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Protocol

Movement-Evoked Pain Versus Pain at Rest in Postsurgical Clinical Trials and Meta-Analyses: Protocol for a Follow-Up Systematic Review

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Abstract

Background: Postoperative pain is one of the most prevalent and disabling complications of surgery that is associated with personal suffering, delayed functional recovery, prolonged hospital stay, perioperative complications, and chronic postsurgical pain. Accumulating evidence has pointed to the important distinction between pain at rest (PAR) and movement-evoked pain (MEP) after surgery. In most studies including both measures, MEP has been shown to be substantially more severe than PAR. Furthermore, as MEP is commonly experienced during normal activities (eg, breathing, coughing, and walking), it has a greater adverse functional impact than PAR. In a previous systematic review conducted in 2011, only 39% of reviewed trials included MEP as a trial outcome and 52% failed to identify the pain outcome as either PAR or MEP. Given the recent observations of postsurgical pain trials that continue to neglect the distinction between PAR and MEP, this updated review seeks to evaluate the degree of progress in this area.

Objective: This updated review will include postsurgical clinical trials and meta-analyses in which the primary outcome was early postoperative pain intensity. The primary outcome for this review is the reporting of MEP (vs PAR) as an outcome measure for each trial and meta-analysis. Secondary outcomes include whether trials and meta-analyses distinguished between PAR and MEP.

Methods: To be consistent with the 2011 review that we are updating, this review will again focus on randomized controlled trials and meta-analyses, from Medical Literature Analysis and Retrieval System Online and EMBASE databases, focusing on pain treatment after thoracotomy, knee arthroplasty, and hysterectomy in humans. Trials and meta-analyses will be characterized as to whether or not they assessed PAR and MEP; whether their pain outcome acknowledged the distinction between PAR and MEP; and, for trials assessing MEP, which pain-evoking maneuver(s) were used.

Results: Scoping review and pilot data extraction are under way, and the results are expected by March 2020.

Conclusions: It is our belief that every postsurgical analgesic trial should include MEP as an outcome measure. The previous 2011 review was expected to have an impact on more widespread assessment of MEP in subsequent postoperative pain treatment trials. Thus, the purpose of this follow-up review is to reevaluate the frequency of use of MEP as a trial outcome, compared with PAR, in more recently published postoperative pain trials.

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International Registered Report Identifier (IRRID): DERR1-10.2196/15309

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KEYWORDS

postoperative pain; clinical trials; evoked pain; spontaneous pain; pain measurement

Introduction

Background

Postoperative pain is one of the most prevalent and disabling complications of surgery that is associated with personal suffering, delayed functional recovery, prolonged hospital stay, perioperative complications, and chronic postsurgical pain [1]. Previous studies have distinguished between pain at rest (PAR) and movement-evoked pain (MEP) after surgery [2,3].

In most studies including both measures, MEP has been shown to be substantially more severe in intensity than PAR [4]. Furthermore, as MEP is commonly experienced during normal activities (eg, breathing, coughing, and walking), it has a greater adverse functional impact than PAR [5,6].

In 2011, a previous systematic review by Srikandarajah and Gilron showed that only 39% of reviewed trials included MEP as a trial outcome and 52% failed to identify the pain outcome as either PAR or MEP [4]. Consequently, an accompanying editorial by Kehlet and Dahl [7] confirmed that there has been no progress in the quality of assessment despite the need to include movement-associated pain in perioperative analgesic trials being emphasized almost 20 years previously [2]. Given the recent observations of postsurgical pain trials that continue to neglect the distinction between PAR and MEP, this updated review seeks to evaluate the degree of progress in this area. This previous systematic review focused on 3 surgical procedures—thoracotomy, knee arthroplasty, and hysterectomy—because postoperative analgesic clinical trials involving these procedures are relatively abundant in the literature and also because MEP is thought to be clinically relevant after these surgeries. To provide an appropriate estimate of change of the frequency of assessment of PAR versus MEP in postoperative analgesic trials, we chose to focus on these same 3 procedures in this review update.

Objectives and Goal of This Study

The goals of this review are to evaluate postsurgical pain treatment trials for their ability to assess the frequency of use of PAR versus MEP as a trial outcome, the distinction between the 2, and what methods are used to assess MEP.

Main data to be extracted will be designation of MEP as the trial primary outcome, designation of PAR as the trial primary outcome, distinction between MEP and PAR in assessing pain, and method of evoking pain for the assessment of MEP.

Methods

To be consistent with the 2011 review that we are updating, this review will, as much as possible, use the same methodology as used previously [4].

Information Sources and Search Strategy

Clinical Trials

Analgesic clinical trials of pain after thoracotomy, knee arthroplasty, or hysterectomy will be searched on Medical Literature Analysis and Retrieval System Online and EMBASE databases (January 2014 to December 2019) as per a predefined search strategy (Multimedia Appendices 1-3). We chose a start date of 2014 so as to allow some time for the 2011 review to have been reflected in subsequent analgesic trials. Results, limited to randomized controlled treatment interventions involving humans, will be reviewed for inclusion. The search results from the 2 databases will then be combined for each surgical procedure, and any duplicates will be eliminated. For identified trials, articles will be eliminated if they are not randomized controlled trials (RCTs), involve a mix of surgeries, do not deal with results following surgery, did not measure pain scores, measured pain only after 1 week postoperatively, were not available in English, or could not be obtained. As the focus of this review is on pain outcome measurement only, the reviewed trials will not be evaluated with respect to trial quality or risk of bias.

Meta-Analyses

To search for meta-analyses specific to thoracotomy, knee arthroplasty, and hysterectomy, search strategies similar to those described in Multimedia Appendix 1 will be used, with the insertion of the term “meta-analysis” in place of the clinical trial search terms.

Data Extraction and Analysis

The included trials will be characterized according to whether they measured MEP or not, whether they measured PAR or not, and whether the pain outcome(s) used in the trial acknowledged the distinction between MEP and PAR. We will also record, for each trial, which pain-evoking maneuver(s) were used (eg, coughing, walking, and joint flexion or extension) to facilitate the measurement of MEP. The included meta-analyses will be characterized according to whether they distinguished between PAR and MEP, whether they declared trials that failed to distinguish between PAR and MEP, and how they addressed the distinction (or lack thereof) between PAR and MEP across reviewed trials. Descriptive statistics will be used to synthesize extracted data. As the results from this review are not expected to be appropriate for statistical analysis, simple comparisons of the results of this review (ie, frequency of MEP measurement) with the results of the 2011 review will be made. For RCTs that measured MEP, the condition or maneuver associated with MEP assessment (eg, participant questioning about pain upon movement vs assessment of pain evoked by an investigator-witnessed standardized maneuver such as cough, force expiration, sitting from supine position, standing from seated position, and standardized walk test) will be tabulated across trials.

Results

This review has been registered in the International Prospective Register of Systematic Reviews registry, CRD42019125855 [8]. Literature review and pilot data extraction are under way, and the results are expected by March 2020.

Discussion

Overview

Postoperative pain is one of the most prevalent and disabling complications of surgery. It can contribute to personal suffering, delayed functional recovery, prolonged hospital stay, and chronic postsurgical pain [1]. Over 50% of patients report moderate to severe pain in the early postoperative period, eg, postoperative day 0-3, and MEP is at least 200% more intense than PAR during this period [4]. Thus, it is critical to distinguish between MEP and PAR as the intensity of MEP is usually greater than that of PAR.

Mechanisms underlying MEP might be different from those underlying PAR [9,10]. In addition, MEP may respond differently to analgesic treatments than PAR [3]. Avoiding movement and activity by patients to minimize pain evoked by movement means that MEP can contribute to postoperative functional impairment [2].

Studies have shown [4] that MEP can be 95% to 226% more intense than PAR. As MEP is commonly experienced during normal activities (eg, breathing, coughing, and walking), it has a greater adverse impact on function and postoperative recovery than PAR. MEP affects the ability to relieve postoperative atelectasis, affects ambulation to improve blood flow, and reduces the risk of thromboembolism and other normal physical functions to promote musculoskeletal recovery, eg, after arthroplasty.

As stated previously, a previous systematic review by Srikandarajah and Gilron [4] showed that only 39% of reviewed trials included MEP as a trial outcome and 52% failed to identify the pain outcome as either PAR or MEP. In addition, 38% of reviewed trials did not specify the physical maneuver used to assess MEP, and 61% of trials did not capture the most severe pain condition. Furthermore, 5 out of the 7 (71%) meta-analyses did not distinguish between PAR and MEP.

Conclusions

These gaps in methodology have implications with regard to trial precision, assessment, and treatment of pain during various activities. Different analgesics may have differential effects on PAR and during mobilization. It is important to distinguish between MEP and PAR and their response to novel treatment modalities when establishing a postsurgical analgesic trial. The assessment of pain should involve a standardized maneuver after a period of rest, ie, sitting from supine position. The maneuver for assessing MEP should be clinically relevant, ie, joint range of motion after arthroplasty.

It is our belief that every postsurgical analgesic trial should include MEP as an outcome measure. The previous 2011 review was expected to have an impact on the use of MEP as an important outcome measure in subsequent postoperative pain treatment trials. Thus, the purpose of this follow-up review is to evaluate the frequency of use of MEP as a trial outcome, compared with PAR, in more recently published postoperative pain trials.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Thoracotomy search strategy.
[DOCX File , 12 KB - resprot_v9i1e15309_app1.docx]

Multimedia Appendix 2
Arthroplasty search strategy.
[DOCX File , 12 KB - resprot_v9i1e15309_app2.docx]

Multimedia Appendix 3
Hysterectomy search strategy.
[DOCX File , 12 KB - resprot_v9i1e15309_app3.docx]

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Abbreviations

MEP: movement-evoked pain
PAR: pain at rest
RCT: randomized controlled trial

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Protocol

Mobile Apps for Health Behavior Change: Protocol for a Systematic Review

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Abstract

Background: The popularity and ubiquity of mobile apps have rapidly expanded in the past decade. With a growing focus on patient interaction with health management, mobile apps are increasingly used to monitor health and deliver behavioral interventions. The considerable variation in these mobile health apps, from their target patient group to their health behavior, and their behavioral change strategy, has resulted in a large but incohesive body of literature.

Objective: The purpose of this protocol is to provide an overview of the current landscape, theories behind, and effectiveness of mobile apps for health behavior change.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols will be used to structure this protocol. The focus of the systematic review is guided by a population, intervention, comparator, and outcome framework. A systematic search of Medline, EMBASE, CINAHL, and Web of Science will be conducted. Two authors will independently screen the titles and abstracts of identified references and select studies according to the eligibility criteria. Any discrepancies will then be discussed and resolved. One reviewer will extract data into a standardized form, which will be validated by a second reviewer. Risk of bias was assessed using the Cochrane Collaboration Risk of Bias tool, and a descriptive analysis will summarize the effectiveness of all the apps.

Results: As of November 2019, the systematic review has been completed and is in peer review for publication.

Conclusions: This systematic review will summarize the current mobile app technologies and their effectiveness, usability, and coherence with behavior change theory. It will identify areas of improvement (where there is no evidence of efficacy) and help inform the development of more useful and engaging mobile health apps.

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KEYWORDS

telemedicine; mobile health; mobile apps; cell phone; health behavior; intervention

Introduction

Health care is becoming increasingly more digital. Digital interventions to engage patients with their health management have become popular, particularly since the first smartphone (iPhone) was released in 2008. Patient engagement has become a focus of health care research and has a significant role in preventative health care [1,2]. Recently, there has been much research about the use of digital technologies to enhance specific

health behaviors [3,4]. Positive health behaviors include a wide variety of actions aimed at preventing problems and maintaining and improving patients' health [5]. This covers a range of lifestyle choices and health condition management: primarily drug and alcohol use, diet, and physical activity, although other behaviors such as sun protection, sex safety, medication adherence, doctor's appointments, vaccinations, self-management of chronic conditions, and mental health can also be included [6,7].

Thousands of different internet- and mobile-based interventions, including apps, texting, emails, social media platforms, voice agents, and customized interactive chatbots, have been developed to help patients improve their health behaviors [8-11]. Given the widespread ownership, frequent use, and computing power of smartphones and a large number of currently available mobile health apps [12], they are a particularly promising platform for targeted interventions. Smartphones can be used to collect data, including tracking physical activity, mental health, sleep patterns, and basic physiological measures, and make inferences about health and well-being [13]. Apps can also connect patients with their health information and health care providers, primarily by allowing them to access and contribute to their electronic health records [13,14]. However, mobile health apps are most commonly used to deliver interventions aimed at improving a wide variety of patients' health behaviors [15]. Concerningly, many of the current interventions are not based on any behavior change theories or techniques, and their effectiveness is not correctly evaluated [9,14,16]. Thus, there is a great scope for mobile health (mHealth) apps to improve their abilities to promote and maintain positive health behavior change.

A search of "mobile health" or "mHealth" on PROSPERO reveals many systematic reviews that are currently exploring mobile health interventions. However, with few exceptions [14,17], these systematic reviews have a narrow focus on particular types of health behaviors, patient groups, or a combination of both. Han and Lee conducted a systematic review in 2017 to examine the effectiveness of mobile health apps to improve patients' health behaviors [14]. The authors only included randomized controlled trials (RCTs) to examine apps that aimed to change health behaviors but did not exclude any studies based on a particular type of patient, health behavior, or app intervention. Thus, because their review only included RCTs and used broad search terms, many relevant mobile health apps were likely excluded.

Payne et al also conducted a systematic review to identify the current state of health behavioral intervention apps, which behavioral features they used, and their acceptability and effectiveness [17]. The majority of the studies included in the review examined apps for exercise and diet interventions; other interventions included mental health, diabetes management, and addiction. The authors concluded that the available evidence supported the acceptability and efficacy of most of the apps reviewed. However, they noted that most of the papers were pilot studies with small sample sizes, and further research was needed to provide more robust evidence of the utility of mobile health app interventions [17]. Their search strategy was focused on literature published until September 2014, and the state of mobile health app interventions is likely to have changed since then.

Therefore, there is a need for both an update and an expansion of these reviews, to reveal the current state of mobile health app technology, to consider the effectiveness, and to consider the behavioral change techniques that drive positive change. An overview of the different types of cutting-edge mobile app technologies and their uses will make it easier to identify the behavioral change techniques and strategies that may be most effective at engaging participants and improving health behaviors and outcomes.

This review will be focused on three main research questions. First, how effective are mobile health apps at improving and maintaining positive health behavior changes, and in which health behaviors are they the most effective? Second, what types of behavior change techniques are being used to support patient engagement with their health behaviors? Finally, what are patient perceptions of the feasibility, functionality, and overall user experience of the mobile health apps they use?

Methods

Overview

We will use the population, intervention, comparator, and outcome template and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [18] to identify appropriate Medical Subject Headings (MeSH) for the literature search and structure the review. This systematic review will be composed of a literature search, article selection, data extraction, quality appraisal, data analysis, and data synthesis. This review was prospectively registered on PROSPERO (CRD42019155604).

Eligibility Criteria

The following population, intervention, comparator, and outcome framework is based on the three research questions stated above.

- Population: The population will include people of any age (adults, adolescents, or children) who have interacted with the health care system or their health management using digital technologies or interventions. However, the review will focus on the general population, and specific subgroups such as pregnant women and patients with specific diseases (including HIV, posttraumatic stress disorder, alcoholism, and depression) will be excluded.
- Intervention: Mobile apps that are aimed at delivering interventions to improve and maintain positive health behaviors.
- Comparator: No specific comparator is required for studies to be included in this systematic review.
- Outcomes: The primary objective is to identify the types of mobile apps used in health care and behavioral change support and their effectiveness. This includes outcomes such as the extent and maintenance of behavior changes, adoption and adherence rates of the technology, patient-reported experience, feasibility and usability assessments, and coherence of the technology with behavioral change techniques.

- Studies: Due to an expectedly large volume of retrieved citations, the final set of included studies will be limited to randomized controlled trials.

Search Strategy

We will search the following databases: Medline, Embase, CINAHL, and Web of Science. Key terms relating to digital health technologies were extracted from an initial review of the literature. Specific search terms, including health behaviors and health conditions, were identified in a preliminary scan of the literature and chosen in consultation with a medical librarian. Search terms will include MeSH terms and keywords related to mobile phones, mobile apps, health behaviors, and evaluation. Tablet devices capable of running mobile apps were not included in the search to narrow the scope, but studies that included the use of apps on mobile tablets were not excluded. The search terms that will be used in this review are grouped into four themes presented in Table 1. All terms in the MeSH and Keywords columns are included with the structure: Mobile (MeSH OR Keywords) AND Applications (MeSH OR Keywords) AND Health Behavior (MeSH OR Keywords) AND Evaluation (MeSH OR Keywords). Due to an unexpectedly large number of included studies, reference lists of included studies and grey literature will not be searched. Authors of conference and poster abstracts selected for inclusion will be contact to see if a full text is available to include.

Table 1. Search terms.

Category	MeSH[a]	Keywords (in title or abstract)
Mobile	Cell Phone OR Telemedicine	Smartphone OR “mobile phone” OR “mHealth” OR “mobile health”
Applications	Mobile Applications	App OR apps OR “mobile app*” OR “smartphone app*”
Health Behavior	Health Behavior OR Health Promotion OR Exercise OR Weight Loss OR Obesity (diet therapy, prevention & control, rehabilitation, therapy) OR Nutrition Therapy OR Diet OR Smoking Cessation OR Smoking Reduction OR Tobacco Use Cessation OR Alcohol Drinking (prevention & control, therapy) OR Mental Health OR Safe Sex OR Behavioral Medicine OR Chronic Disease	“Health behaviour” OR “health behavior” OR “behaviour change” OR “behavior change” OR (Exercise ADJ3 (increase or start or maintain*)) OR “physical activity” OR “Weight loss” OR “healthy weight” OR “five a day” OR “diet” OR “nutrition” OR ((Maintenance OR maintain* OR achiev* Or retain*) ADJ4 (weight goal OR “weight loss” OR “goal weight” OR BMI)) OR (Smoking ADJ4 (cessation OR stop* OR quit* OR reduc*)) OR (Alcohol ADJ4 (reduc* OR limit* OR decreas* OR “cutting down” OR “cut down” OR “cut back” OR less* OR curb* OR abstain OR “dry January”)) OR “Protection from sun” OR “sun protection” OR “sun safe*” OR ((Sex OR “sex* behaviour” OR “sex* behavior”) ADJ4 (safe* OR protect*)) OR ((Alzheimer* disease OR arthritis OR asthma OR cancer OR COPD OR Crohn* disease OR cystic fibrosis OR dementia OR diabetes OR epilepsy OR heart disease OR HIV OR AIDS OR mood disorders OR bipolar OR depression OR anxiety OR multiple sclerosis OR Parkinson* disease) ADJ4 (manag* OR “self help” OR “self manag*” OR coping OR cope)) OR “Health management”
Evaluation	Outcome Assessment (Health Care)	Feasibility OR usability OR “evaluat*” OR “outcome*” OR acceptability OR adherence OR “effectiv*” OR “adoption” OR “assess*”

[a]MeSH: Medical Subject Headings.

Inclusion Criteria

We will include studies published between 2014 and 2019. Only the previous five years of research will be examined because technology has been evolving very rapidly, and this review is concerned with the current state of digital health technologies [19]. This period also provides an update to Payne et al’s systematic review that covered 2007-2014 [17]. Studies that evaluated at least one mobile app designed to monitor or improve patient health behaviors will be included. Any nationalities, geographic locations, or health behaviors will be included, provided that mobile app technologies are being used to help users improve, adopt, or maintain positive health behaviors and are the main focus of the study.

For the initial search, all study types will be included to ensure that no randomized controlled trials are missed. However, the studies included in the final review will be refined to include only RCTs.

Exclusion Criteria

We will exclude studies that are not published in English, studies of mobile app interventions that are not focused on health behaviors, and studies of mobile apps designed for use by health care professionals. Studies will also be excluded if their focus is on behavior change theory without reference to mobile apps, or if they examine interventions that use mobile phones or wearable technology but do not involve apps (eg, interventions based solely on text messaging or emails). However, if the mobile app is the focus of the study, but data collection involves wearables, it will be included. Mobile apps will not be considered the main focus of the study when they are only a minor component of an intervention, and their independent effect on health behavior is not examined. Studies will also be excluded if they do not evaluate the mobile app(s) considered.

This review will focus on the general population, so specific subgroups such as pregnant women will be excluded. However, reviews will not be excluded if they focus on particular demographic subgroups (for instance, based on age or nationality).

Screening and Article Selection

All the articles identified from the database searches will be stored in the citation management software Mendeley, which will be used to eliminate any duplicates. Two independent reviewers will screen the titles and abstracts of all the studies. Studies that fail to meet the eligibility criteria will be excluded,

with any disagreements being discussed until there is consensus. The full text of the remaining studies will then be examined by one reviewer and validated by the other to determine final eligibility, with any disagreements being resolved by a third reviewer. A PRISMA flow diagram will be used to record the details of the screening and selection process so that the study can be reproduced.

Data Extraction

One reviewer will examine the full text of all the papers included in the final selection to extract the predetermined outcomes, which will be validated by a second reviewer. Outcomes will be extraction into a preestablished, custom-built form. Disagreements will be resolved by discussion, and if consensus cannot be reached, a third reviewer will be consulted. The broad scope of the review means that there will likely be high heterogeneity in the data reported by various studies. However, an initial review of the literature has suggested various measures of effectiveness that are commonly used, which have been included in the data extraction table (see Textbox 1). Missing data will be considered in the risk of bias assessment, but due to time limitations, authors will not be contacted.

Textbox 1. Article information and data extracted.

General study information

- Year of publication
- Countries of study
- Study setting (primary location of app use, if relevant)
- Analyzed sample size
- Sample demographics (including age, gender, target population)
- Intervention duration and follow-up periods

Behavioral intervention

- Target health behavior(s) and intervention focus
- Theory the intervention is based on
- Behavior change techniques [16,20]

Mobile app technology

- Area of health care used in
- Name of the app
- Developers
- Platform
- Components and design features (eg, provision of feedback, notifications, tracking)

Evaluation

- What outcomes were measured
- Participant health outcomes
- Behavior change outcomes
- Participant engagement/adherence rates
- Participant satisfaction
- Feasibility and usability
- Other key performance indicators reported

Quality Appraisal and Risk of Bias Assessment

After the final selection of the studies, one reviewer will assess the risk of bias of all the papers included in the final selection. A quarter of the studies will be randomly selected for validation by a second reviewer. If there is disagreement in judgment, the reviewers will discuss before consulting a third reviewer. The Cochrane Collaboration Risk of Bias tool will be used to assess the randomized controlled trials included in the review and assign low, unclear, or high risk to the studies for each of the potential biases [21]. A table will be created summarizing the quality of all included studies.

Data Analysis and Synthesis

It is unlikely that a meta-analysis will be feasible due to the anticipated variety of study aims, methods, and reported outcomes. Therefore, we will conduct a descriptive analysis to summarize the extracted data. Each health behavior and patient health outcome will be coded as having no, some, or significant evidence of effectiveness. Significant evidence will be coded

only when the app performs significantly better than a comparator or control. The app will be considered to have some evidence of effectiveness if there is a significant difference over time but not between groups or a significant improvement in only a subgroup of the population. Health behaviors and patient health outcomes will be analyzed separately. Studies will be grouped by target health behavior (eg, smoking cessation) and analyzed together to describe the effectiveness of mobile health apps in general for those target behaviors, and in particular, for behavioral and health outcomes. The discussion will synthesize the data to describe the current state of mobile health apps, draw conclusions about their feasibility, usability, effectiveness, and use of behavioral change techniques, and identify limitations and directions for future research and development.

Results

As of November 2019, the systematic review has been completed and is in peer review for publication.

Discussion

A systematic and transparent review of the literature will provide a better understanding of current state-of-the-art mobile health apps, how they are being used, and to what effect. Strengths, limitations, and implications for the interaction of technology and behavioral health management will help inform and improve the development, acceptability, and effectiveness of future mobile health apps. Based on the data, this section will explore what conclusions can be drawn, what limitations exist in the systematic review, and what the important directions for future research are.

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Authors' Contributions

EM and MMI conceived the study topic and designed the review protocol. MMI prepared the first draft of the protocol with revisions from CL, MVV, and EM.

Conflicts of Interest

None declared.

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Abbreviations

MeSH: Medical Subject Headings
mHealth: mobile health
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
RCT: randomized controlled trial

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Protocol

Teaching Real-World Evidence: Protocol for a Systematic Review

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Abstract

Background: Real-world evidence (RWE) refers to observational health care data beyond clinical trial data. It holds the promise of transforming health care as a new form of evidence to support decision makers in making decisions when developing and regulating medicines. As the importance of RWE is recognized by industry and regulatory bodies, teaching RWE becomes an important matter to evaluate and refine in order to develop future researchers and stakeholders who can better integrate RWE into the routine development of medicine.

Objective: The aim of this review is to understand how RWE is currently being taught. From this landscape study, the insufficiencies of the current education of RWE can be identified and subsequently inform future education policies around RWE and its subfacets.

Methods: We will search MEDLINE, EMBASE, PsycINFO, Healthcare Management Information Consortium, Cochrane, and Web of Science for published studies using a combination of keywords and subject headings related to RWE and education. In addition, a Google search to identify grey literature will be conducted. Two authors will independently screen the titles and abstracts identified from the search and accept or reject the studies according to the study inclusion criteria; any discrepancies will be discussed and resolved. The quality of the included literature will be assessed using the Critical Appraisal Skills Programme systematic review checklist.

Results: Data from eligible publications will be abstracted into a predesigned form in order to better understand the current state of education of RWE and inform future RWE education directions and policies.

Conclusions: The subsequent systematic review will be published in a peer-reviewed journal.

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KEYWORDS

real-world evidence; teaching; public health

Introduction

Real-world evidence (RWE) is a subset of evidence-based medicine that refers to health care information gathered through means outside of the typical clinical research settings. Evidence-based medicine (EBM) is the use of best available clinical evidence from systematic research combined with clinical expertise to deliver the best possible clinical care to patients [1,2]. Since its advent in the 1990s, EBM has been shown to be the cornerstone of the medical profession, raising awareness of using reliable, published evidence to aid decision making in medicine [3,4]. Sources of RWE data can come from electronic health records (EHRs), health surveys, claims and billing data, product and disease registries, mobile health apps, and personal smart devices. Collectively, the real RWE base

can generate invaluable insights and findings on diseases, products, and patient populations [5,6].

Regulatory bodies around the world are gaining interest in RWE. Notably, the US Food and Drug Administration has recently announced a $100 million project to build a modern system that will gather RWE from approximately 10 million individuals [7], and the European Union has funded over 170 initiatives related to RWE, of which 65 received over 734 million euros of public funding [8]. According to a report from McKinsey and Company [9], pharmaceutical companies have recognized the impact of RWE and are actively applying it to safety, postmarket, and end-to-end product development to facilitate research and development and commercial and safety decisions.

The anticipated importance of data collection and analysis of RWE in the future of clinical trials and development of medicines is evident. In order to meet the future demands of RWE researchers in terms of realizing the true potential of RWE in transforming health care, it is important to educate stakeholders such as researchers, clinicians, and policy makers in RWE in an appropriate way.

EBM has long been taught to medical professionals, including clinicians and nurses [10-12], and due to its importance in clinical care, teaching EBM in medical school has been investigated in various studies. Smith et al [13] conducted a controlled trial to look into the effectiveness of EBM courses for residents. Another recent study conducted by Nasr et al [14] evaluated four EBM workshops taught to residents-in-training and postgraduates in medical school. Interestingly, Slawson et al [15] suggested the importance of information management in the teaching of EBM back in 2005, and with the rapid development of big data, better computer processors, and the maturation of machine learning in recent years, information management is more important than ever in EBM. However, it is unknown how RWE is being taught and what the effects are.

This systematic review aims to answer the following research questions:

- What are the current methods used to teach RWE, and what are the effects of those methods?
- Who are the stakeholders teaching and learning about RWE?

Methods

Review Conduct

This systematic review will be conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. The protocol methods will be reported following the 2015 PRISMA checklist [17]. The protocol will be registered with PROSPERO.

Eligibility Criteria

Inclusion Criteria

In accordance with PRISMA Protocols (PRISMA-P) checklist recommendation, the inclusion criteria for this protocol are in accordance with participants, interventions, comparators, and outcomes (PICO). Details of PICO to be included in the review are described in Textbox 1.

Textbox 1. Participants, interventions, comparators, and outcomes for review inclusion criteria.

Population:

- Participants with real-world evidence teaching

Intervention:

- Any form of real-world evidence teaching

Comparator:

- No real-world evidence teaching

Outcomes:

- Learner-focused outcomes such as attitudes, cognitive changes, learner satisfaction

Study type:

- Any study type (study type will not be subjected to any restrictions)
- Must describe relevance to real-world evidence and its application in health care
- Must describe a teaching method
- English-language publications

Exclusion Criteria

Education methods that do not describe their relevance to RWE and its applications to health care will be excluded to limit the scope of the review to RWE-focused education and courses. Websites and articles describing RWE (although helpful for those actively seeking to learn more about RWE) will be excluded as there are no methods of teaching included. Studies not published in English are excluded due to the language barrier.

Search Strategy

The following databases will be searched: MEDLINE, EMBASE, PsycINFO, Healthcare Management Information Consortium, Cochrane, and Web of Science. In addition, a Google search for grey literature such as blog posts, opinion pieces, press releases, and online courses will be conducted. Online course platforms such as Coursera, edX, FutureLearn, and OpenClassrooms will be searched to identify relevant courses. Textbox 2 shows the search concept and keywords to be searched for this review. Search strings will be constructed using a combination of RWE-related and education-related keywords.

Textbox 2. Concepts and keywords for search term development.

Real-world evidence:

- Real world evidence, RWE, big data analytics, real world data, electronic health record*

Teaching:

- Medical education, medical student*, medical curriculum, medical school*, health professionals

Study Selection

EndNote X8 software (Clarivate Analytics) will be used for the removal of duplicates. Textbox 1 describes the inclusion criteria of the review. Two independent reviewers will screen the titles and abstracts of papers to minimize the risk of bias and the risk of not including eligible papers due to oversight. Papers that are ineligible will be eliminated, and the full text of those that appear to meet the review's eligibility criteria will be obtained and read in full to ensure eligibility. Any contradictions or discrepancies between the reviewers that arise will be discussed until consensus is reached. Valid studies will be assessed for their quality before any extraction of information.

Quality Assessment and Risk of Bias

Two reviewers will independently check each article to minimize bias using the Cochrane Collaboration's risk of bias tool as described in the Cochrane Handbook for Systematic Review of Interventions [18]. All included articles will be judged for their quality based on the Critical Appraisal Skills Programme systematic review checklist [19] and data analysis.

Data Extraction

Eligible sources will subsequently be reviewed in detail, and key relevant challenges will be extracted, categorized, and recorded into a predesigned Excel spreadsheet (Microsoft Corp). A sample data abstraction form can be found in Figure 1.

Figure 1. Sample data abstraction form.

Inclusion criteria		
Population	-	Participants of real world evidence teaching
Intervention	-	Any form of RWE teaching
Comparator	-	No RWE teaching
Outcomes	-	learner-focused outcomes such as attitudes, cognitive changes, learner satisfaction
Study Type	-	Any study type (study type will not be subjected to any restrictions) - Must describe relevance to RWE and its application in healthcare - Must describe a teaching method - English publications

Results

A sample search was conducted using PubMed, and the sample search string returned 943 results: ("real world evidence" OR "RWE" OR "big data analytic*" OR "real world data" OR "electronic health record*") AND ("medical education" OR "medical student*" OR "medical curriculum" OR "medical school*"). The search string will be further fine-tuned in the review.

Discussion

Principal Findings

This study will offer a comprehensive overview of how RWE is taught to different stakeholders of the research and application of RWE in health care. However, traditional means of teaching, such as university lecturies, may not be published and hence may be underrepresented in this protocol.

Conclusions

This protocol will be executed in 2020 and published in a peer-reviewed journal in accordance with PRISMA guidelines. Any deviations in the execution shall be noted in the subsequent systematic review publication. The findings from this review will be used to inform the education strategy of RWE.

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Authors' Contributions

The protocol was written by CL with revisions from MHvV, HC, EM.

Conflicts of Interest

None declared.

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Abbreviations

EBM: evidence-based medicine
EHR: electronic health record
PICO: participants, interventions, comparators, and outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
RWE: real-world evidence

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Protocol

The Association Between Selected Molecular Biomarkers and Ambulatory Blood Pressure Patterns in African Chronic Kidney Disease and Hypertensive Patients Compared With Normotensive Controls: Protocol for a Longitudinal Study

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Abstract

Background: Chronic kidney disease (CKD) is a burgeoning epidemic in sub-Saharan Africa. Abnormal blood pressure variations are prevalent in CKD and potentiate the risk of cardiovascular morbidity and mortality. Certain genetic variants (angiotensin II receptor type 1 1166 A>C and angiotensin-converting enzyme insertion and deletion polymorphisms) and biomarkers such as interleukin–6, tumor necrosis factor, soluble (s) E-selectin, homocysteine, and highly sensitive C-reactive protein have been shown to affect blood pressure variability among non-African CKD, hypertensive. and nonhypertensive CKD population. However, the contributions of the pattern, genetic, and environmental determinants of ambulatory blood pressure in African CKD have not been characterized. Understanding these interactions may help to develop interventions to prevent major cardiovascular events among people with CKD.

Objective: The overarching objective of this study is to identify, document, and develop approaches to address related phenomic, genetic, and environmental determinants of ambulatory blood pressure patterns in African CKD and non-CKD hypertensive patients compared with normotensive controls.

Methods: This is a longitudinal short-term follow-up study of 200 adult subjects with CKD and 200 each of age-matched hypertensives without CKD and apparently healthy controls. Demographic information, detailed clinical profile, electrocardiography, echocardiography, and 24-hr ambulatory blood pressure measurements will be obtained. Blood samples will be collected to determine albumin-creatinine ratio, fasting plasma glucose, lipid profile, electrolytes, urea and creatinine, C-reactive protein, serum homocysteine, fibroblast growth factor–23, and complete blood count, while 2 mL blood aliquot will be collected in EDTA (ethylenediaminetetraacetic acid) tubes and mixed using an electronic rolling system to prevent blood clots and subsequently used for DNA extraction and genetic analysis.

Results: A total of 239 participants have been recruited so far, and it is expected that the recruitment phase will be complete in June 2020. The follow-up phase will continue with data analysis and publications of results.

Conclusions: This study will help stratify Nigerian CKD patients phenotypically and genotypically in terms of their blood pressure variations with implications for targeted interventions and timing of medications to improve prognosis.

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KEYWORDS

chronic kidney disease; cardiovascular disease; ambulatory blood pressure

Introduction

Background

Chronic kidney disease (CKD) is rising in public health importance in Nigeria and contributes significantly to the increased burden of cardiovascular disease (CVD) in the country and sub-Saharan Africa in general [1-4]. It has been estimated that approximately 36 million people are currently living with CKD in Nigeria with the most common causes being glomerulonephritis and hypertension [4,5]. The disease is associated with high morbidity and mortality and exorbitant cost of treatment [6,7]. Most patients requiring renal replacement therapy are unable to afford the cost of maintenance dialysis or kidney transplantation [8].

Poorly managed CKD is often associated with rapid progression to end-stage renal disease (ESRD) and cardiovascular disease (CVD) [9,10]. The rapidity of progression is especially higher among individuals of African descent [9]. Most deaths from CKD arise from cardiovascular complications, among which are heart failure, coronary artery disease, arrhythmia, and stroke [11]. In addition, many of the patients often present late, thus making early detection and cardiovascular risk assessment among patients with CKD challenging. Efforts to improve cardiovascular outcomes in CKD in sub-Saharan Africa require an improved risk stratification scheme and early detection so that resources can be targeted at those CKD patients who are at increased risk of CVD events.

Association Between Selected Molecular Biomarkers and Ambulatory Blood Pressure Pattern

CKD's contribution to CVD is through many pathophysiologic mechanisms, cardinal among which is the failure of nocturnal blood pressure (BP) dipping. Studies have shown that being a nondipper increases the risk of CVD by 2.4 fold in patients with CKD [12-14]. Furthermore, nondipping of BP has been shown to increase susceptibility to CKD progression to ESRD, CVD, and poor responses to antihypertensive medications despite optimal compliance to treatment [12,14].

Previous studies have identified various biomarkers in non-African non-CKD hypertensive blacks to be associated with BP variability, including interleukin–6, tumor necrosis factor–alpha, soluble (s) E-selectin, homocysteine, and high-sensitivity C-reactive protein [15-18]. Some of these biomarkers are also linked to CVD adverse events in apparently healthy individuals [19].

Renin-Angiotensin-Aldosterone Pathway Genetic Polymorphisms in Circadian Blood Pressure Variations

The current approach to reducing the CVD burden is chronotherapy, through which 24-hour optimal BP control is ensured. However, not all patients respond well to chronotherapy, suggesting that the mechanism underlying the nondipping of BP and nocturnal hypertension in CKD is not completely understood [12,20]. Studies in non-Africans have suggested that the genetic variants in the renin-angiotensin-aldosterone pathway may play a critical role in the nondipping of BP, and the two genetic variants implicated are the angiotensin II type 1 receptor 1166 adenine to cytosine (AGTR1 1166 A>C) polymorphism and the insertion/deletion mutant of the angiotensin converting enzyme (ACE I/D) gene [21,22].

The mutations in the two genes have been shown to cause abnormal activation of the renin-angiotensin-aldosterone system (RAAS) with characteristic elevations in the systemic levels of renin, aldosterone, and angiotensin II, which eventually lead to potassium ion loss and sodium ion retention, left ventricular hypertrophy, and atrial fibrillation [22,23]. Abnormally activated RAAS also leads to vasoconstriction of the arteries including the coronary artery and other vessels, inducing cellular proliferation of these vasculatures and stimulating extracellular matrix protein synthesis [24]. Both are required for fibrotic changes in the heart muscle and kidney and blood vessels [24]. The angiotensin II receptor and ACE mediate RAAS pathophysiological activities through two distinct functional polymorphisms of their genes. These polymorphisms are AGTR1 1166 A>C and the ACE I/D gene [23,24].

This study seeks to identify, document, and develop approaches to address related phenomic, genetic, and environmental determinants of ambulatory BP patterns in African CKD and non-CKD hypertensive patients compared with normotensive controls. We will also explore the associations between genetic variants in the RAAS pathway and nocturnal BP variations and its cardiovascular sequelae among CKD patients.

Aims

1. Evaluate the contributions of traditional and novel sociodemographic, clinical, and environmental risk factors to ambulatory BP patterns in African CKD and hypertensive patients compared with normotensive controls
2. Determine AGTR1 1166 A>C and ACE I/D genotypes and allele distributions among nondipper Nigerians with CKD and nonhypertensive CKD while comparing the same among dippers and nondippers

3. Determine the association between AGTR1 1166 A>C and ACE I/D genotypes and ambulatory BP phenotypes (diurnal BP variability)
4. Determine the association between AGTR1 1166 A>C and ACE I/D genotypes and cardiovascular risk factors (hyperuricemia, hyperglycemia or diabetes, hypertriglyceridemia) among Nigerians with CKD and nonhypertensive CKD
5. Determine the association between AGTR1 1166 A>C and ACE I/D genotypes and major cardiovascular events (stroke, myocardial infarction, heart failure, atrial fibrillation, and abnormal left ventricular geometry) among Nigerians with CKD and nonhypertensive CKD
6. Determine the genes by environmental interactions that are associated with nocturnal BP variability among Nigerians with CKD

Hypotheses

1. Unique environmental risk factors will contribute to ambulatory BP pattern in African CKD and hypertensive individuals of African ancestry.
2. Polymorphisms of AGTR1 1166 A>C and ACE I/D are higher among CKD dippers compared with CKD nondippers.
3. Polymorphisms of AGTR1 1166 A>C and ACE I/D are associated with ambulatory BP phenotypes and cardiovascular risk factors in CKD and non-CKD hypertensives.
4. Polymorphisms of AGTR1 1166 A>C and ACE I/D are associated with cardiovascular risk factors among patients with CKD.
5. Polymorphisms of AGTR1 1166 A>C and ACE I/D do not interact with environmental factors (body mass index, cigarette smoking, alcohol intake, and medication adherence) in the development of nondipping.

Methods

Design

This is a longitudinal short-term follow-up study of 200 adult subjects with CKD and 200 each of age-matched hypertensives without CKD and apparently healthy controls. The CKD cases and non-CKD hypertensive patients will be recruited from the medical outpatient clinics at the University College Hospital, Ibadan, and the Nigerian Institute of Medical Research (NIMR) [25], Yaba, Lagos. Controls will be recruited during medical outreaches organized in communities from which CKD patient referrals are received.

Ethics Approval and Consent to Participate

The study was approved by the University of Ibadan/University College Hospital Research Ethical Committee with approval number UI/EC/18/0291. Participants are required to give written informed consent to participate in the study.

Study Sites

The study will be carried out in the NIMR and the Department of Medicine, University of Ibadan University College Hospital, a teaching hospital with a 850-bed capacity and several community care centers in Ibadan and other sites within the state from where CKD cases are referred. It has full complements of all clinical and nonclinical departments. The hospital provides both preventive and curative services and is equipped with cardiac, neuroimaging, and other laboratory facilities. From the registry, a monthly average of 50 cases of CKD are seen in the renal clinic.

NIMR is the hub for research, human resource capacity building, and collaboration for national development in the country. It is a foremost health research institute established in 1977 to conduct basic, applied, and implementation science research on infectious and noncommunicable diseases of public health importance in Nigeria. NIMR is made up of five major divisions: Microbiology, Public Health, Biochemistry and Nutrition, Molecular Biology and Biotechnology, and Clinical Sciences and has three support research units: Centre for Human Virology and Genomics, Centre for Tuberculosis Research, and Centre for Alternative Medicine and Research.

Inclusion and Exclusion Criteria

Chronic Kidney Disease Participants

The inclusion criteria for the study are being aged ≥18 years and having a diagnosis of CKD, while the exclusion criteria are diagnosis of autosomal polycystic kidney disease or sickle cell nephropathy (Textbox 1).

Textbox 1. Variables and definitions.

- Chronic kidney disease: estimated glomerular filtration rate less than 60 mL/min/1.73 m2 on two or more occasions at least 3 months apart
- Hypertension: systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or both and on antihypertensive medication
- Diabetes mellitus: fasting blood sugar ≥126 mg/dL or on medications for diabetes
- Waist circumference: >102 cm (male) and >88 cm (female)
- Obese: body mass index ≥30 kg/m2
- Dyslipidemia: total cholesterol >200 mg/dL (male/female), high-density lipoprotein <40 mg/dL (male), <50 mg/dL (female), or low-density lipoprotein >130 mg/dL (male/female)
- Hyperuricemia: serum uric acid >7 mg/dL (male) and >6 mg/dL (female)

Hypertensive Participants

The inclusion criteria for the study are being aged ≥18 years and having a diagnosis of hypertension, while the exclusion criteria are diagnosis of autosomal polycystic kidney disease, sickle cell nephropathy, or CKD (Textbox 1).

Controls

The inclusion criteria for the study are being aged ≥18 years and apparently clinically normal, while the exclusion criteria are subjects with autosomal polycystic kidney disease, sickle cell nephropathy, or CKD.

Evaluation of Cases and Controls

The study will be in 2 phases. In the initial phase, data will be collected in standard case report form (available on request) and information regarding bio-data, risk factors for CVD, lifestyle, stage of CKD, and comorbidities will be obtained. Other important variables will include clinical features and medication use of participants.

Demographic information, detailed clinical profile, electrocardiography, echocardiography, and 24-hour ABPM will be obtained. In addition, the dialysis vintage, frequency of comorbidities, family history of hypertension and kidney disease, medication, and medication adherence using pill count will be accessed.

Follow-Up Strategy

Participants will subsequently be assessed at 6 months, 1 year, and 2 years for any cardiovascular adverse outcomes. Major adverse cardiovascular events such as cardiac death and hospitalization for cardiac events will be assessed while noncardiovascular death and events will also be noted. Serum creatinine will be assessed.

Anthropometric Measurements

Anthropometric measurements (height, weight, and hip and waist circumferences) will be performed using World Health Organization guidelines [26,27]. A semiautomated digital BP machine will be used to measure BP in accordance with World Health Organization guidelines, and the average readings will be recorded.

24-Hour Ambulatory Blood Pressure Monitoring

24-hour ABPM will be done using Spacelabs 90207 monitors (Spacelabs Healthcare) which will be placed on the nondominant hand within the first week of recruitment. The machine will be programmed to read every half hour from 7:00 am to 10:00 pm and hourly from 10:00 pm to 7:00 am during weekdays. Patients will be encouraged to proceed with their routine daily activities but avoid strenuous physical activities and keep motionless at the time of measurement. Dipping pattern, white coat effects, and nocturnal and daytime hypertensions will be deduced from the readings.

Body Fluids Sampling Strategy

Venous blood samples (5 mL) will be drawn from each study participant after an overnight fast by medical personnel with phlebotomy training at each site. All tests and examinations will be performed between 8:00 am and 10:00 am daily. Three mLs aliquot of the blood sample will be collected in plain tubes to determine albumin-creatinine ratio, fasting plasma glucose, lipid profile, electrolytes, urea and creatinine, C-reactive protein, serum homocysteine, fibroblast growth factor–23, and complete blood count, while the remaining 2 mL aliquot will be collected in EDTA (ethylenediaminetetraacetic acid) tubes and mixed using an electronic rolling system to prevent blood clots and subsequently used for DNA extraction and genetic analysis.

Early morning urine and fasting blood sample will be collected. Estimated glomerular filtration rate (eGFR) will be calculated using the Modification of Diet in Renal Disease 4-variable equation. Subjects will be followed up at 3-month intervals for 1 year.

Genetic Analysis

Angiotensin Converting Enzyme Gene II/ID/DD Polymorphism

QIAamp DNA Blood Mini Kits (Qiagen) will be used to extract DNA from blood cells. A 287-bp I/D polymorphism in the intron 16 of the ACE gene will be examined by polymerase chain reaction (PCR). The sequences of the sense and antisense primers were 5′-CTG GAG ACC ACT CTT TCT-3′ and 5′-GAT GTG GCC ATC ACA TTC GTC AGA-3′, respectively. Both forward and reverse primers will be synthesized by Inqaba Biotec. The PCR will be performed in a final volume of 20 µL, containing 100 ng of genomic DNA, 40 pmol of each primer, 200 µmol each of the four dNTP, 3 mM $MgCl_2$, 50 mmol KCl, 10 mmol Tris-HCl (pH 8.3), and 1.5 U of Taq polymerase (Promega Corp). Amplification will be carried out for 30 cycles with steps of denaturation at 94°C for 1 minute, annealing at 54°C for 1 minute, and extension at 72°C for 1 minute. The PCR products were subjected to electrophoresis in 1% agarose gels. Amplification of the D allele resulted in a 190-bp DNA fragment and amplification of the I allele resulted in a 490-bp fragment. Homozygotes had a single 190 (DD)– or 490 (ID)–bp band; heterozygotes had one 190-bp and one 490-bp band. The PCR products will be analyzed on 2% agarose gels with a 100-bp DNA Ladder (Promega Corp), and images were acquired and analyzed using a gel imaging system.

Angiotensin II Type 1 Receptor 1166 Adenine to Cytosine Polymorphism

The AGTR1 gene will be genotyped for 1166 A>C polymorphism by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method as described by Zhu et al [20] using the following primers: 5′AATGCTTGTAGCCAAAGTCACCT and 5′ GGCTTTGCTTTGTCTTGTTG. PCR amplification will be performed in a 20 µl reaction containing 100 ng of genomic DNA, 1.5 mM $MgCl_2$, 200 µM each of the deoxynucleotide triphosphates, 10 picomoles each of the forward and reverse primers, and 1.5 U of Taq DNA polymerase. PCR amplification will then be carried out in the SimpliAmp Thermal Cycler (Applied Biosystems). The conditions for PCR amplification consisted of 2 minutes denaturation at 94°C, followed by 40 cycles of 1 minute at 94°C, 1 minute annealing at 60°C, extension for 2 minutes at 72°C, and final extension for 10 minutes at 72°C. The resulting PCR products of the expected

size (850-bp) will subsequently be analyzed by agarose gel electrophoresis with 1% agarose gel prestained with 0.5 μg/mL ethidium bromide in Tris-borate-EDTA buffer (pH 8.3) at 70 volts for 1 hour. To characterize the polymorphism, PCR products will be digested overnight with the restriction endonuclease Dde I (BioLabs Inc) at 37°C. This is expected to cut the product into two pieces, 600-bp and 250-bp long. An additional Dde I recognition site will be created in the C-type variant at nucleotide 1166, which is located within the 250-bp fragment. Therefore, the homozygote AA is expected to produce two bands (600-bp and 250-bp long), heterozygote AC to produce four bands (600-bp, 250-bp, 140-bp, and 110-bp long), and homozygote CC to produce three bands (600-bp, 160-bp, and 110-bp long). Analysis of the digested PCR products will also be done by agarose gel electrophoresis by using 3% agarose gel prestained with ethidium bromide in Tris-borate-EDTA buffer (pH 8.3), using gel electrophoresis apparatus (Promega Corp) and ultraviolet transillumination (Applied Biosystems). All the PCR products will be analyzed with a 100-bp DNA Ladder (Promega Corp), and gel images of DNA bands will be acquired and analyzed using a gel imaging system.

Outcomes

The primary outcomes will be a composite of cardiovascular events (myocardial infarction, heart failure, and stroke) requiring hospitalization and death. Secondary outcomes will be a composite of ESRD, 50% decline in eGFR, and doubling of serum creatinine. Composite of hospitalization from cardiovascular events such as myocardial infarction, heart failure, and stroke will be significantly higher among CKD subjects compared with controls.

Statistical Analysis and Power Calculation

The statistical analysis will be carried out using R (The R Foundation), and all categorical variables will be compared by chi-square test or Fisher exact test where indicated. Continuous variables that are normally distributed will be compared by means of the Student *t* test and analysis of variance where there are more than 2 groups. Continuous variables not normally distributed will be compared by the Mann-Whitney U test or the Kruskal-Wallis test where there are more than 2 groups. Correlations between two continuous variables will be assessed using Pearson correlation statistics. Linear and multiple logistic regression analyses will be used to determine factors predicting nondipping of BP and cardiovascular sequelae. The allele frequencies of the candidate gene variants will be determined for the AGTR1 1166 A>C and ACE I/D in CKD nondipper and controls. A test for associations between the variants and BP phenotypes will be performed by fitting covariate-adjusted logistic regression models in which each variant will be presented as a predictor variable whose values are equal to the number of copies of the minor allele (0, 1, 2; ie, additive mode) or presence of at least one copy of the minor allele (0, 1; ie, dominant mode) or presence of two copies of the minor allele (0, 1; ie, recessive mode). All tests of association will be adjusted for gender, age (to account for possible residual effects due to incomplete matching), severity of CKD, and other relevant covariates. Both ACE DD/ID and AGTR1 1166 A>C polymorphisms will also be evaluated for Hardy-Weinberg Equilibrium in the control group. The logistic model can be represented as logit[(pr=D)] = $\alpha + \beta 1G + \beta 2Sex + \beta 3Age$ (D denotes diurnal BP variation status, G denotes genetic variants coded as additive or dominant or recessive, β denotes the corresponding coefficient for each variable in the model [single-nucleotide polymorphisms, sex, or age] and its exponential is the corresponding odds ratio). Statistical significance for the adjusted odds ratio will be set at 0.05.

The power analysis for the genetic analysis is based on the primary analysis to assess the main effects of AGTR1 1166 A>C and ACE I/D polymorphisms and their interaction with environmental factors in Nigerians with CKD. Based on minimum allele frequencies of 0.12 and 2×105 for AGTR1 1166 A>C and ACE I/D polymorphisms, respectively. We will also assume that three genotypes of AGTR1 1166 A>C are equally distributed, and the probability of developing nondipping in the reference genotype group is 0.3. Data will be analyzed using SPSS version 20 (IBM Corp). Given a sample size of 600 (200 per group), this study design would have at least 80% power to detect a minimum odds ratio of 2.0 in patients with any of the three gene variants, using Bonferroni correction with type I error of 5%.

Results

The study is supported with an International Society of Hypertension (ISH) Research Scholar Grant Award. A total of 239 participants have been recruited so far, and it is expected that the recruitment phase will be complete in June 2020. The follow-up phase will continue with data analysis and publications of results.

Discussion

The prevalence of CKD and the associated adverse outcomes are on the increase in Nigeria [4,5,9,10]. These come with enormous socioeconomic implications, most especially in the light of inadequate understanding of BP variability among CKD patients through which appropriate strategies for treatment and prevention can be developed. It is therefore imperative to study the phenomics, genetics, and environmental determinants of ambulatory BP patterns in black CKD and non-CKD hypertensives.

There is evidence of association of AGTR1 1166 A>C and ACE I/D polymorphisms with CKD and cardiovascular diseases, their roles in non-BP dipping at night, and nocturnal hypertension, but this remain unclear among African blacks. The effects of these polymorphisms on Nigerian CKD patients either in the context of BP regulation or response to antihypertensive medications and other cardiovascular risk factors (hyperuricemia, hyperglycemia or diabetes, hypertriglyceridemia) have not been evaluated.

Given the fact that genetic environment influences the pathogenesis of CKD, cardiovascular risk factors, and cardiovascular diseases, there is a need to stratify Nigerian CKD patients genotypically using a translational research approach prior to integrating supportive therapy of CKD management for improved prognosis. Unraveling the role of these genetic

polymorphisms among nondipper Nigerian patients with CKD will provide insight into the mechanisms underlying nondipping and CVD complications. This will also guide appropriate stratification into risk of ESRD progression and CVD risk profiling for adequate treatment plans, prevention plans, and appropriate policy changes.

Furthermore, identification of CKD patients at risk of nondipping using molecular and genetic markers will guide in appropriate use of cardiovascular risk stratification and predicts response to chronotherapy.

This case control study of 600 participants with 3 arms of 200 each, comprising CKD nondippers, CKD dippers, and apparently healthy controls will use comprehensive phenotyping and genotyping of RAAS pathway variants to identify genetic risk markers among CKD nondippers. It will be the first major study to assess this among African blacks.

This study will also explore the potential of the use of PCR-RFLP as a laboratory test for CKD with hypertension prior to treatment initiation for better stratification of patients for morning or night antihypertension medications in Nigeria. This innovative tool is rapid, cost effective, and highly applicable to larger cohorts of CKD patients compared with the more laborious, time-consuming conventional ABPM required for the identification of nondippers and patients with nocturnal hypertension. The PCR-RFLP technique will become a routine point-of-care test for personalized treatment of hypertension among affected CKD patients in the country.

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Authors' Contributions

AMA, OMA, BI, and BOT contributed to the design of the study. AMA, OMA, and BA were responsible for clinical studies and data acquisition. AMA and OMA contributed to the literature search and manuscript preparation. AMA, OA, and BI performed the data analysis, and OA and BI performed the statistical analysis. AMA was the guarantor. All authors contributed to the concept, definition of intellectual content, and manuscript review and editing. This manuscript has been read and approved by all authors, and the requirements for authorship were met. All authors believed that the manuscript represents honest and reliable work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report 1 from the University of Ibadan/University College Hospital Research Ethical Committee.
[PDF File (Adobe PDF File), 249 KB - resprot_v9i1e14820_app1.pdf]

Multimedia Appendix 2
Peer-reviewer report 2 from the University of Ibadan/University College Hospital Research Ethical Committee.
[PDF File (Adobe PDF File), 308 KB - resprot_v9i1e14820_app2.pdf]

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Abbreviations

ABPM: ambulatory blood pressure monitoring
ACE: angiotensin-converting enzyme
ACE I/D: insertion/deletion mutant of the angiotensin converting enzyme
AGTR1: angiotensin II type 1 receptor
AGTR1 1166 A>C: angiotensin II type 1 receptor 1166 adenine to cytosine
BP: blood pressure
CKD: chronic kidney disease
CVD: cardiovascular disease
EDTA: ethylenediaminetetraacetic acid
eGFR: estimated glomerular filtration rate
ESRD: end-stage renal disease
ISH: International Society of Hypertension
NIMR: Nigerian Institute of Medical Research
PCR: polymerase chain reaction
PCR-RFLP: polymerase chain reaction–restriction fragment length polymorphism
RAAS: renin-angiotensin-aldosterone system

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Protocol

A Smartphone App Combining Global Positioning System Data and Ecological Momentary Assessment to Track Individual Food Environment Exposure, Food Purchases, and Food Consumption: Protocol for the Observational FoodTrack Study

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Abstract

Background: Our understanding of how food choices are affected by exposure to the food environment is limited, and there are important gaps in the literature. Recently developed smartphone-based technologies, including global positioning systems and ecological momentary assessment, enable these gaps to be filled.

Objective: We present the FoodTrack study design and methods, as well as participants' compliance with the study protocol and their experiences with the app. We propose future analyses of the data to examine individual food environmental exposure taking into account the accessible food environment and individual time constraints; to assess people's food choices in relation to food environmental exposure; and to examine the moderating role of individual and contextual determinants of food purchases and consumption.

Methods: We conducted a 7-day observational study among adults (25-45 years of age) living in urban areas in the Netherlands. Participants completed a baseline questionnaire, used an app (incorporating global positioning system tracking and ecological momentary assessment) for 7 days, and then completed a closing survey. The app automatically collected global positioning system tracking data, and participants uploaded information on all food purchases over the 7-day period into the app. Participants also answered questions on contextual or individual purchase-related determinants directly after each purchase. During the final 3 days of the study, the participants also uploaded data on fruit, vegetable, and snack consumption and answered similar ecological momentary assessment questions after each intake.

Results: In total, 140 participants completed the study. More than half of the participants said they liked the app (81/140, 57.9%) and found it easy to use (75/140, 53.6%). Of the 140 participants, 126 (90.0%) said that they had collected data on all or almost all purchases and intakes during the 7-day period. Most found the additional ecological momentary assessment questions "easy to answer" (113/140, 80.7%) with "no effort" (99/140, 70.7%). Of 106 participants who explored their trips in the app, 20 (18.8%) had trouble with their smartphone's global positioning system tracking function. Therefore, we will not be able to include all participants in some of the proposed analyses, as we lack these data. We are analyzing data from the first study aim and we expect to publish the results in the spring of 2020.

Conclusions: Participants perceived the FoodTrack app as a user-friendly tool. The app is particularly useful for observational studies that aim to gain insight into daily food environment exposure and food choices. Further analyses of the FoodTrack study data will provide novel insights into individual food environmental exposure, evidence on the individual food environment-diet interaction, and insights into the underlying individual and contextual mechanisms of food purchases and consumption.

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KEYWORDS

ecological momentary assessment; eating behavior; environmental exposure; mobile apps; smartphone; geographic information systems; food preferences; diet records

Introduction

Background

The prevalence of obesity- and nutrition-related noncommunicable diseases, such as type 2 diabetes and cardiovascular diseases, has increased substantially in recent decades [1]. Multiple factors contribute to these increased prevalences, although the changed food environment is regarded as an important driver [2]. Although the associations between temporal food environmental changes and diet and obesity have been described extensively [2-4], a better fundamental understanding is needed of how and where people purchase and eat food in contemporary obesogenic environments.

Many studies have focused on the community food environment, operationalized as the number, type, location, or accessibility of food outlets [5]. This is often expressed for a certain area—often the residential food environment (eg, supermarket or fast-food outlet availability within 1 km of the home address)—and how this fixed environment affects food choices [6] or health [7]. However, there are several limitations when studying only associations between the residential community food environment and food choices.

First, a person's food environment is not limited to the residential area [8,9]. People undertake several activities during the day (eg, going to work, shopping, and participating in recreational activities) that usually require them to travel beyond their residential area. The compilation of all visited places, and the trips in between, should therefore be the basis on which to define a person's daily food environmental exposure. This notion has been more frequently acknowledged in recent years, and researchers have used diverse spatiotemporal approaches and statistical methods assessing daily activity spaces to define the food environmental exposure [10-12]. Although such activity space–based food environments provide a more realistic picture of an individual's total exposure than the picture obtained by focusing only on what is available in the residential neighborhood, action spaces do not encompass the totality of people's accessible food environment [13]. Thus, the calculation of food environment exposure based on activity spaces ignores the food outlets that individuals potentially would have been able to visit because they were reachable within the time-space window available for food shopping at that point in time, but that were not on the individual's route. In addition, such calculations are affected by selective daily mobility bias. For example, when an activity (eg, going out to eat) influences both the place visited (eg, fast-food outlet) and the activity practiced (eg, eating fast food), the spatial access to environmental resources is calculated based on these intentionally visited places (which participants would not have been exposed to had they not intended to conduct the activity) [14]. Activity spaces do not account for this bias and therefore may result in overestimation of the association between the activity space–based fast-food environmental exposure and fast-food consumption.

Second, food environmental exposure is most often studied in association with dietary intake, and not with food purchases. However, food purchase behavior is conceptually more directly linked than dietary intake is to food environment exposure (although some products are directly consumed at the outlet where they are purchased), and including both eating and purchasing behavior will best enable an understanding of the link between the environment and obesity. So far, only a few studies have focused on food purchases in association with food environmental exposure [15-17].

Third, studies assessing the environment-diet relationship often ignore the perspective of time, defined as "time of the day" or "individual time perspectives." We do not yet understand the role of time in the environment-diet relationship. On the sociobehavioral level, time pressure is reported as a barrier to eating a healthy diet [18], influenced by demands such as employment or childcare responsibilities [19]. People's use of or susceptibility to the food environment may differ over the time of day. In addition, concepts from time geography [20], in particular space-time paths and space-time prisms, could play an important role in research on time constraints. A space-time path identifies stable daily routines, such as work, home, and leisure activities, in space and time. A space-time prism identifies the places that are within reach of a person within a given time window. Both concepts can be used in geographic information systems (GISs) to make time-dependent assessments [21] of both spatial food habits and alternative behavior under temporal constraints.

Fourth, the mechanisms through which the daily food environment affects food choices (ie, food purchases and consumption) are still unknown. Individual and contextual factors may interfere in the environment-diet relationship. For example, individuals under stress may have less control over food choices and are more susceptible to unhealthy food consumption [22,23].

Novel smart technologies for data collection allow the aforementioned limitations and gaps in the literature to be addressed and will improve the understanding of the role of day-to-day food environments in food choices. The FoodTrack study uses a specially developed smartphone app for its main measurements. It includes a novel interface to report food purchases and consumption, and incorporates such technologies as a global positioning system (GPS) and ecological momentary assessment (EMA).

Objectives

The FoodTrack study has four aims: to examine individual food environmental exposure in a fine-grained manner (aim 1), taking into account the accessible food environment and individual time constraints; to assess people's food choices (purchases and consumption) in relation to food environmental exposure (aims 2 and 3); and to examine the moderating role of individual and contextual determinants (eg, mood, companion, time of the day) of food purchases and consumption (aim 4).

Here, we present the protocol and study design of the FoodTrack study, and describe the smartphone app. We also discuss the participants' compliance with the study protocol and their experiences with the FoodTrack smartphone app.

Methods

Design and Setting

We used a smartphone app incorporating GPS tracking and EMA during a 7-day observational study to collect data from adults (25-45 years old) living in urban areas in the Netherlands. We set the minimum age at 25 years to exclude those undertaking full-time studies at an educational or training institute; as such, study participants were not representative of the country's population. The study did, however, include the majority of generation Y (millennials) and the youngest wave of generation X, whom we included in the study because we had hypothesized that during their daily lives, these people juggle many activities (eg, work, caregiving, leisure activities) that could interfere with health behaviors (such as food choices). The study was funded by the Netherlands Organization for Scientific Research and approved by the ethical committee of the Faculty of Social Sciences of Utrecht University, the Netherlands (FETC18-014).

Recruitment and Study Procedure

Between March and July 2018, we recruited participants via online platforms (eg, Facebook, news websites) and through advertisements in national and local newspapers. Additional interest in the study was generated through interviews with the involved researchers about the FoodTrack study broadcast by national and local radio stations. Adults who were willing to participate were invited to visit the FoodTrack website [24], where they could read more about the study, watch a short video clip about the study, or request more information via email, if needed. If they were interested, potential participants were asked to complete an online application form, which included questions related to the inclusion criteria. Those who met the inclusion criteria were invited to complete the online informed consent form and were then directed to the online baseline questionnaire (pretested on usability and technical functionality). Once they had completed it, they were sent an email confirming their initial participation and providing further details (eg, their log-in name and password, the start day of the research). The start day (Monday-Sunday) of the study was randomly assigned to each participant, so that data on fruit, vegetable, and snack consumption would be collected for both weekdays and weekends. Participants were sent a separate text message with a link to download the app, which was freely available from the App Store (Apple Inc, Cupertino, CA, USA) or Google Play (Google LLC, Mountain View, CA, USA). Once logged in, participants were asked to allow the app to access their location (thus allowing GPS tracking) and to receive push messages (ie, reminders). The study website provided an introductory video, as well as a video outlining the use and functionalities of the smartphone app. An online manual (in pdf format) explaining the use and functionalities of the app in more detail was also provided. Participants were able to contact the research team by calling or messaging us during the entire study period with any study-related questions or problems.

The smartphone app automatically collected GPS tracking data in the background. The participants used the app to upload information on all food purchases over the 7-day period and to answer EMA questions about contextual and individual purchase-related factors. These questions popped up whenever they uploaded data about a food purchase. Purchases were defined as food and drink products purchased for immediate consumption (eg, restaurant meals, snacks on the go), to be consumed later (eg, groceries, small packaged foods), or to also be consumed by others (eg, groceries for the entire household). In addition, during the final 3 days of the 7-day period, participants also collected data about the consumption of fruit, vegetables, and snacks (including fast foods) and answered EMA questions about contextual and individual consumption-related factors whenever they uploaded data about food they consumed. The participants were rewarded with an online non–food shopping voucher worth €30 (about US $33) if they completed all elements of the study. At the end of the 7-day period, they completed the online closing survey. The original questionnaires were in Dutch but we translated the responses into English for this paper.

Inclusion Criteria

People were eligible to participate in the FoodTrack study if they self-reported that they met the following criteria: (1) living in an urban area in the Netherlands, (2) aged between 25 and 45 years, (3) not being a full-time student, (4) possessing a smartphone (iOS or Android device), and (5) not having 1 or more of the following conditions: physical disability influencing daily mobility (eg, wheelchair); prescribed or medical diet (by a medical doctor or dietitian); gastric bypass; eating disorder; or taking medication affecting appetite.

The FoodTrack Smartphone App

Development

The FoodTrack smartphone app was developed for this study in collaboration with a commercial company, Locatienet [25]. It was based on an existing tracking app [26] with new elements—the registration tools for food purchases and consumption, and the EMA questions—built in. During the development phase, we pilot tested (n=20; unpublished data, 2017) and then further refined the app. For example, we added the ability to see an overview of the food purchases and consumptions already submitted. In addition, we added the time and date of purchase or consumption as an extra item to improve data quality, as well as a few extra answer options to improve the convenience of the app. The app's details and functionalities

are specified below. Multimedia Appendix 1 provides several screenshots.

Tracking Locations and Trips

The app ran in the background and used the smartphone's sensing capabilities (eg, GPS, accelerometer) to detect, record, and quantify the movements of participants, the trips they made, and the places they visited [26]. We will use these data to calculate individual places visited and purchases made within the living environment (aim 1).

The app's menu included a button labelled "see trips" that enabled participants to see the trips they had made and the locations they had visited during the day, including the date, time, and start and stop locations. They could also view each trip on a map by clicking on the trip concerned.

Tracking Food Purchases and Consumption

We asked the participants to upload their purchases as soon as possible after they had paid for them. They could either take a photo of the receipt listing the products bought along with their prices and their weights, or enter their purchases manually (product and amount purchased, eg, 1 kg of sugar; or predefined serving, eg, 1 candy bar, 35 g) by means of the integrated food database. This database was built upon the Web-based food diary Eetmeter of the Netherlands Nutrition Centre [27], which includes food products available in the food databank of the National Institute of Health and Environment and the Netherlands Nutrition Centre [28]. Although the databank includes many products, it does not include all products (ie, not all specific brands or types are present). Therefore, participants were instructed to enter the food product that most closely corresponded to what they ate if the specific product or brand type was not available (eg, when eating a Big Mac, they entered this as cheeseburger) and the number of items or the estimated serving size (in grams). Participants also recorded their consumption of fruit, vegetables, and snacks (including fast foods) by manually entering their consumption into the FoodTrack app. Participants were not asked to take photos of the food consumed.

After entering the types and amounts of food products they had purchased or consumed, the participants added information concerning when and where they had done so and answered short questions about the contextual and psychosocial determinants of the consumption, by means of the short EMA survey outlined below.

Ecological Momentary Assessment to Collect Contextual Factors of Food Purchases and Consumption

We integrated an EMA survey instrument into the smartphone app (using Survey Project [29]), allowing for the collection of data on food purchases, food consumption, and individual- or contextual-related food choice determinants (Multimedia Appendix 2). After participants had entered the food products purchased or consumed, short EMA questions concerning the following variables were provided.

Characteristics of the Purchase or Consumption

We assessed the type of purchase by asking whether the purchase was a "snack/drink" ("in between meals") or "a meal" or "groceries." We also asked participants whether the food purchase was for "themselves," "for others," or for "both themselves and others."

To determine the type of consumption, we asked participants whether they consumed fruit, vegetables, or snacks "in between meals" or "as part of a meal."

Participants selected from multiple response options to indicate whether their food purchase or consumption was spontaneous (impulsive), planned (a routine), or a combination of both.

Spatiotemporal Characteristics of the Purchase or Consumption

Participants reported information about the location of their purchase or consumption either immediately after the purchase or consumption by clicking on the "current location" button, or at a later point in time by entering the location data manually, although this was highly discouraged.

Participants selected from multiple response options (which included an open answer box) to indicate the type of food outlet or the location where they purchased or consumed the food.

Participants were asked to report the exact time and date of the food purchase or consumption. The current time and date were presented as the default.

Social Characteristics of the Purchase or Consumption

Participants selected from multiple response options (which included an open answer box) to indicate whether they had a companion or companions during the purchase or consumption event (eg, being alone, with family, with colleagues).

Participants selected from multiple response options (which included an open answer box) to indicate whether they were involved in an activity during the purchase or consumption event (eg, doing nothing else, shopping, working).

Individual Characteristics of the Food purchase or Consumption

Participants selected from multiple response options ("not at all," "a little," "somewhat," "very much") to indicate whether they felt "tired," "stressed," or "in a rush" during the purchase or consumption event.

Overview of the Food purchases or Consumption

On the app menu, participants could see either their registered food purchases or their registered food consumption. An overview of the registered products purchased or consumed was provided per day, including details concerning the type of purchase, type of outlet (eg, supermarket), location (address), and company (eg, family).

Reminders and Prompts

The day before the start of the study, participants received a push message saying (translated from Dutch) "Welcome to the study. Please register your food purchases as of tomorrow." During the morning of the fifth day, participants also received the push message "From today onward, please also register what you consume." During the rest of the study, participants received 2 reminders each day (at 2 PM and 8 PM), but only if

they had not registered any purchases or consumption ("Did you purchase something today? Please register it."). Participants were not able to customize the reminders.

In addition to the reminders sent automatically via the app, we sent preprogrammed reminder messages to keep participants engaged in the study and encourage them to ask questions if they had any difficulties with the data collection.

Settings

The app's settings menu enabled participants to verify whether the Wi-Fi, GPS, and mobile network were functioning properly and to consult the Frequently Asked Questions section concerning the app and the study (eg, "How do I register vegetables?" "What are 'snacks?"). Participants were also able to change their password via the settings and to use the menu to log out.

Measures

Online Baseline and Closing Survey

We used the online baseline survey to assess sociodemographic characteristics and weight status, and to briefly screen healthy (ie, fruit) and unhealthy (ie, savory snacks) food products. We also measured psychosocial variables associated with eating behavior.

The closing survey assessed several additional food choice-related questions. Multimedia Appendix 2 shows a detailed overview of the measures included in the baseline and the closing surveys and item examples.

Food Environment: Geographic Information System Measures

To assess food environmental exposure, we will link the GPS tracks measured by the app with the retail food outlet database maintained by Locatus [30]. This database contains retail information independently sourced via annual onsite surveys, including data on 27 types of food outlets (eg, supermarkets, fast-food outlets, greengroceries, bakeries, shops selling fresh and fried fish, and restaurants).

Process Evaluation of Experiences With the App and Participants' Compliance With the Study Protocol

We used 2 items to assess the app's general ease of use and likeability. We also assessed whether the participants had noticed the messages that were sent automatically by the app to remind them to register data on food purchases and consumption, and whether these had helped to improve compliance (2 items). With respect to entering food choices in the app, we also used 2 items to assess the completeness of the food product database and how easy it had been for the participants to estimate and enter the portion sizes of the products purchased or consumed, and how accurate they had been.

We used 4 items to assess the use and operability of the app. We assessed whether participants had allowed it to track them throughout the research period, whether they had explored the trips that the app had tracked automatically, and whether they considered these tracks accurate. We also assessed whether they had experienced a dead battery during the research period.

We used 5 items to assess whether the participants had entered all their groceries and other purchases (eg, snacks on the go), and their intake of fruits, vegetables, and snacks. If they had deliberately not done so, we assessed the reasons for this. We also asked the participants whether they had entered the products immediately after purchase or consumption (as requested) or at a later time. Finally, we assessed how easy it had been to answer the additional questions with respect to individual or contextual factors related to the food choice event, and how much effort doing so had required. Finally, the participants could use an open question to provide any comments they wanted with respect to the app or the overall study.

Data Analyses

In this paper, we provide insight into the descriptive statistics of the participants' compliance with the study protocol, and their experiences with and evaluation of the smartphone app and the study. To assess food environmental exposure in future studies, we will assess individual space-time paths using individual GPS tracks to extract home and other important locations. Subsequently, we will assess the individuals' accessible food environment, by extracting food events from GPS tracks and by computing corresponding space-time prisms using GISs to identify the location of food outlets that are within reach of a person. After assessing individual exposure, we will assess the association between individual food environmental exposure and food choices (purchases and consumption) using linear mixed-model analyses. We will assess effect modification by means of psychosocial variables (eg, "Is the association between environmental exposure and food purchases different for individuals who experience time pressure and those who do not?").

Results

Participant Characteristics

In total, we screened 648 people who expressed an interest in participating in the study. Of these, 304 (46.9%) met the inclusion criteria (n=344 did not, mainly because they were too young or too old, or were still studying). However, 70 of those who met the criteria did not provide their contact details (email, telephone number), and were therefore excluded from the study. We sent the remaining 234 potential participants a link to an online informed consent form; 152 signed the form and confirmed that they wished to participate. Of this latter group, 143 participants filled out the baseline survey and used the FoodTrack app; however, 3 of these participants did not complete the closing survey (Figure 1). Table 1 provides the sociodemographic characteristics of the 140 participants who completed the study. Of the 140 participants, 120 (85.7%) were women; the mean age was 33.8 (SD 6.36) years; 111 (79.8%) had attained a high educational level; 5 (3.6%) had a low educational level; 54 (38.6%) reported daily fruit intake; and 75 (53.6%) reported daily vegetable consumption.

Figure 1. Flowchart of the FoodTrack study. GPS: global positioning system.

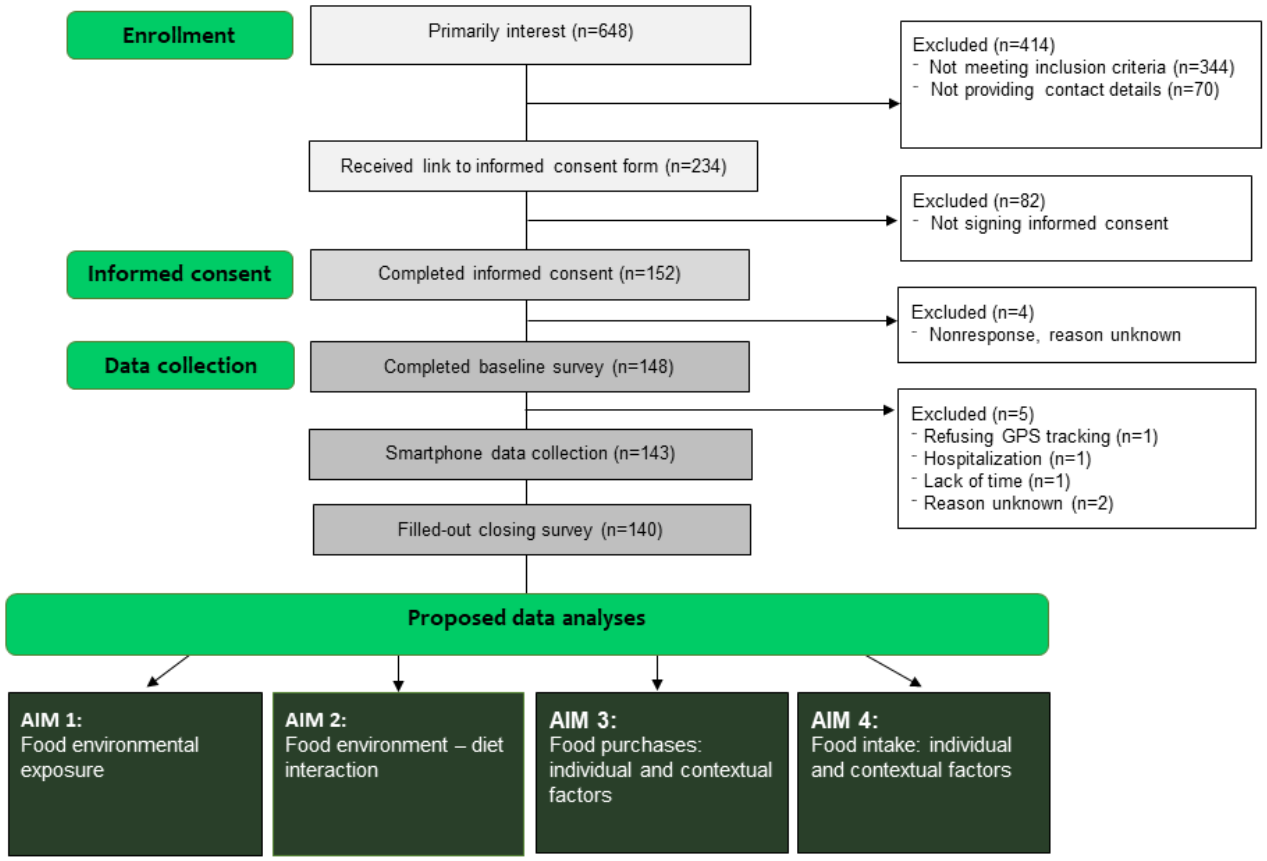

Table 1. Characteristics of the participants who completed the entire study (N=140).

Characteristics	Mean (SD) or n (%)
Age (years), mean (SD)	32.8 (6.4)
Female sex, n (%)	120 (85.7)
Dutch origin, n (%)	131 (93.6)
Marital status, n (%)	
Married or registered partnership	30 (21.5)
Unmarried	95 (67.9)
Divorced	5 (3.6)
Other	10 (7.1)
Household composition, n (%)	
2 adults, no children	44 (31.7)
2 adults, with 1 or more children	29 (20.8)
1 adult, with 1 or more children	6 (4.4)
Single adult	51 (36.7)
Living with others (parents, group)	6 (4.3)
Other	3 (2.1)
Educational level, n (%)	
Low	5 (3.6)
Middle	23 (16.6)
High	111 (79.8)
Household income, in euros/month, n (%)	
<1500	14 (10.0)
1500-2500	53 (37.9)
>2500-4500	36 (25.7)
>4500	25 (17.9)
Not stated	12 (8.6)
Food consumption behavior, n (%)	
Daily fruit consumption	54 (38.6)
Daily vegetable consumption	75 (53.6)
≤3 times/month sugar-sweetened beverage consumption	77 (55.0)
≤3 times/month small snack consumption	15 (10.7)
≤3 times/month large snack consumption	40 (28.6)

Participant Experience of the App

Table 2 provides a detailed overview of the operability and use of the smartphone app. More than half of the 140 participants said they liked the app (n=81, 57.9%) and found it easy to use (n=75, 53.6%). However, the majority of the participants reported, for example, that they could not enter a specific brand, taste (eg, elderflower lemonade), or type of product (green pepper). In addition, composite meals or products (eg, a salad from the salad bar, or ready-to-eat meals) were mentioned as not being available in the app. Of the 140 participants, 21 (15.5%) had experienced a dead battery during the data collection period. Of 106 participants who explored the trips, 17 (16.0%) did not track all trips and 3 (2.8%) did not track any trips, which led to incomplete GPS tracking data collection.

Table 2. Process evaluation outcomes of FoodTrack app use (N=140 participants).

Response	n (%)
Liked the app	
≤2 (negative)	14 (11.5)
3 (neutral)	43 (30.7)
≥4 (positive)	81 (57.8)
App was convenient to use (easy to use)	
≤2 (negative)	29 (20.7)
3 (neutral)	36 (25.7)
≥4 (positive)	75 (53.6)
Noticed the app reminders	
Yes	116 (82.9)
No	24 (17.1)
If noticed, reminders (n=116) evaluated as useful	
≤2 (not useful)	11 (9.5)
3 (neutral)	25 (21.6)
≥4 (useful)	80 (69.0)
Food database complete	
Yes, all products	56 (40.0)
No, not all products	84 (60.0)
Ease of estimating the amount (portion size) of the purchased or consumed food	
≤2 (not useful)	49 (35.0)
3 (neutral)	37 (26.4)
≥4 (useful)	44 (38.6)
Accuracy of participant's estimate of food portion	
≤2 (not accurate)	14 (10.0)
3 (neutral)	41 (29.3)
≥4 (accurate)	85 (60.7)
Allowed global positioning system for all days	
Yes	118 (84.3)
No	14 (10.0)
Don't know	8 (5.7)
Explored the trips	
Yes	106 (75.7)
No	34 (24.3)
If yes (n=106), the trips were accurate	
Yes, all	27 (25.5)
Yes, most	55 (51.9)
Yes, some	17 (16.0)
No, trips were not registered	3 (2.8)
Don't know	4 (3.8)
Experienced dead battery during day	
Yes	21 (15.0)
No	114 (81.4)

Response	n (%)
Don’t know	5 (3.6)

Participant Compliance

Table 3 provides a detailed overview of the participants’ compliance with the study protocol during the data collection period. Of the 140 participants, 126 (90.0%) reported that they had collected data on all or almost all purchases and intakes during the study period. The 14 (10.0%) participants who had deliberately not entered all products had various reasons for this, including “product is unhealthy” (n=3) and “too much effort/complicated” (n=4). Moreover, of the 140 participants, 50 (35.7%) had entered most or all of their food purchases and 56 (40.0%) had entered most or all of their consumption more than 15 minutes after the event, although we had explicitly encouraged them to enter the data within 15 minutes. The majority of the participants found the additional EMA questions “easy to answer” (n=113, 80.7%) with “no effort.” (n=99, 70.0%).

Of the 140 participants, 66 (47.1%) answered the open question. They mentioned, for example, not only that it had been “fun to participate” or it was a “nice study” (n=13), but also that they had experienced struggles during the study: “not all products were available in the database” (n=11), “trips were not registered” (n=7), it was not possible to navigate back and forth in the app (n=12), and the “app was slow” (n=16).

With respect to the entire study project, we are analyzing data concerning the first project aim and expect to publish the results in the spring of 2020. We plan to publish further papers providing insights into the additional aims in the next 2 years as well.

Table 3. Process evaluation outcomes of data collection using the FoodTrack app (N=140 participants).

Response	n (%)
Entered groceries	
Yes, all of my groceries	109 (77.9)
Yes, most of my groceries	17 (12.1)
Yes, a few groceries	5 (3.6)
No, I did not enter my groceries	3 (2.1)
No, but I did not do grocery shopping	6 (4.3)
Entered all other food purchases	
Yes, all of my other food purchases	98 (70.0)
Yes, most of my other food purchases	28 (20.0)
Yes, a few other food purchases	6 (4.3)
No, I did not enter my other food purchases	1 (0.7)
No, but I did not purchase any other food	7 (5.0)
Entered vegetables consumed	
Yes, all of the vegetables consumed	74 (52.9)
Yes, most of the vegetables consumed	34 (24.3)
Yes, some of the vegetables consumed	7 (5.0)
No, I did not enter the vegetables consumed	20 (14.3)
No, but I did not eat any vegetables	5 (3.6)
Entered fruits consumed	
Yes, all of the fruits consumed	99 (70.7)
Yes, most of the fruits consumed	19 (13.6)
Yes, some of the fruits consumed	3 (2.1)
No, I did not enter fruit consumed	9 (6.4)
No, but I did not eat any fruits	10 (7.1)
Entered snacks consumed	
Yes, all of the snacks consumed	87 (62.1)
Yes, most of the snacks consumed	34 (24.3)
Yes, some of the snacks consumed	7 (5.0)
No, I did not enter any snacks consumed	7 (5.0)
No, but I did not eat any snacks	5 (3.6)
Time of entering purchase in app	
All purchases entered immediately after purchase (<15 min)	13 (9.3)
Most purchases entered immediately after purchase (<15 min)	72 (51.4)
Most purchases entered at later point in time (>15 min)	38 (27.1)
All purchases entered at later point in time (>15 min)	12 (8.6)
Did not purchase anything	5 (3.6)
Time of entering consumption of snacks, fruit, or vegetables in app	
All foods consumed entered immediately after consumption (<15 min)	8 (5.7)
Most foods consumed entered immediately after consumption (<15 min)	72 (51.4)
Most foods consumed entered at later point in time (>15 min)	31 (22.1)
All foods consumed entered at later point in time (>15 min)	25 (17.9)
Did not consume snacks, fruit, or vegetables	4 (2.9)

Response	n (%)
Deliberately not entered a product	14 (10.0)
Reasons (of n=14) for not entering a product	
Product unhealthy	3 (21.4)
Too much effort, complicated	4 (28.8)
Product I normally do not buy or consume	1 (7.1)
Did not find the app user-friendly	1 (7.1)
Small intake, so negligible	1 (7.1)
No internet	1 (7.1)
Could not find the product (or alternative)	2 (14.3)
Product was for someone else	1 (7.1)
Ease or difficulty of answering the ecological momentary assessment questions	
<2 (negative) = difficult	9 (6.4)
3 (neutral) = neutral	18 (12.9)
>4 (positive) = easy	113 (80.7)
Effort to answer the ecological momentary assessment questions	
<2 (negative) = a lot of effort	19 (13.5)
3 (neutral) = neutral	23 (16.5)
>4 (positive) = no effort	99 (70.0)

Discussion

Principal Findings

This paper outlines the protocol of the FoodTrack study, as well as participants' compliance with the study protocol and their experiences during study participation. We collected data over a 7-day period by means of the FoodTrack app, which uses GPS tracking and EMA to assess real-time individual and contextual variables at the moment of purchase or intake. The GPS tracking will allow us to assess participant activity-travel patterns that in turn will allow us to assess individuals' daily food environmental exposure. The results of this study indicated that participants liked the app and found it easy to use. About 90% of the participants reported that they had collected data on all or almost all purchases and intakes during the 7-day period. However, not all participants complied with the study protocol that encouraged them to enter purchases or consumption right away. Nevertheless, the compliance figures of our study are in line with previous studies that used EMA in diet-related studies [31]. Qualitative insights resulting from the process evaluation also indicated that a minority of the participants encountered a few problems when using the app (eg, the app was too slow, not all products were present). We should carefully consider the likely implications of this when interpreting the results of the proposed studies. The outcomes of our process evaluation, however, provided us with information concerning which participants to include in, and which to exclude from, the proposed analyses. For example, we will exclude from the analyses participants who reported not collecting data on their grocery (n=3) or other purchases (n=1). Although this will decrease power, it will provide us with a more accurate estimation of food purchases in relation to food environmental exposure.

Lessons Learned

To the best of our knowledge, this is one of the first studies that measured not only food outlet exposure and food outlet choice, but also actual food choice behavior within these outlets, as well as related individual and contextual factors, using smartphone technology measurements. This will provide more detailed insights into the food environment-diet relationship. During several phases of our study (eg, development of the app, preparation of the data collection, the process evaluation), we learned some lessons that may help researchers in this field to improve their future studies.

First, the study and the FoodTrack app were designed and implemented by an interdisciplinary team of colleagues from public health and nutrition and from transport and urban geography backgrounds. This interdisciplinary approach provided us with the opportunity to use geostatistical programs to conduct the proposed analyses to assess food environmental exposure. We highly advise nutrition or health scientists (or scientists from similar fields) planning to conduct a similar study using GPS tracking to collaborate closely with GIS experts in the development of their study and especially when analyzing the collected GPS data.

Second, the development of the smartphone app took a considerable amount of time (eg, finding an affordable and reliable party to collaborate with, conducting the app design phases, improving app functionality). Those intending to develop such an app should reckon on a lengthy development process (of, for example, at least 6-12 months). Although we pilot tested

and refined the FoodTrack app in the development phase, some participants had trouble operating the app, especially concerning GPS tracking. Therefore, we will not be able to include all participants in some of the proposed analyses, as we lack their GPS data. Future studies can take account of this by recruiting participants with more advanced smartphones (eg, with better accelerometers) or by complementing smartphones with additional GPS trackers.

Third, despite our efforts to recruit a wide range of participants (eg, through using plain language in recruitment, being visible on social media, participating in interviews by local radio stations, and using audiovisual messages to recruit, such as video clips), the majority of participants were women and highly educated. This is not a representative sample of 25- to 45-year-old adults living in urban areas in the Netherlands [32]. Moreover, we requested that potential participants possess a smartphone, but in 2017, 9% of the adult population of the Netherlands did not own a smartphone [33], which could have led to selection bias. Although it is not the primary aim of the study, this makes it difficult to assess socioeconomic differences in the environment-diet association, due to small study samples. Researchers planning similar studies to assess socioeconomic inequalities in the environment-diet relationship should address this issue by employing recruitment strategies that appeal to a wider range of participants (eg, by recruiting participants face-to-face). Moreover, future studies could lend smartphones to participants who do not possess one.

Fourth, a small number of participants indicated that they had deliberately not entered their purchases or consumption, especially of vegetables. A likely explanation is that they found it difficult to enter vegetables as single products when they were components of a composite meal (eg, the tomatoes in spaghetti bolognaise). To improve compliance, future studies could optimize the app by allowing participants to take a photo of their food and simply describe the vegetables included in the product [34]. Future research using the FoodTrack app could improve it by optimizing GPS tracking, allowing customized settings (eg, prompts), or integrating additional strategies (eg, gamification strategies [35]) to improve usage.

Strengths and Limitations

An important strength of the FoodTrack study is that we will be able to link collected GPS data and individual sourced data to GIS data on food outlet locations, in order to estimate individuals' daily food environment exposure. A limitation of the FoodTrack study is that we relied on self-reported data regarding food purchases and consumption (and psychosocial and contextual variables). In addition, only 3 days of data on fruit, vegetable, and snack consumption were collected, precluding an insight into weekly consumption habits. As emphasized by previous research on dietary assessments [36], and confirmed by our process evaluation, it is clear that the collected data on food purchases and consumption should be included in the analyses in a rather qualitative way (eg, number of items purchased), rather than trying to assess, for example, the exact amount purchased or consumed or the daily nutrients obtained. The process evaluation has provided us with insight into participants' use of the app during the data collection period. For example, some participants did not collect data on their food purchases or consumption during their participation. Although we still rely on self-reported insights, these data will help us to select participants who did comply with the study protocol.

Conclusion

This study protocol provides insights into the design of the FoodTrack study and its procedures. It also provides detailed insights into the practical and operational issues involved in performing the study, including the participants' use of and experience with the FoodTrack app. The FoodTrack study will add to our understanding of the role of day-to-day food environments and contextual factors in food choices, and will provide novel insights into individual food environmental exposure, innovative evidence on food environment-diet relations, and insights into the interplay with the individual and contextual mechanisms involved in food purchases and consumption.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Screenshots of the FoodTrack app.
[PNG File , 133 KB - resprot_v9i1e15283_app1.png]

Multimedia Appendix 2
Overview of the baseline and closing surveys of the FoodTrack study.
[DOCX File , 33 KB - resprot_v9i1e15283_app2.docx]

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Abbreviations

EMA: ecological momentary assessment
GIS: geographic information system
GPS: global positioning system

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Protocol

An Electronic Health Platform for Monitoring Health Conditions of Patients With Hypertension in the Brazilian Public Health System: Protocol for a Nonrandomized Controlled Trial

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Abstract

Background: Chronic noncommunicable diseases such as arterial hypertension have a high impact in the context of public health. Previous studies have shown improvements in blood pressure due to simple lifestyle changes, which were supported by electronic health (eHealth) solutions.

Objective: The aim of this study is to develop an eHealth platform and assess the effects of its use on the health conditions of patients with hypertension, with assistance from health professionals in the public health system of a Brazilian city.

Methods: The platform will include a server that centralizes all the data and business rules, a website dashboard for health professionals, and a mobile app for patients. We will analyze the effects of its use through a controlled, nonrandomized, nonblind, prospective, monocentric clinical trial. We will enroll 68 participants diagnosed with arterial hypertension and under medical follow-up and categorize them into two groups. The participants of the intervention group will use the platform as a monitoring method, whereas the participants of the control group will use conventional methods. In both groups, we will assess and compare the evolution of blood pressure and treatment adherence before, during, and after the intervention.

Results: The project was funded at the end of 2018. We have been developing the software since 2019 with plans to complete it in 2020, and we will enroll patients between 2020 and 2021. We expect to submit the first results for publication in 2020.

Conclusions: For the primary outcome, we expect a reduction and stabilization of blood pressure. For the secondary outcomes, we hope to see improvements in treatment adherence, physical activities and dietary practices, and acceptance of the eHealth

platform. In public health, the technology that favors disease control also helps reduce complications and, consequently, treatment costs. The platform might encourage the adaptation of medical assistance to incorporate this technology into patient monitoring.

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KEYWORDS

hypertension; eHealth; mHealth; public health; Brazil

Introduction

Background

Chronic noncommunicable diseases such as arterial hypertension are responsible for a high frequency of hospitalizations and have a great socioeconomic impact [1]. In Brazil, the direct and indirect costs of these diseases have been increasing significantly [2]. Currently, 32% of the Brazilian adult population, which corresponds to 36 million individuals, has hypertension [3]. However, only about half of the patients under treatment for hypertension report that their blood pressure is within the recommended levels [3,4]. As hypertension is a chronic condition, the best approaches for a healthy life are the awareness, treatment, and management of the disease.

With this perspective, the Brazilian Ministry of Health developed a system called Brazilian Clinical Management System of Arterial Hypertension and Diabetes Mellitus (SIS-Hiperdia) for registering and monitoring patients with arterial hypertension and diabetes mellitus, with assistance from the health professionals in the outpatient clinics of the Brazilian public health network. However, patients' data are required for continued working of this system, and it is not feasible to obtain this information if patients do not have a history of their health conditions available [5]. Moreover, a strategy developed for use only in clinical centers may not be enough to treat the disease and change habits. Developing and using complementary tools is necessary for both physicians and patients [6]. Therefore, the electronic health (eHealth) systems have been attracting an increasing number of users because of the diffusion of mobile devices and the growing interest in better quality of life and health care [7]. The World Health Organization [8] announced that eHealth solutions might transform the resources of health services worldwide. Most regions in the world, including low- and medium-income countries, are working actively on eHealth projects [8], including Brazil.

Previous studies have shown positive results in the improvement of blood pressure from simple lifestyle changes supported by eHealth solutions [9]. The results by Toro-Ramos et al [10] indicated a decrease in diastolic pressure and body weight of the 73 participants. In the study by Ashoorkhani et al [11], tests for 132 patients with hypertension showed an improvement in treatment adherence, weight control, and regular blood pressure verification. The study by Albini et al [12] with 690 hypertensive patients suggests that information and communication technology tools may be effective in providing physicians with dynamic patient control and in improving the monitoring of hypertension and adherence to treatment prescriptions.

In the studies mentioned above [10-12], periodic verification was essential for obtaining favorable results. However, a prominent challenge in the market of mobile apps is maintaining long-term or recurrent use of the app among users engaged with the app, without loss of interest. Among the leading causes of abandonment from the users of these apps are quitting after achieving goals and the lack of resources available [13]. Several techniques have been used to allow greater user engagement with the app, such as gamification, which comprises applying gaming elements to a nongaming context [14].

Prior Work

We have devised a platform for monitoring the health conditions of patients with arterial hypertension. We implemented an initial version, considered a prototype, and made it available to use for initial validations. The platform includes a server that centralizes the data for a website interface [15] that is designed for health professionals, and a mobile app with gamification elements [16] that is designed for patients.

We performed pilot studies with health professionals and patients to assess the prototype functionalities [15] and patient engagement and experience with the app [16-18], respectively. The assessment with health professionals showed some benefits of using the system, such as the optimal visualization of patients' logbooks. Patient assessments showed that gamification favors engagement with health treatment. We also found that participants under follow-up with a health professional interacted more with the app and were more motivated to maintain their health monitoring. Therefore, the use of digital health resources by professionals, along with patients, may promote a higher commitment to monitoring the treatment factors [17]. To verify the clinical effects, we have already conducted a pilot trial [19], including 39 patients with arterial hypertension, to compare the use of the platform's initial version with conventional hypertension monitoring over a period of 3 months. The patients who used the mobile health app had a change in systolic and diastolic pressure toward more adequate levels. In addition, the group had improved levels of glucose and high-density lipoprotein cholesterol and a reduced consumption of ultraprocessed foods.

The main goal of our project is to assess the effects of using the eHealth platform—which will be developed—on health conditions of patients with hypertension, with assistance from health professionals in the public health system.

Methods

Notice MS-SCTIE-Decit CNPq 12/2018: Research on Health Innovation

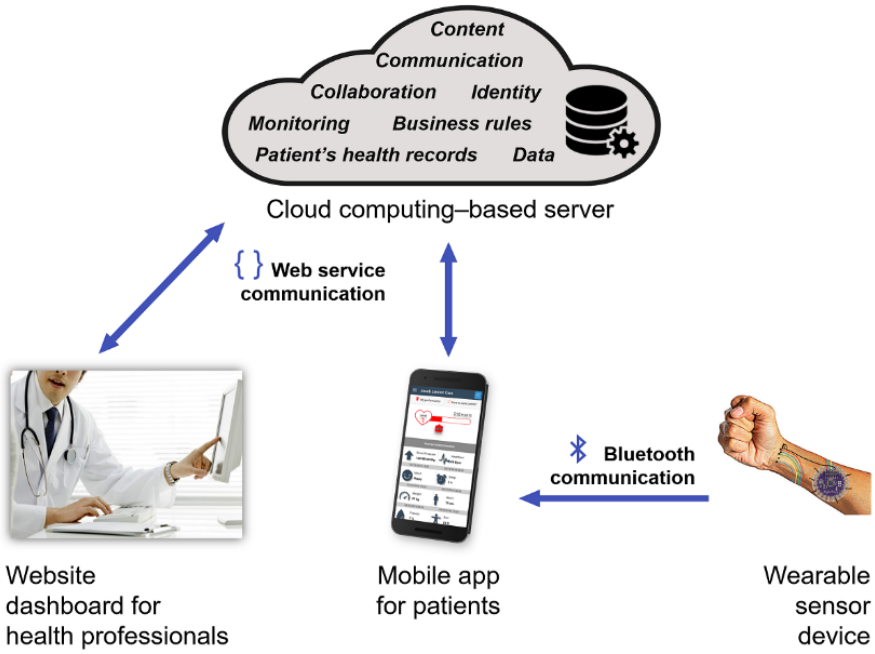
Our eHealth platform potentially favors the public health system by allowing the monitoring of health conditions of patients with hypertension, assessing risk, and supporting behavior changes. However, as it is an initial version, the software still requires improvement and the development of other functionalities and resources. The new characteristics predicted include a nutritional assessment model, a recommendation system, and the integration with wearable devices equipped with physiological sensors to automate data collection.

After a strict selection process of Notice MS-SCTIE-Decit CNPq 12/2018, the Brazilian Ministry of Health and the Brazilian Counsel of Technological and Scientific Development granted our project with research funding. Considering the potential for health innovation, they selected our eHealth platform for full development and testing in the Brazilian public health system.

Software Specification

The eHealth platform (Figure 1) is a solution that aims to monitor patients with hypertension by integrating risk assessment and counseling for healthy habit changes. This occurs with a joint action among resources for registering health conditions and receiving notifications, reminders, and follow-up from health professionals. The platform includes a server that centralizes all data and business rules; a website dashboard for health professionals; and a mobile app for patients, which is integrated with a wearable device. The Brazilian Institute of Industrial Property granted us the registration of the first versions of the website dashboard and the mobile app (documents BR5120170007616 and BR5120180009735, respectively).

Figure 1. Computing architecture of the electronic health platform.



Website Dashboard

We designed the dashboard for health professionals, so that they could follow-up and monitor patients in real time. The professionals have access to patient information, and they may assess risks and advise patients remotely. In addition, the dashboard has an interface for the administrator to control business rules and data processing, with settings related to the frequency of alerts, monitoring the schedule of patient reminders, user access control, clinical guide parameters (eg, blood pressure, body fat, and body mass index), and messaging, among others.

After registration and access, the system forwards the professional to the functionalities of messages and alerts on patient measurements. To start the monitoring of a patient, professionals need to link the patient profile to their account. After patient authorization, the professional will have access to the patient's logbook of blood pressure, heartbeat, weight, mood, waist circumference, body fat, sleep, physical activity, schedule, and dietary intake assessment. The platform can display all the data in graphic, interactive, and associated views.

More than one health professional may assist the patient, for instance, a cardiologist, a dietitian, and a psychologist. Thus, each professional may choose the information they wish to supervise according to each patient and the patient's specific treatment. When selecting an item, the professionals proceed to a screen containing detailed information of the patient's history to select what period they want to visualize. They may also view the reminders included by the patient, enter new reminders, and communicate with the patient through a private chat.

The study by Veiga [15] presented all the details of the functional prototype. The dashboard prototype will be the basis

for the full development of the new version, which will also include new functionalities such as modules for nutritional assessment and recommendation of physical exercises and dietary habits for each patient profile, as developed by Ferreto [20].

Mobile App

The app allows users to record their data, send and receive notifications, communicate with their medical team, and pair the wearable device that will be developed. After installation and first registration, the patient can access the main interface containing his or her last measurements. Through the main interface, users can access the menu with the list of functionalities available, which include height, physical activity, heartbeat, waist, body fat, mood, weight, blood pressure, sleep, reminders, and chat. In the new version, other records will be available, including dietary intake and improvement of physical activity data. When selecting a functionality, patients can view their record information and graphs, and they may include, change, or delete data.

For the measurements, the patient records the date, time, value, and an optional observation. All operations with patient data synchronize with the central server. Periodically, the app displays alert notifications and reminders on the health data recorded, including notes sent by the health professional. Each notification presents a title, a brief description, and buttons with *yes* and *no* options. When clicking *yes*, the system sends the information to the server, showing whether the patient completed the action or reminder presented, for instance, whether they took the medication or visualized the message from the health professional. Such integration aims at continuous monitoring and the stimulus to maintain healthy practices.

We designed all functionalities of the app to engage patients with a regular health follow-up. In addition to the gamification elements, they also receive reminders and notifications on their health and interact with health professionals. The app has a functionality responsible for notifying the patient and the professional about health evolution through counseling based on clinical guidelines. At each insertion of patient data, the system analyzes the information according to the guidelines and issues an alert notification if the measurement is identified as different from the standard patterns. On the basis of these notifications, the patient may analyze and decide what to do next, including using the messaging functionality to contact the health professional for assistance. This integration does not replace personal visits, but it provides both the patient and professional with a fast and accessible communication tool for doubt resolution and guidance. All the records create a lifestyle logbook of the patient under monitoring, which may represent a source of information for the decision-making process of professionals.

The study by Cechetti et al [17] presented all the details of the functional prototype. The app prototype will be the basis for the full development of the new version, which will also include new functionalities corresponding to the ones predicted for the website dashboard.

Wearable Sensor Device

We will build a device equipped with modules of physiological sensors available in the market, such as oximeter and pedometer, compatible with the LilyPad Arduino—a mini-controller board designed for wearables and intelligent textiles. The device will have a communication routine with the mobile app through the Bluetooth protocol to automate the measurement records.

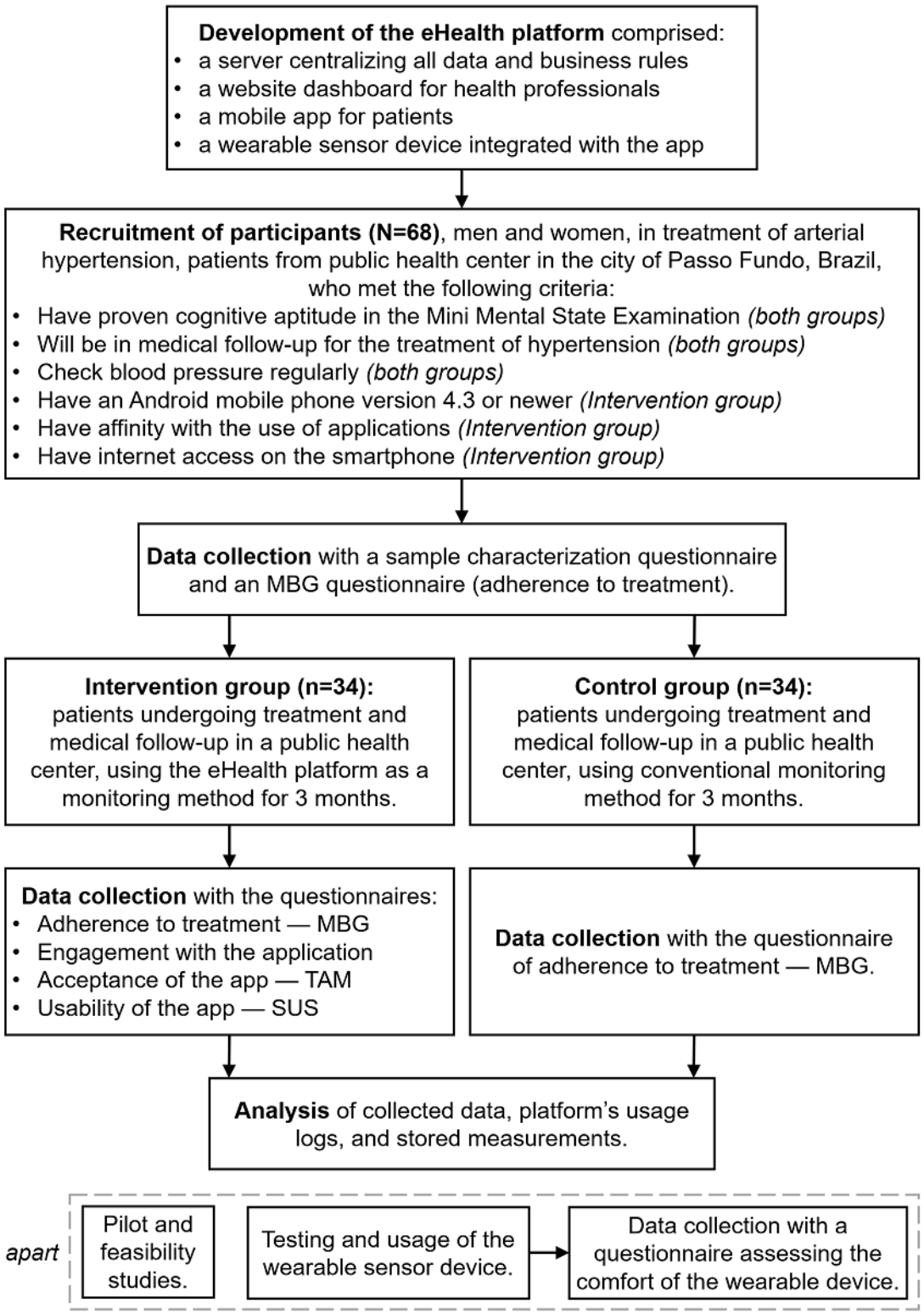
First, we will assess the use of the wearable device in a group of 10 individuals. We will connect the device to a piece of clothing (eg, T-shirt, wristband, and glove) worn by the participant to monitor the physiological signs during daily activities such as walking, lying down, and nonexhaustive work. On the basis of a study by Zhou et al [21], we prepared a questionnaire to assess the level of comfort while using the device. If we detect any nuisance in the comfort assessment, we will adjust the device to suppress such discomfort.

We will perform technical trials to test the correct functioning of the equipment and wireless communication assessments with performance measures (eg, response time, package traffic, and latency) and the request acknowledgment and checksum. We will also evaluate the behavior of electronic components attached to the hardware modules to ensure the reliability and accuracy of the collected data. For this validation, we will compare values obtained by the sensors with values recorded by reliable conventional devices used by health professionals, such as sphygmomanometer, heart monitor, and pulse oximeter. We will perform all assessments of the wearable sensor device separately in substudies, which will not be a part of the main clinical trial.

Nonrandomized Controlled Trial

This is an applied research of technological innovation with software development and analysis of its effects through a controlled, nonrandomized, nonblind, prospective, and monocentric clinical trial. The Research Ethics Committee of the University of Passo Fundo, Rio Grande do Sul, Brazil (report 3.414.793) approved this project, which was registered in the Brazilian Platform of Clinical Trials under the code RBR-2rkkgn (Universal Trial Number U1111-1230-7550). Figure 2 presents the trial design and flowchart.

Figure 2. Trial procedure flowchart. eHealth: electronic health; MBG: Martín-Bayarre-Grau; SUS: System Usability Scale; TAM: technology acceptance model.



Study Population and Sample

The study population will include men and women under treatment for arterial hypertension who will be assisted by health professionals in the public health system of a Brazilian city. After the invitation to take part in the study, the participants will sign a consent form. The effect (primary outcome) is expected to be 80% in the intervention group and 40% in the control group, which means a 40% difference. These proportions are based on the findings of the study by Neumann et al [22], which was conducted with a similar design, and also on more optimistic results obtained from one of our pilots [19]. For sample calculation, we used Epi Info version 6.0 software (Centers for Disease Control and Prevention, Atlanta, Georgia; sample size/2 proportions). We considered an estimate of 40% proportion difference between groups, 95% confidence interval,

and 80% statistical power (beta). The calculation resulted in 28 individuals for each group, but to minimize the effects of loss and refusal during the intervention, we added 20% to the size, yielding a total of 34 individuals in each group.

The allocation of patients in each group will be based on the eligibility criteria. For example, if the patient fits all the criteria but does not have a mobile phone compatible with the app, then he or she will be allocated to the control group. If the patient has a mobile phone compatible with the app, he or she will be allocated to the intervention group. For propensity score calculation, based on the effect of confounding factors or predictors of exposure (to intervention), we will consider demographic variables of age, gender, and socioeconomic status.

We will consider the following inclusion criteria:

- Cognitive ability confirmed by the Mini-Mental State Examination [23] (both groups)
- Current medical monitoring for the treatment of hypertension in the public health system of the city of Passo Fundo, RS, Brazil (both groups)
- Possibility to measure blood pressure in drugstores, hospitals, Family Health Strategies, or centers for comprehensive health care (both groups)
- Possession of an Android mobile phone, version 4.3 or higher (intervention group)
- Familiarity with the use of apps (intervention group)
- Internet access on the smartphone (intervention group).

Evaluation and Assessment Frameworks

We will use the following assessment instruments:

- Mini-Mental State Examination: It verifies the integrity of cognitive functions, assessing the functions of space-time orientation, memory, attention, calculus, language, and constructive praxis. It includes 11 tasks, with a score ranging from 0 to 30 points. Brucki et al [23] adapted it to the Brazilian context. The cut-off points relate to the years of schooling of the subjects, ie, for illiterate individuals, 19 points; 1-3 years of schooling, 23 points; 4-7 years of schooling, 24 points; and more than 7 years of schooling, 28 points.
- Sample characterization and sociodemographic questionnaire: It includes questions on age, level of education, income, and experience in using a blood pressure meter. The project researchers will provide the specifications.
- Martín-Bayarre-Grau questionnaire (MBG): It assesses the therapeutic adherence for arterial hypertension. Alfonso et al [24] developed and validated this instrument, and Matta et al [25] adapted it to the Brazilian Portuguese language.
- Dietary intake questionnaire by the Brazilian Food and Nutrition Surveillance System (SISVAN): from the Brazilian Ministry of Health [26], this questionnaire identifies the intake frequency of some foods and beverages over the last 7 days through 10 questions. Each item may relate to healthy food or nonrecommended unhealthy food.
- Engagement questionnaire: It assesses the attributes of engagement, such as esthetics, sensory appeal, concentration, awareness, challenge, control, feedback, interest, motivation, novelty, and time perception. O'Brien and Toms [27] proposed and validated the model, and Cechetti et al [17] translated it to Portuguese.
- Acceptance questionnaire: This is based on the technology acceptance model (TAM) [28]. The assessment relies on three categories: perceived utility (determines the degree to which a person believes the use of a technology may improve performance and productivity), ease of use (determines the degree to which a person believes the use of a system will be easy to learn and interact with), and external variables (provide understanding about what influences perceived utility and ease of use).
- Usability assessment questionnaire: This is in accordance with the System Usability Scale (SUS), related to the ease of use and use effort. Brooke [29] developed this framework.
- Comfort assessment questionnaire for the wearable device: It aims to verify the comfort and well-being of users while trying the wearable technology. The project researchers will produce this instrument.
- Characteristics of app use: It considers the number of accesses, number of records per period, response to notifications, and reminders. The system usage logs will calculate all this information. We will also use open questions so that participants can report their experience.
- Health professional assessment: We will perform a semistructured interview with health professionals to verify opinions on the characteristics and resources of the eHealth platform. Questions include, but are not limited to the following: (1) As a health professional, do you believe that the app and dashboard's features can facilitate the clinical practice to monitor a patient? In what way? (2) Do you believe that a patient can benefit from the app's features in his or her treatment? In what way? (3) What changes do you suggest for this platform to make it more useful or applicable to clinical practice?

Procedure

We will collect data at three timepoints: preintervention, during the intervention, and postintervention. We will develop the wearable device and assess it in parallel outside the clinical trial.

Preintervention Period

After verifying the inclusion criteria, all participants will have a 1-hour meeting with the researchers for instructions on the objective of the study and for signing a consent form detailing all the study procedures. We will register the participants of the intervention group in the system and instruct them about the app's use. We will collect the preintervention data from both groups from a sample characterization questionnaire and an MBG questionnaire [24].

Intervention Period

Participants from the control group will perform conventional hypertension monitoring using paper logbooks. Participants from the intervention group will use the app for 3 months, periodically registering the values of blood pressure, weight, height, sleep quality, waist circumference, mood, and heartbeats,

among others. Health professionals from the health centers will assist the participants by using the website dashboard to monitor and interact with their patients. Professionals' performance will not be evaluated, but we will ask them to participate by communicating with patients weekly on the platform. We will use all the data recorded by patients and health professionals during the intervention in the final analysis of results, especially the measurements of blood pressure and frequency of physical activity.

Postintervention Period

All participants will have a 1-hour meeting with the researchers for the final data collection. We will collect the postintervention data with an MBG questionnaire [24], an engagement questionnaire [27], an acceptance questionnaire (TAM) [28], and a usability questionnaire (SUS) [29].

Statistical and Qualitative Analysis

Our expectation for the primary outcome is the reduction and stabilization of blood pressure. For the secondary outcome, we hope for acceptance of the eHealth platform and improvements in treatment adherence, physical activities, and dietary intake. A priori levels will be set according to the assessment tool and the expected outcome. The acceptance of the eHealth platform will consider good scores obtained in the analysis of usage logs and questionnaires of engagement, SUS, and TAM. Improved adherence to treatment will consider MBG questionnaire scores measured before and after the intervention. For the analysis of physical activities and dietary intake, a binary outcome will consider whether the patient has adequate levels, diagnosed according to the SISVAN's questionnaire and standards.

For qualitative data, we will use Minayo's guidelines [30]. Numeric data will be analyzed with statistical software SPSS 22 (IBM Corp, Armonk, New York). We will calculate the measures of central tendency and dispersion of the quantitative variables, and we will use the Kolmogorov-Smirnov test to verify normality. Basic quantitative data will be determined by mean, standard deviation, and median. Categorical data will be determined by simple frequency. Blood pressure data will be analyzed with the paired *t* test. Either the paired *t* test (parametric) or the Wilcoxon test (nonparametric) may be applied to compare other quantitative variables before and after the intervention. To assess treatment adherence, physical activity, and dietary intake after intervention, we will apply the Chi-square test while considering the app use as the dependent variable; the independent variables will be treatment adherence, physical activity, and dietary intake. For the MBG questionnaire, we will apply the Mann-Whitney test to compare the score between the groups before and after the intervention. The same test may be used to compare diastolic and systolic blood pressure measurements between the preintervention and postintervention groups. We will consider a 95% confidence interval (P<.05).

To evaluate the findings' heterogeneity (primary and secondary outcomes), we will apply a statistical technique to verify whether the differences observed in the results can be explained by chance. We will apply the Chi-square test with a significance level of P<.10. The magnitude of heterogeneity will be assessed by calculating the I^2 value, which ranges from 0% to 100%. An I^2 greater than 50% indicates substantial heterogeneity, and an I^2 above 75% indicates considerable heterogeneity. For the evaluation of heterogeneity, we will consider the demographic and socioeconomic variables. In the presence of heterogeneity, we will investigate its causes through sensitivity analysis. In the sensitivity analysis, the form of data analysis varies, to identify the impact of this change on the results. All analysis techniques can be adjusted or modified, if required, by the characteristics of the collected data. If feasible, we also intend to analyze the results with logistic regression of preintervention and postintervention data. In this case, the dependent variable will consider the base category *whether* [user] *used the app*, related to independent, categorized, and continuous variables of interest such as sociodemographic variables and the expected secondary outcomes.

Results

The project was funded at the end of 2018. We will develop the software between 2019 and 2020, and we will enroll patients between 2020 and 2021. We expect to submit the first results for publication in 2020. As the final technological product, we will offer an innovative and technological eHealth platform to the public sector. The transfer of technology from the academic environment to the public sector is a strategy to invigorate efforts and enable improved health conditions to the population.

Discussion

The expected results may contribute to improving the quality of life of patients with arterial hypertension. Using eHealth technology will allow a better understanding of the importance of permanent health care. Furthermore, it will provide encouragement for health monitoring and risk assessment, favoring behavior changes toward healthier habits [31-33]. In public and primary health, the technology that favors disease control also helps reduce complications and, consequently, treatment costs [34,35]. The eHealth platform encourages the adaptation of medical assistance to facilitate the incorporation of technology into patient monitoring, especially for those living in rural areas or regions of difficult access [36,37]. Nevertheless, introducing the use of technology may simplify health information records and communication between patients and professionals [38]. The health database created may further benefit and integrate Brazilian systems such as the SIS-Hiperdia.

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authors are solely responsible for designing and performing this study and all its analyses, for drafting and editing the manuscript, and for the final contents.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-EHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 2316 KB - resprot_v9i1e15299_app1.pdf]

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Abbreviations

eHealth: electronic health
MBG: Martín-Bayarre-Grau
SIS-Hiperdia: Brazilian Clinical Management System of Arterial Hypertension and Diabetes Mellitus
SISVAN: Dietary intake questionnaire by the Brazilian Food and Nutrition Surveillance System
SUS: System Usability Scale
TAM: technology acceptance model

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Protocol

A Pain eHealth Platform for Engaging Obese, Older Adults with Chronic Low Back Pain in Nonpharmacological Pain Treatments: Protocol for a Pilot Feasibility Study

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Abstract

Background: Low back pain is a costly healthcare problem and the leading cause of disability among adults in the United States. Primary care providers urgently need effective ways to deliver evidence-based, nonpharmacological therapies for chronic low back pain. Guidelines published by several government and national organizations have recommended nonpharmacological and nonopioid pharmacological therapies for low back pain.

Objective: The Pain eHealth Platform (PEP) pilot trial aims to test the feasibility of a highly innovative intervention that (1) uses an electronic health record (EHR) query to systematically identify a phenotype of obese, older adults with chronic low back pain who may benefit from Web-based behavioral treatments; (2) delivers highly tailored messages to eligible older adults with chronic low back pain via the patient portal; (3) links affected patients to a Web app that provides education on the efficacy of evidence-based, nonpharmacological, behavioral pain treatments; and (4) directs patients to existing Web-based health treatment tools.

Methods: Using a three-step modified Delphi method, an expert panel of primary care providers will define a low back pain phenotype for an EHR query. Using the defined low back pain phenotype, an EHR query will be created to identify patients who may benefit from the PEP. Up to 15 patients with low back pain will be interviewed to refine the tailored messaging, esthetics, and content of the patient-facing Web app within the PEP. Up to 10 primary care providers will be interviewed to better understand the facilitators and barriers to implementing the PEP, given their clinic workflow. We will assess the feasibility of the PEP in a single-arm pragmatic pilot study in which secure patient portal invitations containing a hyperlink to the PEP Web app are sent to 1000 patients. The primary outcome of the study is usability as measured by the System Usability Scale.

Results: Qualitative interviews with primary care providers were completed in April 2019. Qualitative interviews with patients will begin in December 2019.

Conclusions: The PEP will leverage informatics and the patient portal to deliver evidence-based nonpharmacological treatment information to adults with chronic low back pain. Results from this study may help inform the development of Web-based health platforms for other pain and chronic health conditions.

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KEYWORDS

chronic pain; patient portal; Web-based treatments; electronic health records

Introduction

Low back pain is the leading cause of disability worldwide and its prevalence increases with age [1]. The most commonly prescribed drug class for low back pain is opioids [2]. Prescription opioid use has numerous drawbacks with regard to the quality of life and has become a threat to public health. An estimated 17,029 people (5.2 per 100,000 people) died from prescription opioid overdoses in 2017 [3]. This is a particularly pressing concern for older adults due to the increasing incidence of prescription opioid misuse among members of this group [4,5]. Obese, older adults are significantly more likely to have chronic low back pain compared to their normal weight counterparts [6]. Obesity contributes to a higher frequency of intractable pain episodes [7], the use of stronger opioid medications compared to normal-weight adults with chronic pain [7], and increased pain severity [8].

Primary care providers (PCPs) are typically the first clinicians to see patients with pain and treat approximately 52% of patients with chronic pain [9]. Chronic pain is recognized as pain that persists past the normal healing time of 3 months [10]. Despite limited evidence to support their use, opioids are still prescribed in over 30% of primary care visits for chronic pain [11]. The American College of Physicians and the Centers for Disease Control has released guidelines for PCPs, which recommend nonpharmacological and nonopioid pharmacological therapies as the preferred initial treatments for chronic, noncancer pain [12,13]. However, older adults undergoing analgesic drug treatments for pain are more susceptible to the side effects caused by multiple comorbidities, age-related physiological changes, and altered pharmacokinetics and pharmacodynamics of analgesic drugs [14]. With recent efforts to increase legislation limiting opioid medications in many states [15,16], PCPs urgently need effective, evidence-based, nonpharmacological approaches for the management of chronic low back pain in adults.

There is a growing body of evidence showing that nonpharmacological behavioral treatment programs, which promote self-management techniques (like mindfulness meditation [17] and increasing physical activity [18]), are effective treatments for chronic pain. However, the traditional delivery of behavioral treatments relies on time-intensive, in-person sessions with a trained expert. This is a care model associated with numerous access-to-care barriers including time constraints, transportation, and cost [19].

Healthcare systems are tasked with the challenge of how to best implement evolving evidence-based guidelines for treating chronic health conditions like low back pain. The rapidly increasing use of the internet by older patients [20] and the growing presence of patient portals offer expanding opportunities to deliver Web-based behavioral treatments for pain [21]. Web-based portals allow patients to access their personal health information such as laboratory results, upcoming appointments, and medication information. Additionally, patients can use portals for bidirectional communication with their PCPs about their health status and treatments. To receive the maximum payment from Medicare, the Centers for Medicare & Medicaid Services electronic health record (EHR) Incentive Programs apply “meaningful use” criteria that requires PCPs to demonstrate that at least 5% of their patients use Web-based portals, strongly incentivizing healthcare systems to adopt and implement this technology [22,23]. A total of 48% of patients (n=50,190) between the ages of 50-79, seen at least once by a Wake Forest Baptist Health (WFBH) PCP during the 2018 calendar year, have a patient portal account.

Older adult-specific, Web-based treatment tools are quickly becoming commonplace [24-27]. Web-based behavioral treatments for pain have demonstrated efficacy [21] and are well positioned to address treatment barriers such as transportation, cost, time constraints, knowledge of existing Web-based health resources, and both patient and provider access to these resources. To this end, we are developing an innovative Pain eHealth Platform (PEP) that leverages clinical informatics and a patient portal to deliver evidence-based, nonpharmacological treatment information that builds patient knowledge of various behavioral pain treatments and directs patients to existing Web-based health treatment tools.

Methods

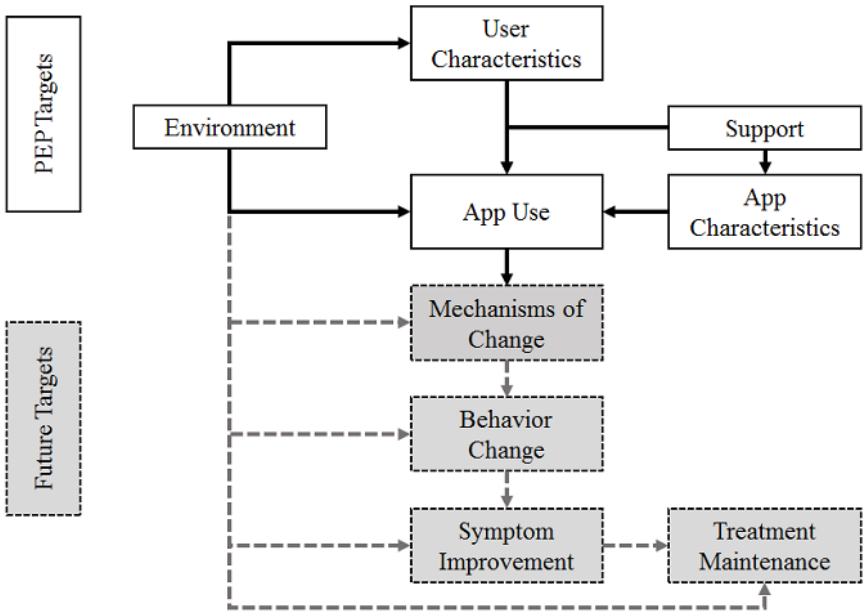
Overview

The form and function of the PEP will be developed in a systematic, patient-centered fashion. The conceptual model for the development of PEP and a description of the three-part PEP study is presented below. The study protocol was reviewed and approved by the Wake Forest School of Medicine Institutional Review Board (IRB00049293) in April 2018.

Conceptual Model

The study is guided by social cognitive theory [28] and the Ritterband model [29] for digital interventions (Figure 1). As noted by Bandura [30], the initiation of successful behavior change is contingent on both the necessary skills and resources to engage in the behavior and confidence in one’s capability to successfully engage in the behavior, ie, self-efficacy [30]. The Ritterband model provides a useful framework for building knowledge and self-efficacy through the use of Web-based health platforms. In the model, *Application Use* is of central importance, as it is the strongest predictor of successful behavior change in internet-based treatments [31]. *Mechanisms of Change* such as improved knowledge and the development of self-efficacy, supported by the appropriate resources for behavior change, is anticipated to impact actual short-term behavior. Behavior maintenance is more likely when the behavior change promotes noticeable symptom improvement [32].

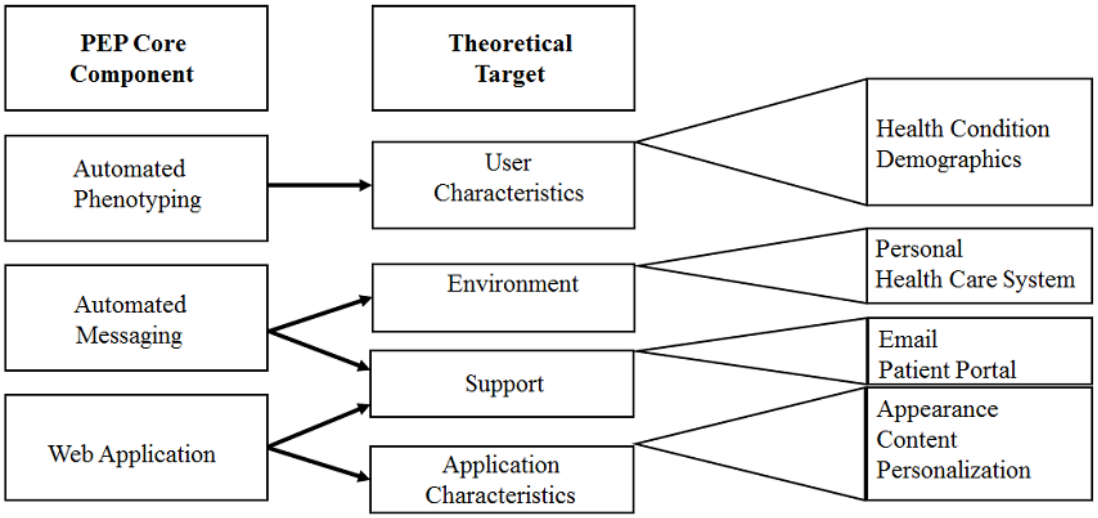
Figure 1. Behavior change model for Web-based interventions (adapted with permission from Ritterband et al [29]). PEP: Pain eHealth Platform.



Core Components of the Pain eHealth Platform

The PEP will consist of an EHR query to identify patients who may benefit from the intervention, an invitation sent to patients via the patient portal to visit the PEP Web app, and the PEP Web app that includes three animated videos with evidence-based information about nonpharmacological treatments for low back pain including mindfulness meditation and physical activity (Figure 2).

Figure 2. Pain eHealth Program core components and theoretical targets. PEP: Pain eHealth Platform.



Electronic Health Record Query

To define the low back pain phenotype to be used for the EHR query, we will employ a three-step modified Delphi method. This method is an iterative process that uses a systematic progression of three rounds of voting and is effective for determining expert group consensus that does not necessitate multiple face-to-face meetings [33]. PCPs from the WFBH system, who spend at least 50% of their time seeing patients in the clinic and have been employed for ≥3 months will be recruited via email or telephone for the expert PCP panel. Content validation for the final EHR query can be satisfied by reaching 80% consensus from the expert panel at each step of the process [33].

Prior to initiating the modified Delphi process, the expert panel will be briefed about the benefits of mindfulness meditation and physical activities for chronic low back pain. In step 1 of the modified Delphi process, PCPs will be contacted via email to vote on a list of preliminary ICD-10 codes for low back pain. The list will also include patient characteristics such as

age≥50-79 years, body mass index (BMI)≥30 kg/m^2, and opioid use.

In step 2, the list of criteria that did not meet consensus from step 1 will be distributed to the group of PCP experts for consideration and another vote will be taken. Finally, in step 3, the expert consensus panel will convene via videoconferencing or face-to-face to deliberate and agree upon the final pain phenotyping for the EHR query. Provider participants will receive a US $50 incentive for their time and participation.

Patient Portal Invitation

The portal invitation will be created using a user-centered design approach [34-36] to refine aspects of the invitation that will make it more effective in patient recruitment for the study. For example, we hypothesize that the sender of the portal invitation will be an important determining factor for viewing the embedded Web app content. Ten PCPs will participate in a 30-minute, semistructured interview to explore their thoughts regarding facilitators and barriers to implementing PEP (eg, time constraints, knowledge of existing Web-based health resources, and access to these resources). In addition, they will be asked for feedback regarding the wording, esthetics, and preferences of the patient portal invitation. They will be asked if they would prefer that the invitation come from "The WFBH Chronic Pain Study Team," "The WFBH Primary Care Clinic, or "Name of Patient's PCP" (Textbox 1). During the interview, we will explore why the PCPs prefer one option over another. We will invite PCPs who participate in the prior Delphi process to participate in the semistructured interviews, and the eligibility criteria will be the same. Provider participants will receive a US $25 incentive for their time and participation.

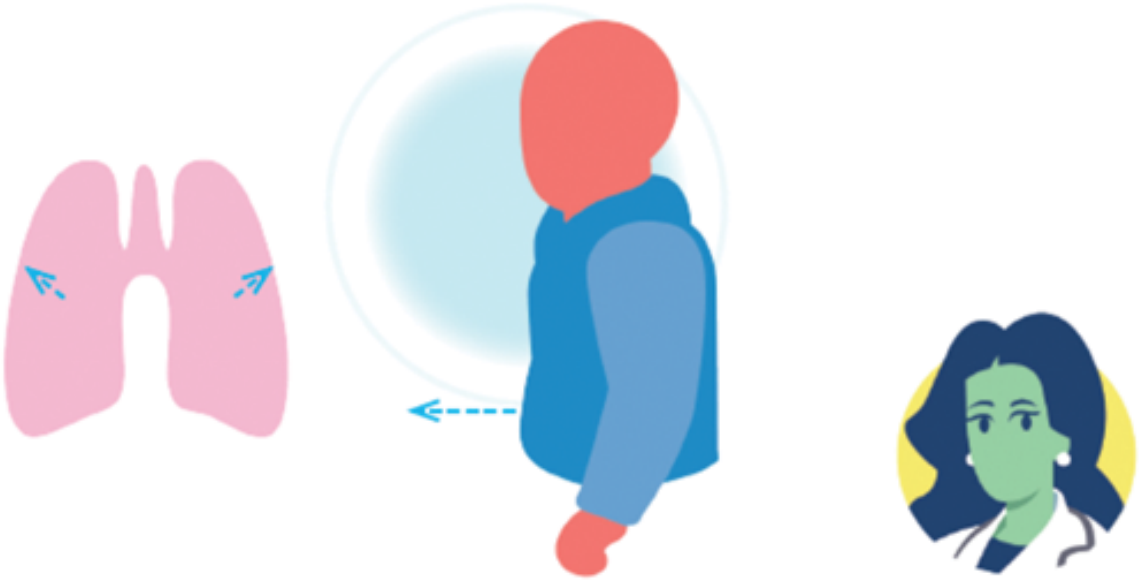
Textbox 1. Sample portal invitation.

From: The WFBH chronic pain study team
Subject: New treatments for low back pain
Dear ____,
An automated analysis of your Wake Forest Baptist Health primary care record indicates you may benefit from new treatment options for low back pain. To learn more, *click here*.

Pain eHealth PlatformWeb App Development

The PEP Web app will be fully Web-based, requiring no downloading, and will be functionally available on both desktop and mobile browsers. Prior to beginning the PEP Web app program, patients will be asked to provide their highest level of education and to rate their low back pain on a sliding scale (0=no pain to 10=worst pain imaginable), on average, over the past week. The Web app will contain three animated videos narrated by a PCP named "Doc" who discusses non-pharmacological treatments for low back pain including mindfulness meditation [17,37] and physical activity [18] (Figure 3). These animated videos were originally created for the Mobile Intervention to Reduce Pain and Improve Health in Older Adults with Obesity (MORPH) study [34]. However, the content is broadly applicable to obese patients with a variety of chronic pain conditions. Upon viewing the animated videos, patients will be given links to additional Web-based mindfulness meditation resources [38,39] and 11 supplemental podcasts that provide tangible ways to increase physical activity created by our study team. These additional resources will help reinforce the concepts presented in the animated videos.

Figure 3. A screenshot from the mindfulness meditation video explaining the basic techniques of mindful breathing, as narrated by "Doc".



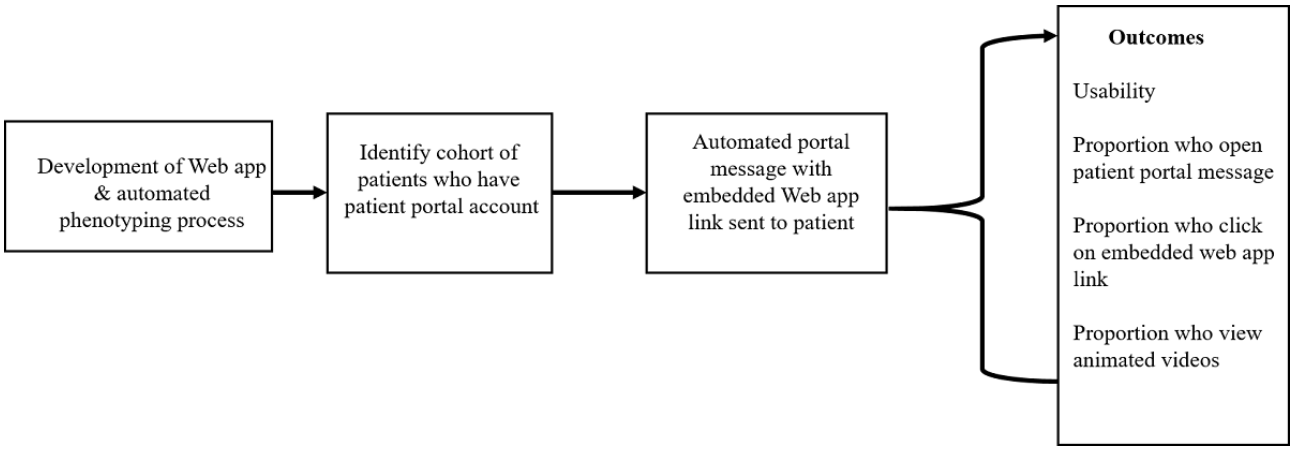
To develop the PEP Web app, we will conduct semistructured, qualitative interviews with obese, older adults with chronic low back pain. Because older adults are likely to have unique requirements, needs, and desires with regard to the Web app design and functionality within the PEP, a user-centered design process is essential [36]. At least 15 patients will sequentially participate in a Think-Aloud protocol: a 30-minute, individual, semistructured interview session in which they will be instructed to "act as though you are talking to yourself but loud enough for others to hear" [36,40]. Eligibility for patients include age≥50-79 years, BMI≥30 kg/m^2, report of low back pain for ≥3 months, and English speaking. Excluded patients will have cognitive impairment, with a Montreal Cognitive Assessment [41] score<22. Eligible individuals will be asked to freely explore the Web app, with the aim of obtaining data related to app esthetics, functionality, and navigation. Audio recordings and detailed notes will be made during the semistructured interview, feedback will be discussed among team members, and modifications will be made to the Web app before the next participant completes the protocol. Audio recordings will be transcribed and coded, which will allow for tracking of changes in usability between participant interviews. Patient participants will receive a US $25 incentive for their time and participation.

Pain eHealth Platform Implementation

We will combine the EHR query, patient portal invitation, and PEP Web app into a seamless system to create the PEP (Figure 4).

Epic serves as the EHR for WFBH. The Web app will run external to Epic. The EHR query will be limited to data elements that are common to all EHRs. Variable names may differ between EHRs, but the query logic will be universal. The EHR query will be validated using iterative testing cycles of 20 randomly selected individuals (10 individuals who meet pain phenotype criteria and 10 individuals who do not meet pain phenotype criteria). Two reviewers who are blinded to the query output will independently review the EHR for these individuals. Disagreements between manual EHR review and query output will be reviewed, and the query will be modified, as needed. Testing cycles will continue until we reach 100% agreement between the query and manual chart review. The final EHR query will run weekly to identify potential candidates who already have an active patient portal account to receive a PEP portal invitation. Upon completion of the validation process, we will send a secure patient portal message to 1000 patients identified by the EHR query, inviting them to view three-animated videos and a list of recommended Web-based treatments about low back pain. The portal invitation will be sent two times, 1 week apart.

Figure 4. Overview of the Pain eHealth Program study design. EHR: electronic health record.



Feasibility Outcomes

To measure usability of the Web app, participants will be prompted to complete items from the System Usability Scale (SUS) [42] after viewing the Web app content. The SUS provides a progressive set of options to assess the usability of a product or service. The SUS comprises 10 statements (eg, ease of use, confidence of use, and user-friendliness), each of which is scored 1-5 points on a Likert scale, from strongly agree to strongly disagree. Higher agreement scores indicate better usability, and scores from 70% to 100% represent good to best imaginable usability.

Secondary outcomes of using the PEP include feasibility and process measures including the reach of our portal outreach strategy (proportion of patients who read the portal invitation, proportion who visit the Web app link within 1 month of the invitation being sent, and proportion who click on all the Web-based treatment links). Effectiveness of the portal message invitation will be measured by the proportion of those who read the message that clicked on the Web app hyperlink. Lastly, a follow-up survey will be sent to patients 1 week after completion of the Web app, asking if they have tried any of the recommended techniques. Reponses to this survey will provide initial evidence regarding uptake of the recommended nonpharmacological treatments. All outcome data will be obtained by querying the EHR and Web app databases.

Analysis Plan

Descriptive statistics for continuous variables (mean and SD) or categorical variables (frequencies) will be presented for patient characteristics and the outcome measures. Multiple linear regression will be used to examine potential associations between SUS scores and participant characteristics such as age, race, gender, and BMI. Logistic regression will be used to

determine which participant characteristics are associated with the proportion who read the portal invitation, those who click on the embedded Web app PEP link, and those who click on all the Web-based included treatments links. These analyses will determine which patients are more receptive to the intervention and which patients may require alternative strategies or messages. A large population of 1000 patients will allow the estimate of primary and secondary outcomes and will provide sufficient variability to plan a future larger study. If 300 patients (30%) complete the SUS, it will be possible to estimate the average usability within 2.8%, with 95% confidence.

Potential Limitations

Internet use among older adults is increasing, with 67% of those aged ≥65 years reporting internet use [20]. However, internet use in this population varies widely by socioeconomic status. Although almost half of patients between the ages of 50 and 79 years have an active patient portal at WFBH, we realize that there may be important demographic differences between portal users and nonusers. We acknowledge that adults aged 70-74 years are less likely to have an active patient portal account than those aged 65-69 years. In addition, non-Hispanic white individuals and Chinese seniors are less likely to have registered patient portal accounts than black, Latino, and Filipino seniors [43]. However, there is growing evidence that adults with multiple chronic health conditions are more likely to access electronic personal records, including patient portals, compared to adults with no chronic health conditions [44]. Moreover, older adults who use patient portals often use fewer features relative to younger populations. In this regard, the PEP Web app will be developed in a user-centered fashion to ensure ease of usability among the target population. Additionally, PCPs are under tremendous time and resource constraints in the clinic. Thus, exploring facilitators and barriers to the implementation of the PEP by PCPs (as described in the PEP Web App Development section) is a vital step of this proposed project.

Results

Qualitative interviews with primary care providers were completed in April 2019. Qualitative interviews with patients will begin in December 2019.

Discussion

This is the first study to examine the usability and reach of a patient portal outreach strategy for delivering evidence-based, nonpharmacological treatment information to adults with chronic low back pain. Given the limited efficacy and frequent adverse effects of opioid medications used to treat chronic low back pain, PCPs require methods for implementing evidence-based, nonpharmacological therapies in their clinical practices without substantial additional burden.

This study is not designed to determine the effectiveness of the Web app. However, the findings from the follow-up survey will provide initial evidence regarding uptake of recommended nonpharmacological interventions. The long-term goals of this project are to test the efficacy of the PEP in a large-scale, hybrid, efficacy-implementation trial that will measure clinical outcomes including pain, physical function, and opioid prescription use over time and to adapt this research platform to a variety of other chronic health conditions including other pain conditions, for which there are established evidenced-based treatment guidelines.

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Conflicts of Interest

None declared.

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Abbreviations

EHR: electronic health record
MORPH: Mobile Intervention to Reduce Pain and Improve Health in Older Adults with Obesity
PEP: Pain eHealth Platform
PCP: primary care providers
SUS: System Usability Scale
WFBH: Wake Forest Baptist Health

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Protocol

Using Mobile Devices to Deliver Lifestyle Interventions Targeting At-Risk High School Students: Protocol for a Participatory Design Study

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Abstract

Background: Unhealthy lifestyle behaviors such as insufficient physical activity, unhealthy diet, smoking, and harmful use of alcohol tend to cluster (ie, individuals may be at risk from more than one lifestyle behavior that can be established in early childhood and adolescence and track into adulthood). Previous research has underlined the potential of lifestyle interventions delivered via mobile phones. However, there is a need for deepened knowledge on how to design mobile health (mHealth) interventions taking end user views into consideration in order to optimize the overall usability of such interventions. Adolescents are early adopters of technology and frequent users of mobile phones, yet research on interventions that use mobile devices to deliver multiple lifestyle behavior changes targeting at-risk high school students is lacking.

Objective: This protocol describes a participatory design study with the aim of developing an mHealth lifestyle behavior intervention to promote healthy lifestyles among high school students.

Methods: Through an iterative process using participatory design, user requirements are investigated in terms of technical features and content. The procedures around the design and development of the intervention, including heuristic evaluations, focus group interviews, and usability tests, are described.

Results: Recruitment started in May 2019. Data collection, analysis, and scientific reporting from heuristic evaluations and usability tests are expected to be completed in November 2019. Focus group interviews were being undertaken with high school students from October through December, and full results are expected to be published in Spring 2020. A planned clinical trial will commence in Summer 2020. The study was funded by a grant from the Swedish Research Council for Health, Working Life, and Welfare.

Conclusions: The study is expected to add knowledge on how to design an mHealth intervention taking end users' views into consideration in order to develop a novel, evidence-based, low-cost, and scalable intervention that high school students want to use in order to achieve a healthier lifestyle.

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KEYWORDS

mHealth intervention; lifestyle behavior; high school students; qualitative methods; participatory design

Introduction

Health Habits Among Youths and the Need for Scalable Interventions

The lifestyles of young people affect not only their current health but also their risk of a number of noncommunicable diseases (NCDs) such as cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes. Insufficient physical activity, unhealthy diet, smoking, and harmful use of alcohol are all modifiable behaviors that increase the risk of NCDs [1-3]. Swedish national surveys have revealed that the majority of young people in Sweden do not consume the recommended daily amount of fruits and vegetables nor do they meet the recommended physical activity guidelines [4-6]. Also, smoking remains a global public health issue, and there is a high prevalence of smoking in youth [7] that also applies to Sweden [6]. Alcohol consumption has declined, but heavy episodic drinking continues to be a problem among alcohol-drinking adolescents [4,8]. Clearly, effective and evidence-based interventions to promote healthier lifestyles in adolescents are warranted.

Adolescence is characterized by rapid physical and psychological changes, together with increasing demands and influences of peers, school, and wider society. It is well documented that behaviors developed during this period influence health in adulthood. Adolescence is the peak period for initiation of substance use, which creates large health burdens in this age group [9,10]. As unhealthy lifestyle behaviors tend to be established in early childhood and adolescence and track into adulthood [11-13], efforts for outreach to high school students are vital. The prevention of diseases related to modifiable behavior has been emphasized as a key component of adolescent health [14]. Part of the success to reduce NCDs requires helping individuals to change their lifestyles to promote health [1,3,10]. According to the World Health Organization (WHO), the education sector can play an important role in health promotion for youths [15]. School health systems, with qualified professionals such as school nurses, welfare officers, and health educators, provide services for students that promote optimum health for their academic success. School multidisciplinary teams provide good accessibility for adolescents and a natural setting for attempting to endorse healthy lifestyle behaviors for as many adolescents as possible [16]. However, to be delivered by school health professionals, interventions require minimal resources and time.

Mobile Health Interventions to Promote a Healthier Lifestyle Among Youths

Over the past decade, interest has increased in providing lifestyle interventions via mobile phones, often referred to as mobile health (mHealth) interventions. mHealth is defined by WHO as a medical or public health practice that is supported by mobile devices [15]. Major advantages with mHealth interventions are that they require fewer resources than traditional face-to-face interventions and they can be delivered at any time. To date, most mHealth interventions have focused on improving one or two lifestyle behaviors such as nutrition and/or physical activity or smoking cessation. However, there is also evidence that lifestyle behaviors may cluster (ie, individuals may be at risk from more than one lifestyle behavior) [17-19]. Interventions targeting multiple lifestyle behaviors at the same time may be beneficial for improving general lifestyle among adults [19,20] and may be more effective and efficient than those targeting a single behavior [21].

To date, although young people are early adopters of technology and frequent users of mobile phones, studies on interventions that use mobile devices to deliver multiple lifestyle interventions to high school students are few, and most interventions target only one or two single behaviors [22]. In this context, it is also relevant to note that a meta-analysis [23] examined the effectiveness of text message–based interventions for tobacco and alcohol cessation within a young adult population. Only 5 of the 14 studies reported significant differences between groups of substance use behavior outcomes. The authors concluded that the included randomized controlled trials (RCTs) lacked detail regarding intervention content. Consequently, replication of the RCTs and the possibility of identifying why and how previous interventions in youth were effective are difficult.

Formative Research Processes

A neglected area of research is the documentation and critical analysis of the formative research processes required in the development and refinement of effective mHealth interventions [24]. A systematic review stressed the need for further research to evaluate the efficacy and effectiveness of intervention approaches in promoting preventive behavior among adolescents [25]. A more recent systematic review emphasized the urgent need to examine development processes for mHealth interventions. The authors concluded that it is important to fully understand how interventions have been developed to allow replication and adaptation of interventions across settings [26].

The prompt expansion of device capability presents many challenges for developers of mHealth interventions, especially when designing interventions that aim to affect multiple individual lifestyle behaviors [27]. As described in Bock et al [27], one set of challenges concerns the structure, content, and tone of the intervention. Previous research has pointed out that the most important factors during the design process are to be flexible and responsive to the input and feedback of the target audience: if they do not enjoy the program they may disengage [28]. A systematic review called for greater transparency in use of theory in developing mHealth interventions [29]. An additional challenge is that of technological cultural consistency (ie, to ensure the developed interventions and modes of access are compatible with the ways in which the intended target group uses technology) [27]. Given the identified challenges and needs regarding development of mHealth interventions, research is needed on how best to design mHealth interventions taking end user assessments into account [28].

Aim

The aim of this research protocol is to describe the research process in developing a novel mHealth intervention to change risky lifestyle behaviors among high school students (LIFE4YOUth).

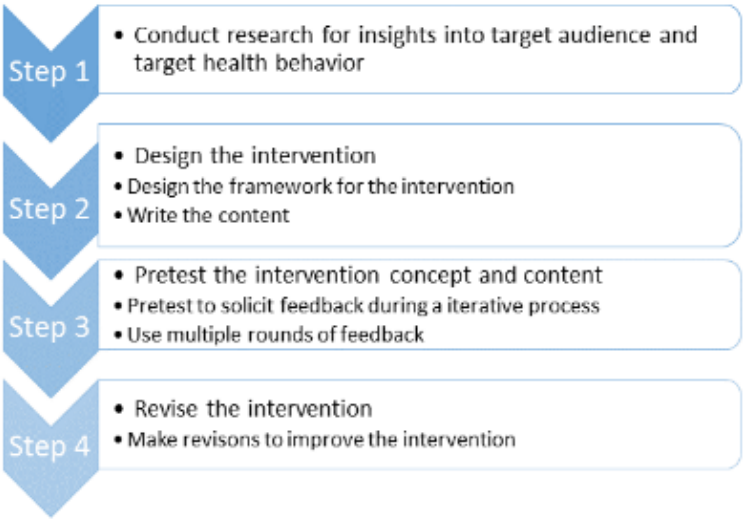
LIFE4YOUth is one of seven mHealth interventions in a research program (funded by Forte 2018-01410; principal investigator: ML) aiming to promote healthy eating, physical activity, smoking cessation, and nonrisky drinking in seven different populations in the health care system [30]. All included studies will follow a harmonized procedure for intervention development, and hence a secondary aim of this protocol is to describe the formative work for LIFE4YOUth as a framework for the included interventions in the research program.

Methods

Study Overview

The development of the LIFE4YOUth intervention is based on a review of the literature and will be inspired by the same phases of development and evaluation as any intervention provided by the National Institutes of Health [31] and further developed and described as recommended by Abroms et al [28] in their guide based on collective experiences in designing, developing, and evaluating mHealth interventions (Figure 1). The recommended steps for developing mHealth interventions include (1) conduct research for insight into target audience and target health behavior, (2) design the intervention, (3) pretest the intervention, and (4) revise the intervention [28]. This paper will focus on step 2 (designing the intervention) and step 3 (pretesting the intervention). The intervention will be designed and pretested during an iterative process, involving multiple rounds of feedback.

Figure 1. A simplified picture of the steps for developing an mHealth intervention (inspired by Abroms et al 2015).



Procedures

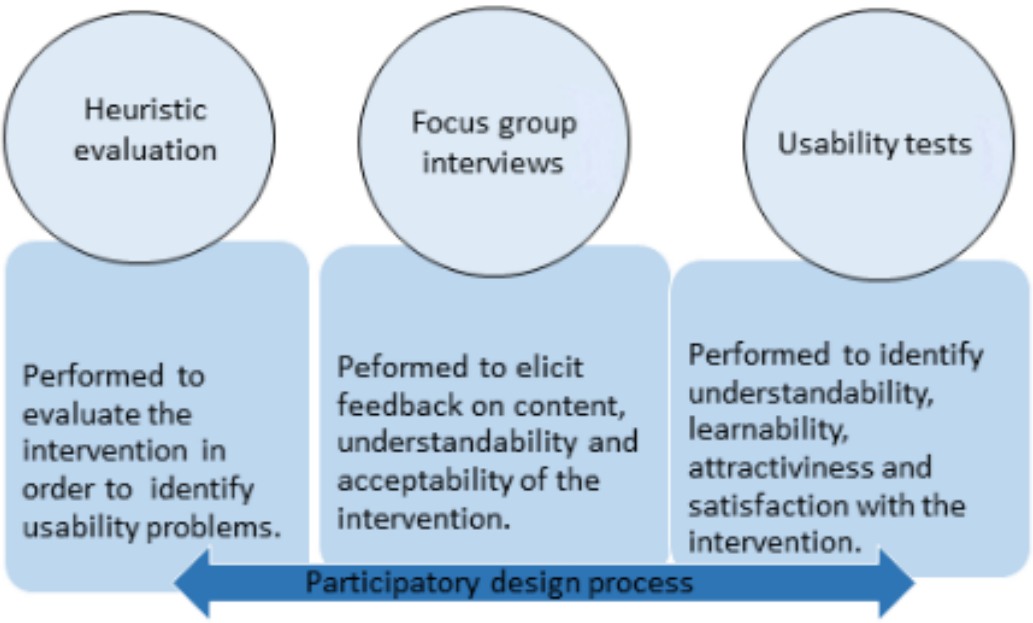
Preparations: Development of a Preliminary Version of LIFE4YOUth

The structure of a preliminary version of LIFE4YOUth was developed in early 2019. The intervention aims to target physical activity, diet, alcohol consumption, and smoking by giving high school students access to a mobile phone app to promote a healthy lifestyle. The structure and content are based on current best practices gathered from scientific literature on lifestyle interventions and behavior change and are inspired by fundamental theoretical constructs such as behavior change theories and psychological models [32,33]. The technical platform is based on our previous research in developing mHealth interventions [34-36].

Participatory Design Processes

The participatory design process used in this study will include three activities: (1) heuristic evaluation, (2) focus group interviews, and (3) usability tests. We will invite end users including high school students and university students and employees at Linköping University. The knowledge, experiences, ideas, and skills of the participants will be used to revise the intervention. Figure 2 presents the activities included in the design of the intervention.

Figure 2. Activities in the development process of LIFE4YOUth.



Heuristic Evaluation

Effectiveness, as part of usability defined by the International Organization for Standardization standard 9421-11:2018, will be investigated using heuristic evaluation [37], a usability inspection method. During heuristic evaluation, trained evaluators review an intervention to find usability problems, assign them to a specific category of heuristics, and ascribe a severity rating in order to provide distinct usability information. The experts recruited for this evaluation are not necessarily usability experts but should have some level of expertise with the subject matter or technology required to use the investigated app. The heuristics will identify usability issues such as problems with unclear functions, confusing navigation, and consistency issues [38-40].

Focus Group Interviews

Initially, a series of focus groups will be conducted to enable the collection and analysis of three complementary forms of data: individual data, group-level data, and data generated from participant interactions [41,42]. Focus groups are semistructured discussions with research participants that aim to explore a specific set of issues [43]. The focus groups will be designed to elicit feedback on content, understandability, and acceptability of the proposed intervention so that modifications can be made.

Usability Tests

Usability tests [44-46] will be completed in order to further modify and improve the intervention. Usability tests consist of a human-computer interaction and refer to evaluating an intervention by testing it with potential end users with the goal of identifying understandability, learnability, and attractiveness and determining participant satisfaction with the intervention. The usability tests will provide information on whether participants are able to complete specified tasks successfully, identify how long it take to complete tasks, and identify changes required to improve user performance and satisfaction [44,47].

Setting, Participants, and Recruitment

Heuristic Evaluation

Participants for the heuristic evaluation will be recruited by members of the research team through paper advertising (posters) in public areas at Linköping University. Participants will register their interest by contacting the research leader by email.

Focus Groups and Usability Tests

School staff at five high schools selected for convenience in Östergötland (Sweden) will be contacted via email and informed about the research project. Approximately 1000 students, both female and male, aged 15 to 18 years, attend these high schools and will all be invited to take part in the focus group interviews and usability tests. High school students at the selected schools are expected to be similar to the overall target population for mHealth interventions.

Participants among high school students will be recruited by the school staff through paper advertising (posters and leaflets), digital advertising (student email and school website), and information in the classrooms. High school students will register their interest by contacting the research leader by email or telephone or by contacting school staff who will send students the telephone number of the research leader.

Selection Criteria

Inclusion criteria for the heuristic evaluation will include university students and employees at the Faculty of Medicine and Health Sciences at Linköping University who are willing to participate and who own a mobile phone. Inclusion criteria for the focus group interviews and usability tests will include high school students aged 15 to 18 years at selected high schools in Östergötland who are willing to participate and who own a mobile phone. A total of 32 to 44 participants are expected. Exclusion criteria for the focus group interviews and usability

tests will be high school students who are not Swedish-speaking or do not own a mobile phone.

Data Collection

Heuristic Evaluations

A total of 15 heuristic evaluators, both students and employees at Linköping University, will be recruited. A research assistant will give participants a short (eg, 45 minutes) training session to instruct them on the main principles of heuristic evaluation during a meeting with all participants. The introduction will take place in a conference room at Linköping University. For the heuristic evaluation, a set of 10 standardized heuristics published by Nielsen [37] will be used. The heuristics for usability evaluation according to Nielsen are listed in Textbox 1.[37]

Participants will be taught how to use the heuristics to evaluate the intervention. All participants will be sent a link with a prototype of the intervention. Each evaluator will go through the prototype one time and independently identify issues tied to a specific heuristic (eg, visibility of system status, plain language, flexibility and efficiency of use, aesthetic design) and give them a severity rating [38-40]. The evaluation will be performed wherever the participants prefer and sent back to the research assistant in a prepaid envelope within 1 week of receipt. Heuristic evaluations will be gathered in May 2019.

Textbox 1. Heuristics for usability evaluation according to Nielsen.

- Visibility of system status: system should always keep users informed about what is going on through appropriate feedback within reasonable time.
- Match between system and the real world: system should speak the users' language with words, phrases, and concepts familiar to the user rather than system-oriented terms. Follow real-world conventions, making information appear in a natural and logical order.
- User control and freedom: users often choose system functions by mistake and will need a clearly marked "emergency exit" to leave the unwanted state without having to go through an extended dialog. Support undo and redo.
- Consistency and standards: users should not have to wonder whether different words, situations, or actions mean the same thing.
- Error prevention: even better than good error messaging is a careful design that prevents problems from occurring in the first place. Either eliminate error-prone conditions or check for them and present users with a confirmation option before they commit to the action.
- Recognition rather than recall: minimize users' memory load by making objects, actions, and options visible. The user should not have to remember information from one part of the dialog to another. Instructions for use of the system should be visible or easily retrievable whenever appropriate.
- Flexibility and efficiency of use: accelerators, unseen by the novice user, may often speed up the interaction for the expert user such that the system can cater to both inexperienced and experienced users. Allow users to tailor frequent actions.
- Aesthetic and minimalist design: dialogs should not contain irrelevant or rarely needed information. Every extra unit of information in a dialog competes with relevant units of information and diminishes their relative visibility.
- Help users recognize, diagnose, and recover from errors: error messages should be expressed in plain language (no codes), precisely indicate the problem, and constructively suggest a solution.
- Help and documentation: even though it is better if the system can be used without documentation, it may be necessary to provide help and documentation. Any such information should be easy to search, be focused on the user's task, list concrete steps to be completed, and not be too large.

Focus Group Interviews

A total of 4 focus group interviews with 3 to 6 participants in each group (12 to 24 participants) will be conducted between May and June 2019. Teachers will not be present during the interviews. The consolidated criteria for reporting qualitative research (COREQ) 32-item checklist [48] will be applied to give an explicit and comprehensive structure to the focus group interviews according to the following domains:

- Research team and reflexivity: a female researcher with a PhD degree and training and experience in qualitative methodology (UM) will be responsible for conducting the focus groups. A female observer (AS) will ask complementary questions at the end of the interview. The interviewer will explain the purpose of the interview and her interests in doing the research.
- Study design: an explorative qualitative approach [41,42] will be used for methodological orientation. All focus group interviews will be conducted in a high school setting. Each semistructured interview will be audiorecorded and will last approximately 1.5 hours. An interview guide (Multimedia Appendix 1) will be used [41]. Interview questions will be framed around the following domains: (1) making lifestyle changes, (2) use of the mobile phone for health informatics, (3) intervention content, (4) overall feedback, and (5) visual prototype. After discussing the first four domains, UM will present a low-fidelity paper-based prototype [49] including a series of printouts of the LIFE4YOUth program.
- Analysis and findings: analyses will be performed using systematic thematic analyses (further described under Data Analysis). Data will be coded by two researchers. Themes will not be identified in advance but will derive from the data. Quotations will be used to illustrate the themes and elucidate the findings.

Usability Tests

A total of 5 usability tests [45-47] will be completed. Five high school students will go through a 60-minute session during which all interactions with the intervention are videorecorded. A high-fidelity prototype [49], including the actual software

start page, menu page, and 4 intervention modules (alcohol, smoking, physical activity, and diet) will be used. During this high-fidelity prototype testing, participants will go through the entire intervention module. A research assistant will ask participants to complete tasks while explaining their actions using a think aloud method [50,51]. An observer (AS) will note potential issues as the given tasks are performed by the participants. The assistant will not offer any help during the task execution to minimize any disruptions of spontaneous thoughts as well as to avoid bias in the results. After completing the session, the participants will be asked to complete a paper version of the system usability scale (SUS). The SUS is a standardized tool to get a global view of the participants' subjective assessments of usability based on 10 questions [52]. The tests will be run on an iPhone and take place in June 2019 in a medical informatics lab room.

Data Analyses

Heuristic Evaluation

All issues from evaluators will be pooled with potential duplicates merged and issues with high average severity ratings rectified [37,53]. Descriptive statistics will be used to summarize heuristic violations and associated severity scores.

Focus Group Interviews

Transcripts will be analyzed thematically in an iterative process of coding [54]. Analyses will focus on end user experiences and opinions regarding making lifestyle changes using the mobile device as a health tool, as well as on content, structure, and implementation of LIFE4YOUth. Systematic thematic analyses will follow a prescribed, sequential process: (1) noting overall impressions, (2) reducing and coding into themes, (3) searching for patterns and interconnections, (4) mapping and building themes, and (5) drawing conclusions. In order to ensure validity of the results and prevent bias in the qualitative analysis process, data will be independently coded by two researchers with a consensus reached by adjudication [41].

Usability Tests

After all user tests have been completed, observers and other members of the research group will discuss whether specific tasks stood out or hindered the progress in development of the program. Analysis of the videorecordings will be informed inspired by inductive program theory development [55].

Analysis will focus on features of the intervention related to design, format, instructions, navigation, terminology, and learnability that need to be redesigned. Descriptive statistics will be used to analyze problem counts and time taken. Average scores from the SUS will be used to identify average satisfaction [52].

Ethics Approval and Consent to Participate

The study has been approved by the Swedish Ethical Review Authority (Dnr 2019-01320). All participants will give written informed consent prior to participation in any study procedure (focus group interview, heuristic evaluation, user test).

Results

Recruitment started in May 2019. Data collection, analysis, and scientific reporting are expected to be completed in December 2019. The study was funded by a grant from the Swedish Research Council for Health, Working Life, and Welfare. Focus group interviews were being undertaken with high school students from October through December, and full results are expected to be published in Spring 2020. A planned clinical trial will commence in Summer 2020.

Discussion

As a growing body of research suggests that health risk behaviors often do not occur in isolation, this study considers interventions that address lifestyle behaviors related to diet, physical activity, smoking, and alcohol. Also, more research is needed into the documentation and critical analysis of the formative research processes required in the development and refinement of effective mHealth interventions [24,26]. This protocol describes a participatory design study with the aim of developing an mHealth intervention to promote healthy lifestyles among high school students that can be delivered via school health staff. This protocol provides a scientific record of the methodologies used when developing the intervention in order to enhance transparency of research. Additionally, as described above, the LIFE4YOUth intervention program is part of a larger research program (funded by Forte, the Swedish funding agency for health and social affairs research) [28], and the formative work presented here will also be used as a framework for the other trials in the program.

Through formative research and participatory design, we believe this study will result in deepened knowledge regarding what aspects of content and structure end users (eg, high school students) consider important for designing mHealth lifestyle behavior interventions. More specifically, the study is expected to give answers as to whether an mHealth intervention that gives access to interactive and personal modules contained within a mobile phone–based dashboard is useful and accepted among high school students. This knowledge is valuable in order to guide further development of a final version of the novel mHealth intervention program LIFE4YOUth targeting high school students. An RCT will be conducted to determine the efficacy of the intervention. If found effective in the RCT, the program has the potential to be implemented nationally through school health services.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[XLSX File (Microsoft Excel File), 11 KB - resprot_v9i1e14588_app1.xlsx]

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Abbreviations

COREQ: consolidated criteria for reporting qualitative research
mHealth: mobile health
NCD: noncommunicable disease
RCT: randomized controlled trial
SUS: system usability scale
WHO: World Health Organization

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Protocol

Development of Serious Games (Equit'Game) to Address Health and Environmental Inequalities: Protocol for an App-Delivered Program to Perform a Territorial Diagnosis

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Abstract

Background: Territorial diagnosis is a prerequisite for local actions concerning public health and for the reduction of social, environmental, and health-related inequalities. To orient local programs or initiatives targeting health inequalities, policymakers need a simulation of territorial diagnosis tools. Yet, very few platforms have been developed for the purpose of guiding public authorities as they seek to reduce these social inequalities.

Objective: This study aimed to describe the design and methods of the development process of a territorial diagnosis tool based on a serious game named Equit'Game that puts learners at the heart of the territorial diagnosis process, asking them to review the current state of health, environmental state, and socioeconomic state of their territory.

Methods: The realistic situations employed in our serious game should encourage players, in a fun and playful manner, to (1) appropriate the data of their own territory, (2) apply their methodological knowledge in a practical way, (3) reflect on the most pertinent statistical or spatial tools for their situation, and (4) ultimately, to acquire new knowledge and skills in the use of territorial diagnosis tools with a spatial dynamic. Equit'Game was deployed over the course of a week's training and structured into 4 levels: level 1, Dataminer (identifying relevant information to respond to the question); level 2, Analyst (selecting the appropriate method of analysis); level 3, Atlas (mapping the data); and level 4, Cluster (extraction of statistical and spatial information). Equit'Game has also been designed as a sort of virtual campus, creating a fun learning environment in which each door represents a level. Users can access Equit'Game via a platform compatible with tablets, PCs, and mobile phones.

Results: In the first step, we tested our application interface designed especially for adults among a panel of local health professionals. The following are some of the most relevant points: font size and colors used, voice accompaniment in texts and messages guiding the user, clear and easy interfaces, and the change between successive game levels. In the second step, we used our application, Equit'Game, with postgraduate students from the School of Public Health (École des hautes études en santé publique). At the end of the game session, we conducted a satisfaction survey, including several items covering both the application interface and the execution of the game.

Conclusions: Equit'Game was developed to help learners with the techniques of territorial diagnosis, with the aim of creating an innovative tool for public health capable of conveying educational messages and providing a structure for training.

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KEYWORDS

serious game; territorial diagnosis tool; health inequality; environmental inequalities; Equit'Game

Introduction

Public policy on health and social matters insists that territorial diagnosis be a prerequisite for all territorial procedures and, on a more general level, for all local development actions [1]. This process involves stakeholders with interests and decision-making powers, which are different but complementary; coordinating their actions is one of the key factors determining the success or the failure of local projects.

Furthermore—to more effectively steer local actions concerning public health and the reduction of social, environmental, and health-related inequalities—it is crucial that we fully understand the socioterritorial constructions that serve to perpetuate or even aggravate health-related inequality.

A review of the extant research conducted with the direct or indirect involvement of local authorities (metropolitan areas or regions) leads us to the following observation: faced with socioterritorial health inequality, territorial stakeholders (elected official and institutions) run up against the same obstacles, particularly the absence of tools for more effectively scheduling and targeting actions on the ground.

For instance, in France, in its evaluation of France's second National Health and Environment Plan (PNSE2), the High Council of Public Health (Haut Conseil de santé publique) clearly highlighted the lack of sufficient tools to help territorial authorities to prioritize and to target their actions on the ground, and thus effectively reduce social and environmental inequality [2].

Researchers also have a role to play in this field, because the absence of tools and methodologies enabling concrete and efficient responses to these local priorities is a significant problem. Moreover, an increasing number of research projects have documented the existence of social inequalities in health [3,4] and, to a lesser extent, the existence of environmental inequalities [5-7]. Yet, very few platforms have been developed for guiding public authorities as they seek to reduce these social inequalities. It appears to us that establishing a full and precise social and health-related diagnosis at the local level is a crucial requirement if we want to optimize and prioritize the use of resources, directing them toward those categories of citizens who accumulate multiple risk factors.

As such, the dissemination of research findings and the transfer of knowledge to establish training and educational targets and to simulate situations that closely reflect reality appears to be a pertinent and promising strategy for spreading the techniques of territorial diagnosis.

It was in this spirit that the *Equit'Game* tool was created; it forms a part of the Equit'Area project [8], focusing on the issue of social inequalities in health.

The primary objectives of Equit'Game are as follows: on the one hand, to teach the methods and approaches required to perform territorial analysis and, on the other hand, to put learners in life-like situations. The idea is to put learners at the heart of the territorial diagnosis process, asking them to review the current state of health, environmental state, and socioeconomic state of their territory while completing a number of compulsory *levels*; these levels ensure that all of the key steps in the process of territorial diagnosis are covered.

This professionally oriented teaching will provide a theoretical framework of realistic situations derived from the Equit'Area research program [9,10], preparing learners to contribute to the creation of similar projects in their own territories.

This paper is divided into several sections: Section 1, Introduction reviews the existing literature on the use of serious games to promote health; Section 3 provides more details on the methods used, the participants, and the design of the game; and Section 4 details the technical results. Finally, Section 5 contains our conclusions and perspectives for future additional development.

The literature review dealing with serious games reveals a multitude of definitions and classifications, which reflect the diversity of approaches and perspectives found in the different sectors concerned (education, media, health, and simulators). Nevertheless, the most widely shared definition seems to be the one written by game designers, Sande Chen and David Michael: "These games have an explicit and carefully thought-out educational purpose, and are not intended to be played primarily for amusement."[11]

In the definition provided by Lelardeu et al [12], the various objectives of these serious games can be divided into 3 main categories: (1) spreading a message, (2) providing training (eg, exergames), and 3) promoting data exchange (eg, datagames).

Among serious games designed to spread a message, we can identify several types of messages: teaching and education (eg, edugames), sharing information (eg, newsgames), and also more marketing-persuasive messages intended to influence or induce certain behavior (eg, advergames).

Since the concept of serious games was first developed, this form of learning has been deployed for users from different sectors, from military personnel to teachers and health care professionals [13]. In the health care sector, since 2002, several serious games have been created, focusing on physical activity, rehabilitation, cognitive stimulation, surgery, or emergency care for both patients and professionals [14-16].

Most serious games developed in recent years are designed to help teach effective decision making in health care matters, making them *an innovative tool for public health*.

As such, modeling of health information may play a role in the creation of tools to be used both for training and decision

making, for example, a serious game that can be used to make diagnoses.

This harks back to the definition offered by Abt [17] over 40 years ago in his work, *Serious Games*: "A game is an activity among two or more independent decision-makers seeking to achieve their objectives in some limiting context."

The tools we are dealing with place learners within a given defined context, obliging them to make choices and decisions [18]; the aim is to push users to adapt their responses to certain situations and then conduct them to transfer these lessons to their day-to-day professional activities.

To make the game environment as realistic as possible, some serious games seek to incorporate data and results based on scientific research, presented in a format that is sufficiently accessible and comprehensible to be used in the decision-making process. One illustration of this approach is the *Time After* application, developed by Reichlin et al in 2011 [19].

An increasing number of public institutions are taking the decisive step to commission serious games, for example, the World Health Organization's yellow fever epidemic application aimed at health care professionals. This app lets players manage various resources and perform actions to control yellow fever epidemics. The review of the existing literature conducted by Ohannessian et al [20] clearly explains that serious games focusing on vaccinations could be a useful educational tool for decision makers.

In France, serious games are beginning to gain traction with territorial authorities. One recent example is the serious game named *Ecoville* developed by the Agency for the Environment and Energy Management (Agence de l'Environnement et de la Maîtrise de l'Énergie [ADEME]), which invites users to create their own environmentally friendly town and to reflect on the consequences of urban sprawl and mixed habitats while learning about the importance of energy management and respecting the environment [21]. A recent addition, again from ADEME, is the application, *Réflexe planétaire*, which aims to educate users in an entertaining way about simple everyday actions that can help protect the environment [22].

In partnership with the National Association for the Prevention of Alcoholism and Addiction (l'Association nationale de prévention en alcoologie et addictologie), the National Territorial Health Insurance Fund (la Mutuelle Nationale Territoriale) has developed an application called *Territorial City*, available to local authorities since September **2015**, designed to help with the decision-making process [23]. The scenario proposed to players involves coordinating local personnel and resources in response to an incident linked to the consumption of psychoactive substances. This simulation helps to (1) equip decision makers with the tools they need to prevent and manage risky behavior involving the consumption of psychoactive substances at work and (2) encourage decision makers and their teams to launch preventive actions in real life.

However, as far as we are aware, no serious game had yet been developed to support and help local authorities and regional health care agencies in their efforts to reduce social inequalities in health.

Our contribution to this process, as researchers, involves the operational development of a *research and training* tool fueled by accessible, comprehensible data derived from our own research [9,10]. Our serious game creates a learning environment that encourages players to think about space, territories, and collective learning for effective action.

Methods

Description of the Experiment

During the development of this project, an initial meeting was organized to determine the most appropriate manner of proceeding. Several key points were discussed, including (1) how to best adapt this serious game to the various requirements outlined and (2) how to define the role of the various stakeholders in the development process. The second phase involved the creation of the different characters and graphical environments contained in the game, and the game's structure (decision tree). The third step was to create the associated educational materials in various formats: videos, interviews, animated PowerPoint presentations, and simulations. The last phase was all about finalizing the design, assembly, and settings of the game using Ludiscape.

Technological Methodology

The system is composed of 2 databases: the first one is used to edit the game, developed in XML, and the second database is for data that are sent over the internet, which is available via a Web-based platform (type: Learning Management System [LMS] Modular Object-Oriented Dynamic Learning Environment [Moodle]) developed in MySQL.

A programming language known as HTML (HTML JavaScript Cascading Style Sheets [CSS]) was used in conjunction with PHP (Hypertext Preprocessor) to develop the activities included in the Web-based system.

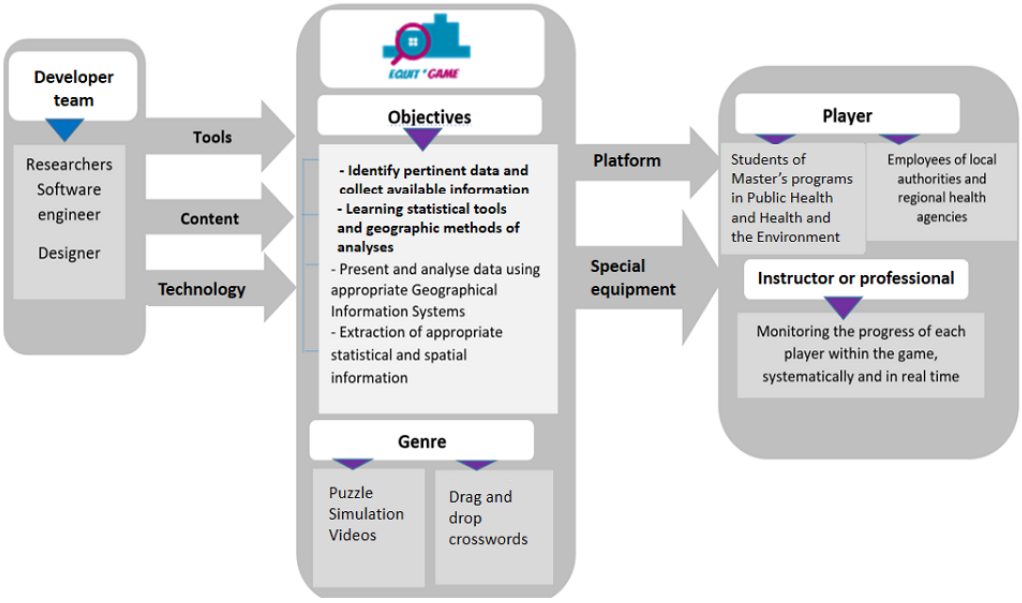
Hardware

This serious game was designed to work on various devices: tablets, PC, and mobile phone. Thanks to the Ludiscape engine, designed for compatibility with all of these devices, no further development was required. This engine is also compatible with all operating systems currently available on the market (Windows, Mac, Linux, iPad and Android tablets, Firefox, and Chrome).

Game Design Elements

The creation of our serious game involved different processes, technologies, and specialists. We used the conceptual model developed by Wattanasoontorn et al [16] to illustrate the core components of Equit'Game (Figure 1).

Figure 1. Game design elements.



Development Team

The creation of our serious game brought together a large panel of contributors from different disciplines: scientists, software engineers, graphic designers, simulation analysts, and educators. The multidisciplinary expertise of this team enabled us to produce an innovative game featuring interfaces and graphical environments designed to fulfill the objectives of Equit'Game.

Tools

The development of Equit'Game was based on 2 essential elements: app design software and the game engine. The design software we used is called Ludiscape, created and developed by Damien Renou [24].

Ludiscape is a collection of integrated tools designed to help users create training content, e-learning modules, and serious games. This technology allows users to create a variety of educational content simply by using the Ludiscape resource library. Each object in this library provides quick access to properties and settings, requiring no prior experience in programming (Figure 2). Full integration of JavaScript with the Ludiscape engine and its extensions ensures maximum flexibility and production speed. Plugins are invisibly integrated into the educational production environment in such a way that they are easy to use.

Figure 2. The Ludiscape environment.

The Ludiscape environment allows users to incorporate educational material in various formats (JPG, WAV, MP3, MP4, and PTT) into a unique project that becomes the game engine. The game engine can then be exported in different formats (HTML, JavaScript, CSS, Shareable Content Object Reference Model [SCORM], EXE, and iOS) toward different platforms (PC, Mac, mobile phone, tablet, phablet, LMS, Moodle, and Dokeos). This unique project contains all of the codes required to control the game and all of the databases that feed into the game. It is this game engine that the graphical user interfaces will open when the user launches the app. On the basis of the decision tree (constructed in one of the first steps of the project), the rules (including the various stages) that announce the success are presented to the learner/player, that is, the levels to be completed to finish the game. When a set of targets have been met, an interface appears to inform the user that the ongoing level is complete and that they can move onto the next level.

Content

As part of their decision-making process, regional health care agencies and local authorities apply national strategies at the regional and/or local scale to develop targeted local actions. To do this effectively, decision makers require a comprehensive territorial diagnosis based on study, cross-comparison, and precise analysis of the available data.

We, therefore, decided to base our interactive serious game, Equit'Game, on the idea that a comprehensive territorial diagnosis combining health, environmental, and social perspectives would represent an invaluable resource in the decision-making process, helping to boost collective action at the territorial level. To achieve this objective, we need to understand and master the different stages involved in the creation of a territorial diagnosis.

All of the data collected by the Equit'Area project from the City of Paris, involving a fine scale of geographical detail, were used in the development of Equit'Game.

As such, at different levels in the game, we provided players with information and tools developed by scientists and experts. These resources take various forms: statistical indicators, maps, and results of analyses.

To describe the state of health care in Paris, the infant and neonatal mortality rates between 2004 and 2009 have been displayed. Thereafter, the average annual levels of nitrogen dioxide, and particles with a diameter equal to or smaller than 10 µm—as modelled by the agency responsible for monitoring air quality in Greater Paris, AirParif—have been used to visualize the spatial distribution of environmental hazards in Paris (air pollution is only one of the factors used to measure environmental hazards). To finish, the population census data were analyzed to profile the neighborhood socioeconomic deprivation.

Technology

In creating this game, we opted to use virtual reality technology; this means creating a simulation that gives players the impression that they are present in a real or imaginary environment. Designers and graphical experts created these different environments to represent (1) *virtual spaces*, such as a university campus, a conference center, a classroom, and an office, and (2) *real spaces*, such as conferences by well-known figures and interviews with experts.

The Equit'Game Tool

Like most serious games in the health care sector, Equit'Game aims to reach several objectives: spreading a message that is informative and educational, while also getting across marketing-persuasive messages intended to induce/influence behavior; in this case, encouraging players to take action and conduct their own territorial diagnosis.

More specifically, the realistic situations employed in our serious game should encourage players, in a fun and playful manner, to (1) appropriate the data of their own territory, (2) apply their methodological knowledge in a practical way, (3) reflect on the most pertinent statistical and/or spatial tools for their situation, and (4), ultimately, to acquire new knowledge and skills in the use of territorial diagnosis tools with a spatial dynamic. These 4 objectives structure our game into 4 levels, as follows:

- Level 1: Dataminer (identifying relevant information to respond to the question);
- Level 2: Analyst (selecting the appropriate method of analysis);
- Level 3: Atlas (mapping the data);
- Level 4: Cluster (extraction of statistical and spatial information).

The serious game was deployed over the course of a week's training and structured in such a way that each learner should complete 1 level per day. The experience involved a combination of teaching scenarios delivered by a computerized app and can be used with or without an instructor as part of classroom training, distance-learning, or a combination of both.

Game Formats

The game offers a number of different learning mechanisms, a variety of approaches combined in Equit'Game, and corresponds to the various objectives set for each level. To help players to appropriate the data of their study territory, there are various *hidden areas* that allow players to interact with the territory. There are also crosswords and drag and drop exercises that allow players to apply their methodological knowledge in practical and concrete ways. We also included quiz sections and dialogues involving virtual interaction via text zones to stimulate reflection on the most appropriate statistical and/or spatial tool. Equit'Game also incorporates educational simulations designed to help players acquire new knowledge and skills. Players are allowed to run the simulations several times, using different input data each time.

Users and Platforms

Our serious game aimed to reach several target groups, including employees of local authorities and regional health agencies. Owing to the diversity and richness of the educational material included in each level, Equit'Game can also be used wholly or partially as part of Master's programs in public health and/or environmental health.

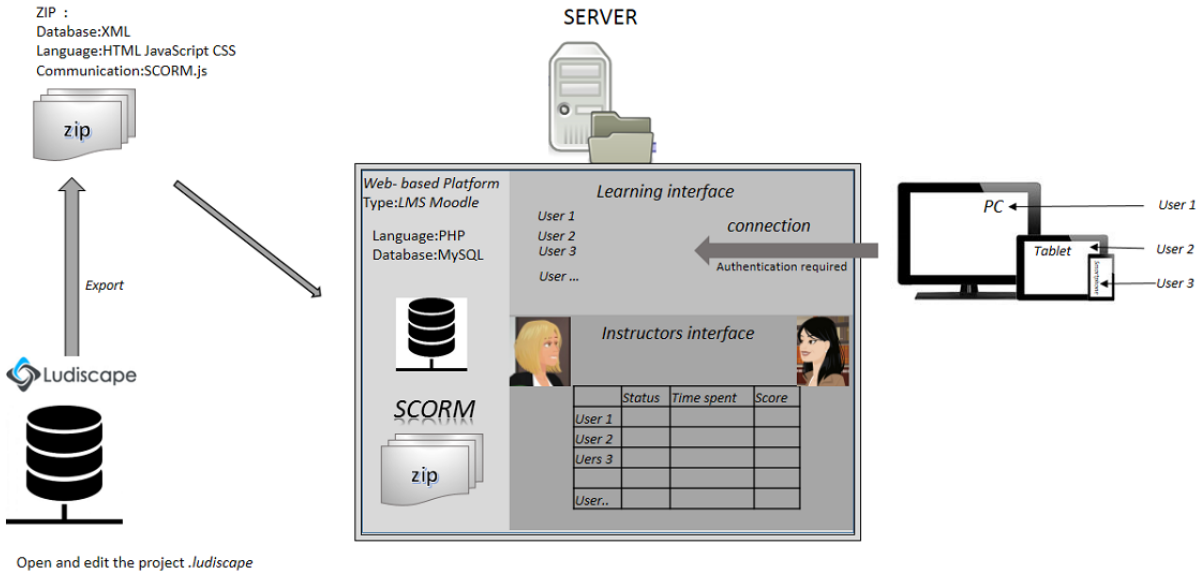
Users can access Equit'Game via a platform compatible with tablets, PCs, and mobile phones and have to enter their user identification to log in. The platform also allows instructors to monitor the progress of each player within the game, systematically and in real time, with help from the indicators and intermediate scores recorded by the platform.

Tool Design

High-Level System Diagram

Equit'Game is composed of 3 blocks (2 principal components and an interface layer) and includes effective databases in XML and MySQL format.

Figure 3. System architecture.



As Figure 3 shows, the structure used allows the Equit'Game administrators to edit the game via the first block, by using an XML database implemented within the Ludiscape software. The game can then be exported as a SCORM.js layer. The SCORM.js interface will be deployed on LMS Moodle or a similar Web-based platform, which operates via the MySQL database and allows players to access Equit'Game.

Therefore, access to Equit'Game, regardless of the device used (PC, tablet, and mobile phone) requires connection to the Web-based platform with personal user ID codes. This final block is where players can save their data to the server via the MySQL database. Instructors can track the progress of players via plugins installed on the Moodle platform, which keep records of different indicators and parameters as users move through the game (eg, time spent on the game and score on each level). Analysis of these indicators, virtually in real time, allows the instructor to follow players through each level of the game and, where necessary, to adapt subsequent training to address any concepts that learners do not seem to have fully understood.

Designing Our Serious Game

This serious game is part of the process of translating the results of the Equit'Area research program into training tools. It was designed and developed for the purposes of training users to perform a territorial diagnosis. Equit'Game is thus based on the following key elements: (1) understanding the needs of a territory in the 3 complementary areas of health, environmental exposure, and neighborhood socioeconomic deprivation and (2) learning to handle the data that best characterize the territory, including data collection, transformation, and analysis, and graphical representations and maps.

To fully satisfy the definition of a serious game, *Equit'Game* meets the following criteria:

- Accompaniment in the form of texts and voice messages, guiding the user;
- Use of realistic elements to simulate real cases;
- Clear and easy interfaces;
- No time limits, as users progress at different speeds;
- Congratulations at the end of each level, encouraging players and facilitating the learning process;
- Lack of animation and sound effects to keep players' attention focused.

Equit'Game has also been designed as a sort of *virtual campus*, creating a fun learning environment (Figure 4) in which each door represents a level. The game environment also incorporates an additional space where learners can look back over previous levels to improve their performance, consult the previous learning materials, and save the information they require.

Figure 4. Equit'Game design: (A) structure of 4 levels and (B) fun learning environment: virtual campus.

As shown in Figure 4 (screen capture), we have used a color code to identify clearly the 4 levels that make up Equit'Game: level 1 is yellow, 2 is blue, 3 is green, and the fourth and final level is orange. To mimic the structure of a diagnosis focusing on social and/or environmental inequalities relating to health, players can only move onto the next level when they have completed the current one and cannot go backward (Figure 4).

Players encounter different characters throughout the game: the first character, the elegant Marie, welcomes and guides players around the campus at the start of each new level, color-coded accordingly (Figure 5). A second character, Robert the robot, helps players to get to grips with methods and learn how to handle data.

Figure 5. The design of main characters of Equit'Game.

To make Equit'Game more realistic, expert interviews, feedback, and video clips, staged in realistic surroundings, examine the following issues: social health inequalities, environmental inequalities, and health inequalities relating to perinatal health.

A Game Constructed Around 4 Levels and 2 Scenarios: Gameplay

Players are presented with 2 scenarios: (1) a diagnosis focusing on socioeconomic factors and health or (2) a diagnosis focusing on environmental factors and health. They must make a choice based on the information provided at the outset of Equit'Game, and the way that the game plays out will change accordingly. For example, if a player decides to focus on environmental inequality, they will have access to the relevant environmental and health data but not the socioeconomic data and vice versa. The structure of each level is described below.

Level 1

In this first level, the goal was to identify pertinent data and to collect the information that is available and is necessary to achieve the stated objective (Multimedia Appendix 1). Players

define their objective on the basis of the territory under consideration and the existing literature, justifying their choice.

To this end, the level was broken down into a series of interrelated steps. Upon first connecting to Equit'Game, Marie (a key character in the game) greets the learners and they are taken to a virtual conference where they see several videos. Players must then take part in a type of *board game* exercise, which functions as an evaluation test of knowledge, before leaving the conference. They then set off to *hunt down* the necessary information, taking the train to Paris to gather information on the ground. Back on the campus, they must learn to store these data within a workspace laid out like an office. Various simulations and learning models are available to help learners to construct databases that are understandable and usable for multiple contributors.

Players thus move between 3 game environments (the conference, Paris, and their office; Figure 3), completing 30 challenges (crosswords, drag and drop, and puzzles) along the way to complete this first level. By the time learners reach the end of the first level, they should be capable of choosing the diagnosis they wish to conduct for Paris city and identifying the type of data required to achieve this diagnosis.

Level 2

The goal of the second level was to learn how to summarize information using appropriate statistical tools, selected among the available statistical indicators, tables, and graphs (Multimedia Appendix 2). The level was structured as follows: back on campus, Marie (the game's learning companion; Figure 2) guides the learners toward a blue door, which symbolizes the start of the next level—*Analyst*. Players thus move into a new learning environment, accompanied by blue Marie, and learn about basic statistical methods and the different indicators they can use for territorial diagnosis. Robert is on hand to help learners as they watch 3 tutorials on how to use the statistical software Stata and its main analytical functions. They then get to grips with the software's various functions and statistical features with the help of crosswords, drag and drop exercises, and puzzles.

To finish off, learners use the various simulation tools to begin processing the data that they themselves collected in level 1, with a view to producing pertinent statistical indicators, constructing graphs, and conducting the necessary statistical analyses (such as a variance analysis or mean comparison test). With Robert's help, the learners then analyze their results using tools including a quiz and a virtual dialogue session.

Players thus move between 2 game environments (Figure 4): theoretical statistical learning (similar to an actual lecture) and the virtual office (which corresponds more closely to practical work, conducted with or without the help of an instructor).

To complete the level, learners must complete numerous challenges (crosswords, drag and drop, and puzzles). By the end of this level, learners should be able to conduct and interpret statistical analyses on the data they have collected and to present the information clearly.

Level 3

The aim of level 3 was to learn how to present data by using appropriate Geographical Information Systems (GISs), and how to interpret the resulting mapping (Multimedia Appendix 3). To achieve this objective, the level was structured as follows: as in the previous level, Marie guides learners across the virtual campus to a green door that opens onto the *Atlas* level. In this new learning environment, green Marie (Figure 5) accompanies players as they learn about GISs, their use, and their importance for territorial diagnosis. Thereafter, Robert (Figure 5) guides players through 5 tutorials focusing on the ArcGIS software and its function in terms of spatial analysis and geomatic and cartographic features. They then familiarize themselves with the use of the various geomatic and spatial mapping functions and features with the help of exercises, including crosswords, drag and drop exercises, and puzzles.

To complete the level, learners must use the various simulation tools at their disposal to map and interpret the data they collected in level 1, producing their own maps to visualize the health spatial distribution and also the environmental or socioeconomic spatial distribution according to their initial choice. With Robert's help, the learners then analyze their maps using tools, including a drag and drop test, a virtual dialogue session, and a puzzle.

Players thus move between 2 game environments: lessons on the geographical tools (similar to an actual lecture) and the virtual office (which corresponds more closely to practical work, conducted with or without the help of an instructor).

To complete this third level, learners must complete a total of 40 challenges (crosswords, drag and drop exercises, and puzzles). By the end of this level, learners should be able to summarize information using appropriate mapping tools and present essential information clearly.

Level 4

The aim of level 4 was to learn how to cross-compare data using appropriate geographical tools and correctly interpret their spatial distribution (Multimedia Appendix 4). To achieve this objective, the level was structured as follows: back on campus, Marie guides the learners toward an orange door, which symbolizes the start of the next level—*Cluster*. In this new learning environment, orange Marie (Figure 5) guides players as they learn the theoretical foundations of clustering techniques, their use, and their importance to establish a territorial diagnosis. Robert (Figure 4) then accompanies them as they watch 4 tutorials on the Satscan software (for scan statistics analysis) and its spatial analysis functions.

To complete the level, learners must use the various simulation tools at their disposal to analyze the data they collected in level 1, identifying the most vulnerable areas of Paris city and disseminating results of the territorial diagnosis. With Robert's help, the learners then interpret these spatial analyses using tools, including a quiz and a virtual dialogue session.

Players thus move between 2 game environments: a learning environment focused on spatial learning (similar to an actual lecture) and the virtual office (which corresponds more closely

to practical work, conducted with or without the help of an instructor).

To complete this fourth level, learners must complete a total of 35 challenges (crosswords, drag and drop exercises, and puzzles). By the end of this level, learners should be able to produce a spatial representation of the data using appropriate geographical tools and present the resulting territorial diagnosis.

Organization and Management of the Serious Game, Equit'Game

The schematic representation of the structure of Equit'Game, comprise a main block (dispositif.ludiscape) that contains the game's 4 levels along with external files that contain smaller .ludiscape blocks for each level.

The main block contains all of the levels that make up Equit'Game, including all resources, databases, and videos, and the tests and quiz modules.

The external files contain the tutorials, videos, and simulation modules, incorporating large databases that have been deliberately separated from the main block to reduce the size of the game, facilitating updates, and speeding up the handling of various game scenarios.

Results

This study was a success because of the cooperation between teachers and researchers from different disciplines, including epidemiology and health geography, specialist of pedagogy and e-learning, and designer of serious games. They participated in the development of all the steps from design to validation of the Equit'Game app.

Our serious game has been presented in several meetings organized in the School of Public Health (École des hautes études en santé publique [EHESP]) and in the Université Sorbonne Paris Cité, who provide financial support for the development of Equit'Game. We also finished the conception of the teaser available on the Web which has been used to communicate the objectives of the game. Several meetings were held with the *Department of Pedagogies-EHESP* to validate the development process. In addition, the demo version of the serious game is available to all on the Web [25].

In the first step, we planned to test our app interface, designed especially for adults (professional and postgraduate students) among a panel of local professionals who work directly with interested students and professionals. These are some of the most relevant points:

- Font size and colors used.
- Voice accompaniment in texts and messages, guiding the user.
- Use of realistic elements to simulate a real case.
- Clear and easy interfaces.
- No time limits.
- The change between successive game levels.
- Conclusions after each game level to encourage users and facilitate the learning process by repeating concepts.
- Animations and sound effects to keep the attention of the user.

In the second step, we planned to use our application, Equit'Game, with postgraduate students of EHESP in the next academic year. This educational development will be part of different modules. It will consolidate teaching modules of spatial analysis, information systems, biostatistics, and risk assessment related to the urban environment toward students enrolled in the Master of Public Health and Environmental Risks (about 20-25 students/year). It will also be a part of the teaching in the Master's degree in Engineering and Risk Management in Environmental and Occupational Health, particularly within the *Spatial approach as a tool for territorial diagnosis* module coordinated by the bearer of this project (about 10-15 students/year).

The variables analyzed concern both the application interface and the running of the game. The point studies were time, number of attempts, and errors.

All the sessions, both for the design and system validation, will be carried out during the class with the presence of a teacher.

At the end of the game session, we will perform a satisfaction survey, including several items:

- Did you like Equit'Game and its different interfaces?
- Whether they would play again (Will you play again?);
- Did you find the game complicated?
- Did you have fun? (whether the users had fun playing);
- Did you know/have you ever played with serious games before?

The teacher will detail all the questions orally in a clear and simple way to facilitate the level of understanding of all users. Then, users can answer all questions on the Web.

Some items will be evaluated with binary answers (Yes or No), while others assess the level of difficulty using a 10-point scale.

In addition, from our platform, which allows us to monitor the progress of each player within the game, an objective assessment based on parameters implemented in the system can be made, including time spent in performing the different activities and number of attempts or level played.

In the long term, this original development will be adapted to propose the game as an e-learning program.

Discussion

Equit'Game was developed to help learners with the techniques of territorial diagnosis, with the aim of creating an *innovative tool for public health* capable of conveying educational messages and providing a structure for training. Equit'Game provides a fun learning environment in which players learn how to approach a territory and conduct spatial analyses by using a combination of methods, tools, and data, ensuring that information is not misinterpreted. This educational tool can be adapted to other territories, and the approach adopted in this project is transposable in other public health issues.

Acknowledgments

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Authors' Contributions

SD and WK had the original idea for this serious game named Equit'Game. DR carried out the application development. SD, WK, and DR carried out the game development. SD, WK, DR, AM, WH, and DZN had worked to adapt the development of the application to the needs of the final users more easily. All the authors drafted the paper and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Equit'Game level 1.
[PNG File , 544 KB - resprot_v9i1e11786_app1.png]

Multimedia Appendix 2
Equit'Game level 2.
[PNG File , 547 KB - resprot_v9i1e11786_app2.png]

Multimedia Appendix 3
Equit'Game level 3.
[PNG File , 658 KB - resprot_v9i1e11786_app3.png]

Multimedia Appendix 4
Equit'Game level 4.
[PNG File , 482 KB - resprot_v9i1e11786_app4.png]

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Abbreviations

ADEME: Agence de l'Environnement et de la Maîtrise de l'Énergie
CSS: Cascading Style Sheet
EHESP: École des hautes études en santé publique
GIS: geographical information system
LMS: learning management system
Moodle: modular object-oriented dynamic learning environment
SCORM: shareable content object reference model

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Protocol

Evaluation of a Health Information Technology–Enabled Panel Management Platform to Improve Anticoagulation Control in a Low-Income Patient Population: Protocol for a Quasi-Experimental Design

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Abstract

Background: Warfarin is one of the most commonly prescribed medications in the United States, and it causes a significant proportion of adverse drug events. Patients taking warfarin fall outside of the recommended therapeutic range 30% of the time, largely because of inadequate laboratory monitoring and dose adjustment. This leads to an increased risk of blood clots or bleeding events. We propose a comparative effectiveness study to examine whether a technology-enabled anticoagulation management program can improve long-term clinical outcomes compared with usual care.

Objective: Our proposed intervention is the implementation of an electronic dashboard (integrated into a preexisting electronic health record) and standardized workflow to track patients' laboratory results, identify patients requiring follow-up, and facilitate the use of a validated nomogram for dose adjustment. The primary outcome of this study is the time in therapeutic range (TTR) at 6 months post intervention (a validated metric of anticoagulation quality among patients receiving warfarin).

Methods: We will employ a pre-post quasi-experimental design with a nonequivalent usual-care comparison site and a difference-in-differences approach to compare the effectiveness of a technology-enabled anticoagulation management program compared with usual care at a large university-affiliated safety-net clinic.

Results: We used a commercially available health information technology (HIT) platform to host a registry of patients on warfarin therapy and create the electronic dashboard for panel management. We developed the intervention with, and for, frontline clinician users, using principles of human-centered design. This study is funded until September 2020 and is approved by the University of California, San Francisco Institutional Review Board until June 22, 2020. We completed data collection in September 2019 and expect to complete our proposed analyses by February 2020.

Conclusions: We anticipate that the intervention will increase TTR among patients taking warfarin and that the use of this HIT platform will facilitate tracking and monitoring of patients on warfarin, which could enable outreach to those overdue for visits or laboratory monitoring. We will use these findings to iteratively improve the platform in preparation for a larger, multiple-site, pragmatic clinical trial. If successful, our study will demonstrate the integration of HIT platforms into existing electronic health records to improve patient care in real-world clinical settings.

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KEYWORDS

population health; warfarin; biomedical technology

Introduction

Background

Warfarin is one of the most commonly prescribed medications in the United States, with more than 20 million Americans taking warfarin anticoagulation therapy to prevent the formation of blood clots. As one of the most common culprits of adverse drug events (ADEs) in outpatient settings [1], warfarin dosing must be individualized to be effective; overdosing of warfarin can cause serious bleeding complications, whereas underdosing does not provide adequate protection against thromboembolism. As such, the National Action Plan for ADE Prevention targets blood thinners as a high priority for intervention [2].

Despite more than 50 years of clinical experience, studies suggest that patients taking warfarin fall outside of the recommended therapeutic range 30% of the time [3]. Therapeutic range is based on a laboratory test called the international normalized ratio (INR), and a patient's time in therapeutic range (TTR) is associated with lower risk of developing blood clots from underdosing of warfarin or bleeding events from overdosing [4]. Therefore, warfarin treatment requires periodic monitoring with blood tests to inform dose adjustment [5].

Unfortunately, solutions for efficient monitoring of warfarin treatment are still lacking, especially in settings such as safety-net clinics with relatively limited resources and health technology infrastructure. In safety-net clinics caring for low-income, uninsured, or underinsured patients, maintaining warfarin in the therapeutic range poses an additional challenge because of limited health literacy and educational attainment for a large proportion of the patient population [6,7], prevalent impairment in cognitive function [8], and various socioeconomic challenges [9]. Hence, proactive and efficient strategies that support outpatient warfarin monitoring are urgently needed.

As anticoagulation therapy relies on well-established, standardized care protocols with clear safety and efficacy targets (eg, INR monitoring), it is well suited to health information technology (HIT) approaches that can identify patients who need a specific treatment, monitoring, or intervention and help health care providers execute the appropriate management plan. These software platforms have been widely used for outreach and management of chronic illnesses, including diabetes, asthma, cancer, depression, and congestive heart failure [10-14], where their use improves health outcomes and is cost-effective [15-17]. However, many HIT interventions are not adequately integrated with current electronic health records (EHRs), forcing health systems to add layers of complexity to clinician workflow that are seldom feasible in safety-net clinics with limited resources [18]. Moreover, current platforms are not customized for anticoagulation therapy to facilitate the attainment and tracking of safety and efficacy targets. This study aims to resolve this limitation by implementing a locally customized, user-designed HIT tool that interfaces with the EHR and focuses on improving the quality of anticoagulation therapy.

Objective

In this study, we propose to design and test an electronic dashboard for panel management of patients taking warfarin anticoagulation therapy at a large university-affiliated safety-net clinic. We have previously developed an electronic registry of patients taking warfarin and a team-based workflow for scheduling or rescheduling clinic appointments for patients outside of the therapeutic range [19]. This prior pilot intervention led to an improvement in patient attendance to visits for anticoagulation management [19]. We will use a commercially available HIT platform to host our patient registry and create an electronic dashboard for panel management that will enable providers to track patients' INR, implement a workflow for scheduling patients to visits, and use a validated electronic anticoagulation treatment nomogram for dose adjustment during the visit.

Methods

Study Design

This is a pre-post quasi-experimental design with a nonequivalent usual care comparison site. We will use a difference-in-differences approach to compare the effectiveness of a technology-enabled panel management anticoagulation program with usual care in improving TTR.

Study Population and Setting

Clinical Sites

The site that will undergo the intervention is a large university-affiliated anticoagulation clinic within a network of 12 safety-net clinics in San Francisco that serve a racially and ethnically diverse population of low-income patients. A team of 3 part-time clinical pharmacists, 1 part-time nurse practitioner, a clinical coordinator, and a physician medical director provides care to approximately 250 patients who receive primary care in any of the 12 clinics in the city's public health network. This network is operated by the San Francisco Department of Public Health (SFDPH), and its member clinics use the same electronic health records. Our comparison site is another anticoagulation clinic site within this network, which is chosen for its similarity with the intervention site with regard to its university affiliation and the demographic composition of its patient population. The comparison site delivers anticoagulation to approximately 50 patients receiving primary care at the family health center; 2 part-time clinical pharmacists and a physician medical director staff this clinic.

As both clinics are within the SFDPH, they follow the same protocols for standard management (monitoring intervals of 4 weeks before establishing therapeutic control and 12 weeks once therapeutic control has been achieved for 3 consecutive visits). The standard management includes a protocol for patients scheduled to undergo high-risk surgical operations. Over the past 3 years, these clinics have sought to use an internal guideline for switching patients from warfarin to direct-acting

oral anticoagulants (DOACs) based on the duration of treatment, most recent INR, warfarin medication adherence, drug-drug interactions, indication for anticoagulation, and kidney and liver function.

Time Horizon

The period of analysis will include a 12-month preintervention period and a 12-month postintervention period that will each include an *enrollment* period in the first 6 months of pre and postintervention.

Enrollment Inclusion Criteria

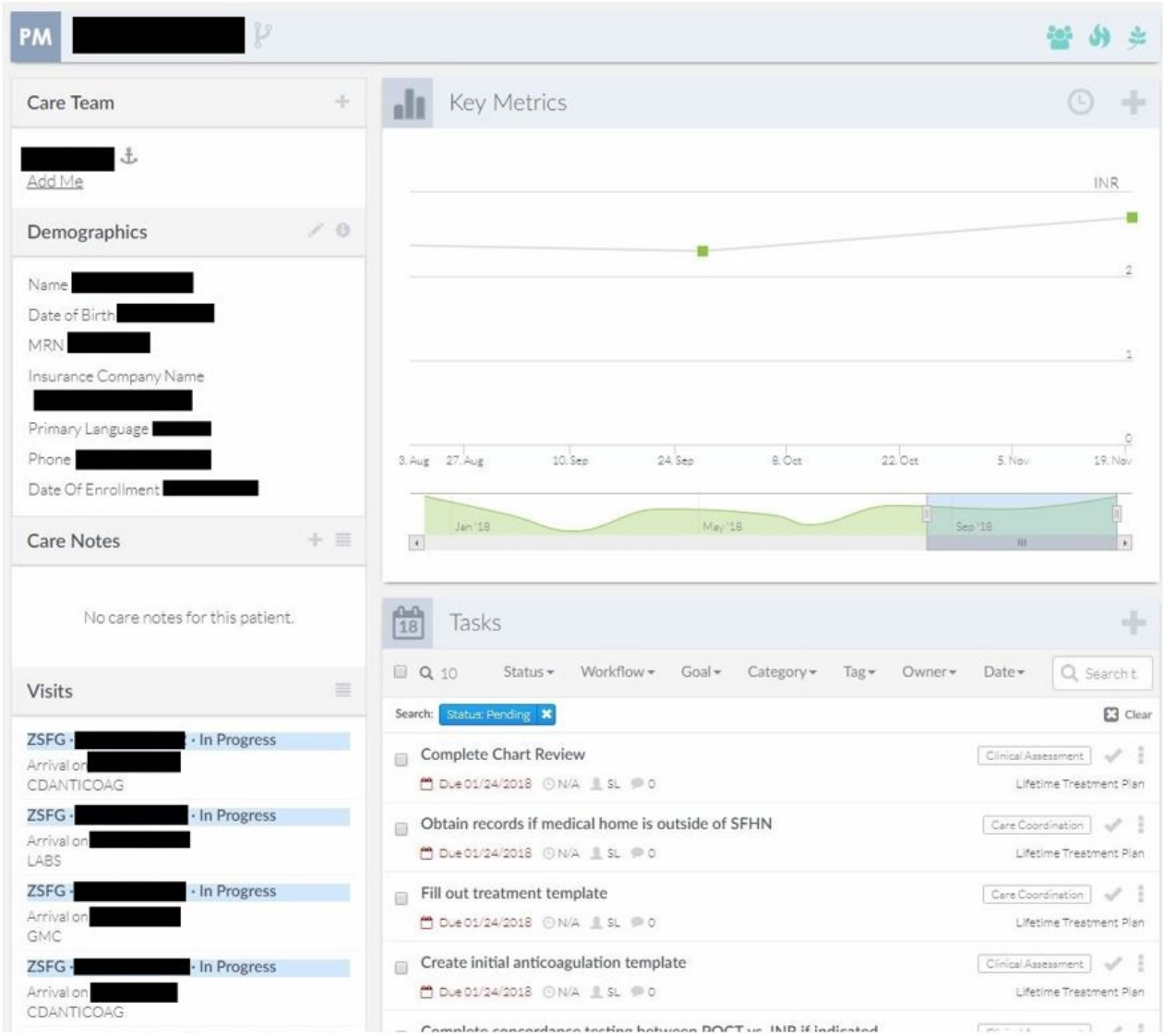
The study will include all adult patients aged 18 years or above on anticoagulation therapy (such as warfarin, apixaban, rivaroxaban, fondaparinux, dabigatran, and edoxaban) identified by ICD-10 (International Classification of Diseases, tenth revision) Z79.01, who present to anticoagulation clinic for initiation or management of anticoagulation therapy over 2 *enrollment* periods of 6 months at the 2 large academic safety-net clinics (intervention and comparison site) before and after the start of the intervention. We chose the enrollment period of 6 months to enable at least 6 months of follow-up for every patient monitored in the study in both pre and postintervention periods.

Intervention

The intervention uses a new electronic dashboard (Figure 1) for panel management of patients on warfarin anticoagulation therapy to improve therapeutic efficacy. The intervention will feature the following elements:

- An electronic dashboard that displays medication information, TTR, and other laboratory results. The dashboard will present relevant data on patients prescribed anticoagulants to facilitate more effective and efficient panel management. The dashboard is customized to show information important for the safe management of these medications (such as current medications, laboratory results, attendance rate to scheduled visits, and language spoken by patients). The dashboard can be used to sort patients according to desired criteria such as diagnoses, specific TTR parameters, or patients with missed scheduled appointments or laboratory monitoring. Finally, the dashboard can be used to create tasks, assign workflow, and send reminders to clinic providers.
- A panel management workflow that will include patient outreach activities, such as appointment reminders and rescheduling of missed appointments; communication from the pharmacist to the patient's primary care provider or medical specialists, such as alerts to consider novel alternative anticoagulation therapy (eg, DOAC); and suspected or pending adverse effects based on early signs, such as bruising or drug interactions.
- Integration of evidence-based treatment nomogram that will be accessible on the platform for use by the pharmacist to guide therapeutic treatment decisions. Although multiple guidelines addressing anticoagulant management are available to clinical providers, they are not integrated at the point of care. The dashboard will display relevant clinical guidelines while providers are managing their patients. As an example, the warfarin dosing nomogram will be shown on the screen at the same time the providers are managing a patient on warfarin.

Figure 1. Screenshot of electronic dashboard and panel management interface.



Electronic Dashboard Development

We developed the dashboard in partnership with our frontline anticoagulation providers using the principles of human-centered design [20], which emphasizes the use of rapid prototyping, early and continuous stakeholder engagement, and iterative development and evaluation of interventions. We partnered with a commercially available health care technology platform (CipherHealth LLC) to host the electronic dashboard [21]. Our study team includes a frontline anticoagulation provider (SL) who conducted informal interviews with other frontline anticoagulation providers at the intervention clinic site to assess their needs and potential usability of the dashboard and an expert cardiologist (DK) who collaborated to create the initial dashboard prototype. We developed subsequent alpha versions of the prototype collaboratively with 2 additional coinvestigators, including an implementation scientist (VF) and a patient safety and digital health technology researcher (US), who are both practicing primary care physicians at the intervention site. We provided the final alpha version to the anticoagulation providers for use over a period of 4 weeks, and we conducted direct observations and informal interviews that led to additional modifications of the platform based on user feedback.

Usual Care Comparison

Under current practice (ie, usual care), patients who receive care at either site are referred to an anticoagulation clinic where a pharmacist or nurse practitioner assesses the patient and manages their anticoagulation therapy on an ongoing basis. At each visit, either in person or virtual (by phone), the provider reviews the indication, treatment duration, and relevant history and proactively screens whether a patient qualifies to be transitioned to a DOAC medication. The frequency of follow-up visits is determined by INR results, INR trends, and other clinically relevant factors, including age and bleeding or clotting risks. Current practice does not include panel management or the use of a HIT tool that facilitates panel management and integration of an evidence-based treatment nomogram at the point of care.

Outcomes and Measurements

Primary and Secondary Outcomes

The *primary outcome* will be TTR, a well-established intermediate clinical outcome that is the most widely used metric of anticoagulation quality among patients receiving warfarin [22-25]. It is defined as the proportion of time during which the INR is within the range deemed therapeutic for the indication for which the patient is receiving warfarin therapy. For instance, an INR between 2 and 3 inclusive is therapeutic for patients receiving warfarin for secondary prevention of venous thromboembolism, but an INR between 2.5 and 3.5 inclusive is considered therapeutic for patients with mechanical mitral valves. We will calculate TTR using the Rosendaal method [26], which uses linear interpolation to assign INR values for each day between consecutive INR values. We will calculate the TTR for patients with at least 5 INR laboratory values over the course of at least 6 months. Patients who stop coming to the clinic before or are transitioned to DOACs before this threshold will be censored. The *secondary outcome* will be proportion in therapeutic range defined as the proportion of laboratory INR values that are within the therapeutic range (ie, number of INR values in range divided by the total number of laboratory INR tests performed, regardless of the interval between these values).

Exploratory Endpoints

We will examine a number of process measures that are on the pathway to achieving therapeutic goals for anticoagulation, including time from out-of-range INR value to patient contact and time from warfarin initiation to first therapeutic INR (Table 1). We will measure other process-of-care metrics, including (1) patient's attendance rate to scheduled visits for anticoagulation management, (2) proportion of patients not meeting monitoring guidelines (defined as those who do not have INR testing at least every 56 days based on National Quality Forum recommendations [16]), (3) appropriate duration of therapy (defined as the days of observed warfarin therapy divided by the recommended days of therapy), and (4) provision of telephonic or other remote visits for anticoagulation management. We will also report clinical endpoints such as bleeding complications (hospital visits for bleeding and minor vs major hemorrhagic strokes), incident deep venous thrombosis (DVT), incident pulmonary embolism (PE), and ischemic stroke, although we are likely not adequately powered to detect statistically significant differences between the control and intervention arms. In addition to these process measures for warfarin patients, we will also measure adherence to protocols for screening and transitioning patients to DOACs, which requires assessing patients for medication adherence, drug-drug interactions, and liver and renal function.

Table 1. Variables, outcomes, and process measures with definitions.

Variables, outcomes, and process measures	Definition	Rationale
Independent variables		
Basic demographics	Age, gender, race and ethnicity, language, and insurance	Assess patient population
Diagnoses	Atrial fibrillation, atrial flutter, stroke, DVT[a], mitral valve replacement, atrial valve replacement, pulmonary arterial hypertension, and PE[b]	Assess prevalence of indications for anticoagulation
SAMe-TT_2R_2 score (sex, age, medical history, treatment, tobacco use, and race)	A clinical scoring system designed to predict which patients on oral vitamin K antagonists (eg, warfarin) will reach an adequate TTR[c] (>65%-70%)	Assess baseline likelihood of achieving/maintaining anticoagulation control
Outcomes		
TTR	Days in range divided by total days on warfarin	Assess overall treatment efficacy
Proportion in range	INR[d] values in range divided by total INR values measured	Secondary measure of treatment efficacy
TWTR[e]	Days from first administration of warfarin to first therapeutic INR value	Assess efficiency of achieving therapeutic control
Process measures		
Time from out-of-range INR value to patient contact	Days until patient outreach after abnormal INR value	Assess responsiveness of the clinic to abnormal values
Attendance rate to scheduled visits	Proportion of visits attended (completed visits divided by scheduled visits)	Assess efficiency of clinical operations
Proportion of patients meeting monitoring guidelines	Proportion of patients who receive regular 56-day monitoring	Assess adherence to treatment guidelines (ie, nomogram)
Appropriate duration of therapy	Observed duration (days) of anticoagulation therapy divided by recommended total duration	Assess the extent of overtreatment
Provision of telephonic or other remote visit for anticoagulation management[f]	Proportion of patients transitioned from in-person to phone visits (related to TWTR)	Assess adherence to workflow protocol and overall clinic performance[f]
DOAC[g] transitions	Proportion of eligible patients screened and/or transitioned to DOACs	Assess adherence to screening and transition protocols
Other clinical outcomes		
Bleeding complications	Incidence of bleeding during treatment	Assess the incidence of adverse events
DVT	Incidence of DVT during treatment	Assess the incidence of adverse events
PE	Incidence of PE during treatment	Assess the incidence of adverse events
Ischemic stroke	Incidence of stroke during treatment	Assess the incidence of adverse events

[a]DVT: deep venous thrombosis.

[b]PE: pulmonary embolism.

[c]TTR: time in therapeutic range.

[d]INR: international normalized ratio.

[e]TWTR: time from warfarin initiation to first therapeutic INR.

[f]The workflow protocol recommends that patients with international normalized ratio values consistently in range must be transitioned from in-person to telephone visits. If the intervention is effective, we would expect an increase in patients switched to remote telephonic monitoring.

[g]DOAC: direct-acting oral anticoagulant.

Independent Variables

We will measure baseline patient demographics such as age, gender, race and ethnicity, and percent poverty in zip code. Other independent variables will include baseline history of chronic kidney disease, ischemic heart disease, stroke, atrial fibrillation, mitral valve replacement (MVR), atrial valve replacement (AVR), DVT, pulmonary arterial hypertension (PAH), and PE.

Analysis Plan

Overview

We will use the difference-in-differences approach to compare the effectiveness of the technology-enabled anticoagulation

management program with usual care in improving TTR. Implementation using a linear mixed model (LMM) will allow us to adjust for patient-level confounders; in addition, many patients will provide TTR outcomes both before and after implementation at the intervention clinic and in the matching periods at the control clinic, providing further natural control of confounding. We will also conduct a series of exploratory analyses of secondary outcomes, subgroup analyses to examine heterogeneity of effect, and exploratory mediation analyses to understand the processes by which the intervention might provide greater effectiveness.

Difference-in-Differences Analytic Approach

The primary analysis will use an LMM for potentially repeated values of TTR, which are calculated for each patient using the Rosendaal method described above and transformed as needed to meet normality assumptions. The LMM will include a random effect for patient to account for the within-patient correlation of the repeated TTRs and will also include fixed effects for clinical site, intervention period (pre vs post), and their interaction. The LMM coefficient for the interaction between clinical site and intervention period will be interpretable as the difference of differences, the focus of interest. In addition, adjusted mean TTRs by clinic and period will be obtained as linear combinations of the coefficients in the model. To further control confounding, the LMM will include patient-level factors, including baseline gender, race, age, desired value of INR, tobacco use, concurrent use of medications that interfere with warfarin, and presence of a high-risk comorbid condition at baseline (hypertension; diabetes; ischemic heart disease; congestive heart failure; stroke; and pulmonary, hepatic, or renal disease). We have chosen these covariates because they are the known predictive factors for the efficacy of warfarin therapy used to calculate the SAMe-TT_2R_2 score (sex, age, medical history, treatment, tobacco use, and race), a widely used clinical prediction rule for achieving and maintaining a desired TTR of greater than 65%, based on common clinical factors that influence INR and anticoagulation control [27]. We define baseline as the time of warfarin initiation for each patient. The model will also adjust for reasons for anticoagulation therapy such as having a baseline diagnosis of atrial fibrillation, MVR, AVR, DVT, PAH, and PE.

Analysis of Process Measures

We will employ the difference-in-differences analytic approach described above, using LMMs or generalized LMMs as appropriate to each outcome, to compare pre-post differences between the intervention and usual care clinics in the process outcomes listed in Table 1.

Subgroup Analysis to Test for Heterogeneity of Treatment Effects

We will produce strata-specific analyses stratified by the demographic characteristics and test for interactions by intervention arm and demographic subgroups such as age groups, race/ethnicity, and gender.

Multiple Hypothesis Testing

We will report the results of the hypothesis test for the primary outcome without adjustment for multiple hypothesis testing. No formal penalization for multiple hypothesis testing is planned for the analysis of process measures or subgroup analyses as these will be treated as exploratory and hypothesis generating. We will report 95% confidence intervals for all our estimates.

Multiple Imputation for Missing Data

We do not anticipate any missing data for our primary outcome. In the event of missing data, we will use a multiple imputation strategy to address missing data. In addition to multiple imputation under the standard assumption that data are missing at random (conditional on observed covariates and outcomes), we would also implement sensitivity analyses using imputation under plausible missing not at random scenarios.

Data Source, Collection, Management, and Safety

Consistent with the principles of pragmatic clinical trials, we will use EHR data for patient identification and assessment of intervention implementation and outcomes. We have established agreements between CipherHealth and the SFDPH to ensure data security. Data will flow between SFDPH EHRs and CipherHealth through secure file transfer protocols. SFDPH and CipherHealth programmers will regularly review data security procedures. All individuals who have access to patient data are either (1) clinicians with prior access or (2) research staff approved by the University of California, San Francisco internal review board, who have completed training in research ethics and compliance. Identifiable data will only be used for standard patient care and management; all data extracted from the platform for analyses will be deidentified.

Minimum Detectable Effects

Preliminary analysis showed that 350 patients would provide 80% power in a test with 2-sided significance level of 5% to detect a difference of differences of 2 to 5 TTR percentage points, based on the proposed analysis using an adjusted LMM. The minimum detectable effect will depend on the intraclass correlation of the repeated TTR measures (assumed range: 0.80-0.95) and the percentage of patients providing measurements in both periods (assumed range: 50%-100%). These calculations assume that the standard deviation of the TTR outcome is 20 percentage points, based on published literature on TTR [28], and these calculations are penalized for covariate adjustment using an adaptation of the variance inflation factor [29].

Results

We used a commercially available HIT platform to host a registry of patients on warfarin therapy and create an electronic dashboard for panel management. We developed the HIT dashboard interface and co-designed the intervention with, and for, frontline clinician users. This study is funded until September 2020 and is approved by the University of California San Francisco Institutional Review Board until June 22, 2020. We completed data collection as of July 2019 and expect to complete our proposed analyses by February 2020.

Discussion

We propose a quasi-experimental study to evaluate the implementation of an integrated HIT intervention for management of anticoagulation and examine pre-post outcomes on clinical and implementation outcomes. The HIT platform will facilitate tracking and monitoring of patients on warfarin and enable outreach to those overdue for visits or laboratory monitoring.

We developed the dashboard in partnership with our frontline anticoagulation providers using the principles of human-centered design [20], which emphasizes the use of rapid prototyping, early and continuous stakeholder engagement, and iterative development and evaluation of interventions. An important constraint was its integration into the existing electronic health record with minimal disruption of the existing workflow of anticoagulation service providers. We believe this emphasis on usability is critical to the successful adoption of a HIT intervention.

We anticipate that the intervention will facilitate tracking and monitoring of patients on warfarin, allowing providers to reach out to those with abnormal results (who may need dose adjustments) as well as those overdue for visits or laboratory monitoring. Coupled with increased use of validated nomograms for dose adjustment (which has been previously shown to be a key predictor of improved TTR), our technology-enabled panel management program will increase the proportion of time in TTR among patients taking warfarin. Insights from this study will help us improve and adapt our HIT platform in preparation for a larger, pragmatic clinical trial powered for clinical outcomes. Such a trial would also examine the cost-effectiveness of the intervention.

This project is innovative with significant implications for use of HIT to improve clinical care. First, use of an HIT-enabled intervention to improve anticoagulation management in resource-constrained settings, such as safety-net clinics, could improve outcomes and reduce adverse events at the national level, as these clinics often provide care for a disproportionate share of high-risk and high-cost patients. A common complaint of many widely used electronic health record systems is the relative lack of customizability for individual health systems and clinicians. We developed a HIT interface with, and for, frontline clinician users in safety-net clinic. Safety-net clinics often lack the resources for HIT-based interventions, yet these sites might gain the most from such interventions given the clinician's workload and disease burden. Patients experiencing socioeconomic vulnerabilities tend to have chaotic lives; modest interventions involving reminders and other notifications have the potential to make significant improvements to appointment adherence and thereby therapeutic control. Moreover, technology-enabled panel management, as in our intervention, will help clinicians triage patients according to risk for harm or loss to follow-up and thereby more efficiently allocate limited resources in this setting.

If successful, our study will demonstrate an example of integration of HIT platforms into existing electronic health records to improve patient care in real-world clinical settings. As we designed the intervention to work within the existing clinic personnel and electronic health record, it also promises to be sustainable and adaptable to other clinics within and outside of the network that share a similar data infrastructure, allowing for the retention of customizations made at pilot sites. However, modified panel management workflows will vary from site to site as the ability to tailor the intervention is, in part, what makes it novel. Finally, the intervention facilitates the use of evidence-based dosing algorithms, thereby promoting the adoption of evidence-based practice in anticoagulation clinics—an important strategy to optimize health outcomes at the population level.

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Authors' Contributions

VF contributed to conceptualization of the study and played the leading role in constructing the study design and writing the manuscript. DK played a leading role in conceptualization of the study, designing the intervention, and development of the dashboard. He also contributed to writing, reviewing, and editing the manuscript. RC played a leading role in coordinating the dashboard development and implementation of the intervention. He also played a significant role in writing the manuscript. SYL contributed to designing the intervention and led its implementation. She also contributed to writing, reviewing, and editing of the manuscript. US played the leading role in conceptualization of the study, designing the intervention, developing the dashboard, and reviewing and editing of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ADE: adverse drug event
AHRQ: Agency for Healthcare Research and Quality
AVR: atrial valve replacement
DOAC: direct-acting oral anticoagulant
DVT: deep venous thrombosis
EHR: electronic health record
HIT: health information technology
INR: international normalized ratio
LMM: linear mixed model
NIH: National Institutes of Health
MVR: mitral valve replacement
PAH: pulmonary arterial hypertension
PE: pulmonary embolism
SFDPH: San Francisco Department of Public Health
TTR: time in therapeutic range

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Protocol

Screening University Students for Health Checks With an Electronic Health Questionnaire in Finland: Protocol for a Retrospective, Register-Based Cohort Study

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Abstract

Background: Health questionnaires and health checks are an established part of preventive health care services in Finland. However, only very limited research of these has been conducted. The Finnish Student Health Service (FSHS) provides primary health care services to all bachelor's and master's degree university students (approximately 134,500 students) in Finland. FSHS's statutory health examination process of university entrants includes an electronic health questionnaire (eHQ) and, based on the students' eHQ responses, a subsequent health check if necessary. To our knowledge, no previous studies have been published on the use of questionnaires for screening students for general health checks.

Objective: The general aim of the study is to evaluate the health examination process of university entrants. The objectives are to determine how students' self-reported health in the eHQ and participation in the health examination process are associated with graduation, mental health problems, and the use of student health care services.

Methods: This is an ongoing, nationwide, retrospective, register-based cohort study with a 6-year follow-up. The study population is the cohort of university entrants (N=15,723) from the 2011-2012 academic year. These students were sent the eHQ, which consisted of 26 questions about health, health habits, social relations, and studying. Based on the eHQ responses, students were referred to one of the following interventions: (1) a health check, (2) an appointment other than a health check (eg, physiotherapy), or (3) electronic feedback to support a healthy lifestyle, when the other interventions were not necessary. Multiple comparisons will be made within these groups using logistic regression. The primary outcome variables are graduation, having a mental health problem, and attending a health check. The use of FSHS health care services will be studied with the cluster analysis method. The data have been obtained from three nationwide registers: the eHQ register, the medical records of FSHS, and the Higher education achievement register. The data have been linked using personal identity codes.

Results: As of August 2019, the data collection and processing are complete and the statistical analyses are in progress. Preliminary results are expected in autumn 2019. Further publications are expected in 2020, and two PhD theses are expected to be completed by the end of 2022.

Conclusions: Studying practical procedures in primary health care is highly important for resource allocation and the development of evidence-based processes. This study will be the first to assess the usage of a health questionnaire in screening students for health checks. The findings of this study will contribute to the field of preventive health care. The main practical implication is the development of the FSHS's health examination process. We hypothesize that participation in the health examination process enhances academic achievement and the detection of university students' mental health problems early on in their studies.

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KEYWORDS

electronic health questionnaire; health check; screening; students; student health services; digitalization; register study; preventive health services

Introduction

The well-being of university students has raised concerns [1,2]; the awareness of students' mental health problems, especially, has grown [3-5]. In Finland, health questionnaires and health checks are essential preventive measures for the early detection of health concerns in student health care [6,7]. However, only very limited research has been conducted on these measures [8-10]. In general, the evidence on the effects of health checks is inconclusive, both in the student and the general populations [8,11-15].

Finland has a strong tradition of offering preventive health care services to its residents (see Multimedia Appendix 1) [16]. Student health care is a part of this statutory preventive health care provision (see Textbox 1) [7]. The promotion of the health and study ability of the students at the level of individuals and communities forms a central part of student health care services (see Multimedia Appendix 2) [17].

The Finnish Student Health Service (FSHS) provides student health care services to all bachelor's and master's degree university students in Finland (approximately 134,500 students) [18,19]. FSHS has provided health checks to all university entrants since the 1970s. However, in the beginning of the 21st century, universal health checks were identified to be an area for development due to low participation rates. As a solution, FSHS developed a two-stage health examination process. The process included an electronic health questionnaire (eHQ) and, based on the students' eHQ responses, a subsequent health check if necessary. The eHQ includes 26 questions about health, health habits, social relations, and studying (see Multimedia Appendix 3). Providing a digitalized health questionnaire to all university entrants instead of universal health checks was believed to increase the number of students reached. Further, the process was aimed to facilitate identification of students with health problems and to target health checks to these students.

The two-stage health examination process was developed by following the ideology of the plan-do-study-act cycle [20]. Feasibility of the eHQ was tested in 2005 [9]. A pilot study of the process was conducted in 2008 [21]. Based on the results of these studies, the eHQ was further developed. The health examination process was implemented nationally in 2009. The data collected over time now enable studying the process again.

To our knowledge, no previous studies have been published on the use of a questionnaire for screening students for general health checks. However, multiple studies exist about different questionnaires that are used to detect specific symptoms [22-24] or to evaluate health behavior and social conditions [25-28] in student populations. The eHQ aims to provide an overview of the health and well-being of university entrants rather than to identify specific conditions.

The general aim of this study is to evaluate the health examination process of FSHS. The specific research questions are as follows:

1. Is responding to the eHQ and attendance at the health check associated with completing a bachelor's or master's degree in the 6-year follow-up?
2. How are mental health problems associated with completing a bachelor's or master's degree in the 6-year follow-up?
3. How are responding to the eHQ and attendance at the health check associated with the use of FSHS' health care services?
4. How are university entrants' responses to the eHQ questions associated with:
   a. completing a bachelor's or master's degree?
   b. health check attendance?
   c. mental health problems?
   d. the use of FSHS health care services?

Textbox 1. Student health care services of university students according to the Finnish Health Care Act [7].

- Triennial checks on health and safety in educational institutions and welfare promotion among learning communities
- The monitoring of students' health, welfare, and fitness to study, including a health questionnaire during the first year of study leading to a health check if necessary
- The provision of health and medical care services for students, including mental health and substance abuse services, advice on sexual health, and oral health care
- Early identification of any special needs and tests required by students, support, and, if necessary, referral to further tests or treatment

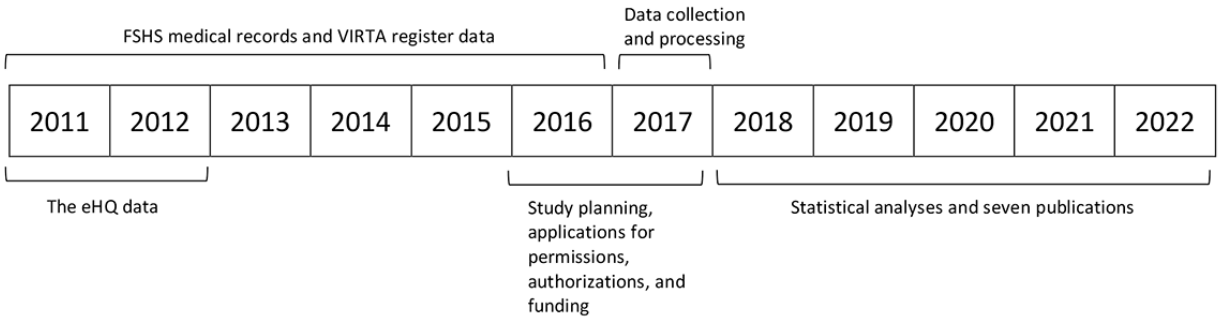
To the best of our knowledge, this type of health examination process will be studied for the first time. We hypothesize that the health examination process enhances university students' academic achievement and the early detection of mental health problems.

Methods

Design

This is a nationwide, retrospective, register-based cohort study with a 6-year follow-up (see Figure 1). The study population is the cohort of Finnish university entrants from the 2011-2012 academic year (N=15,723). Data from three nationwide registers have been linked and will be analyzed in order to answer the research questions.

Figure 1. The study timeline. eHQ: electronic health questionnaire; FSHS: Finnish Student Health Service; VIRTA: higher education achievement register.



Study Population

As stated, the study population is comprised of university entrants who enrolled in the 2011-2012 academic year (N=15,723). According to Statistics Finland, 2.7% (N=145,800) of the Finnish population were studying for a bachelor's or master's degree in one of the 13 universities in 2012 (see Table 1); 19% of men and 26% of women in the 19-21-year-old age class had entered a university [29]. In 2017, the median time to complete a bachelor's degree was 3.8 years and the median time to complete a master's degree, including a bachelor's degree, was 5.9 years [30].

The Finnish Student Health Survey has been conducted every 4 years since 2000 [31]. The survey indicates that Finnish university students are, in general, healthy. In 2016, 75% reported good or very good overall well-being [31]. However, mental health problems are a significant challenge in the Finnish student population. Every third student reported mental health problems in a 12-item general health questionnaire, and 7% were identified to be burnt out according to the study burn-out inventory [24,31].

Table 1. University students in Finland in 2012 according to Statistics Finland[a].

Students' degree status	Total, N	Female, n (%)	Male, n (%)
Studied either a bachelor's or master's degree	144,279	76,979 (53.35)	67,300 (46.65)
Started a bachelor's degree	15,218	8624 (56.67)	6594 (43.33)
Started a master's degree	4874	2538 (52.07)	2336 (47.93)

[a]Statistics Finland provides publicly available statistical information.

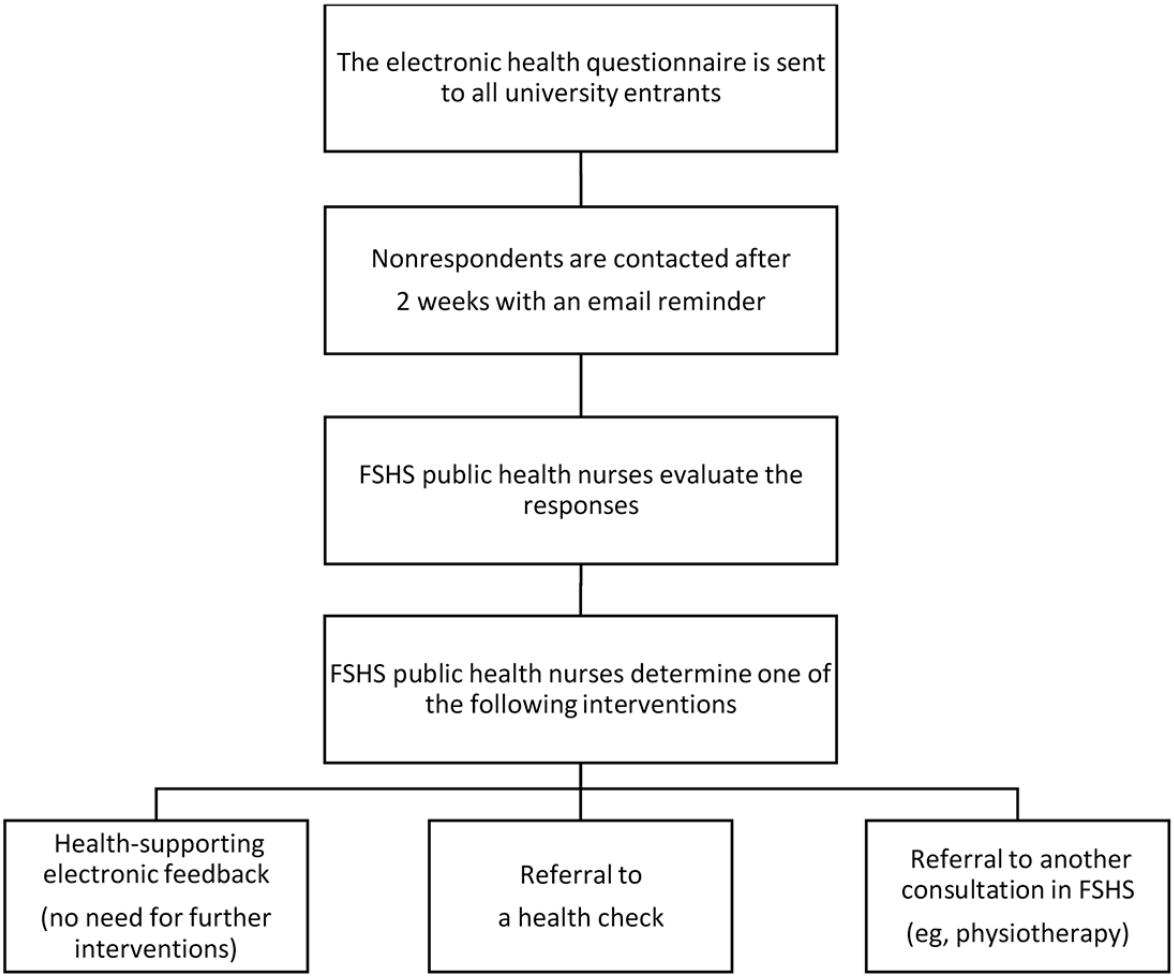
The Health Examination Process of the Finnish Student Health Service

The health examination process of FSHS includes an eHQ sent to all university entrants and a subsequent health check if necessary (see Figure 2). The process produces data about students' health and risk behaviors for FSHS. The data are used to develop student health care services and study environment.

The purpose of the eHQ is to give an overview of students' well-being and to identify students who have potential risk factors for study ability (see Multimedia Appendix 2). Students with potential risk factors are offered a chance for a health check conducted by a public health nurse. In the health check, the eHQ serves as a basis for discussion. In addition to being a screening tool, the eHQ is thought to be an intervention itself by motivating students to consider their health behavior.

It has been suggested that to detect health problems associated with academic functioning, a health questionnaire in student health care should include questions about social support; general, physical, and psychological health; study-related issues; help-seeking behavior; and life events in the past [32]. The eHQ covers all these subjects except for past life events.

Figure 2. The health examination process of the Finnish Student Health Service (FSHS) in the 2011-2012 academic year.

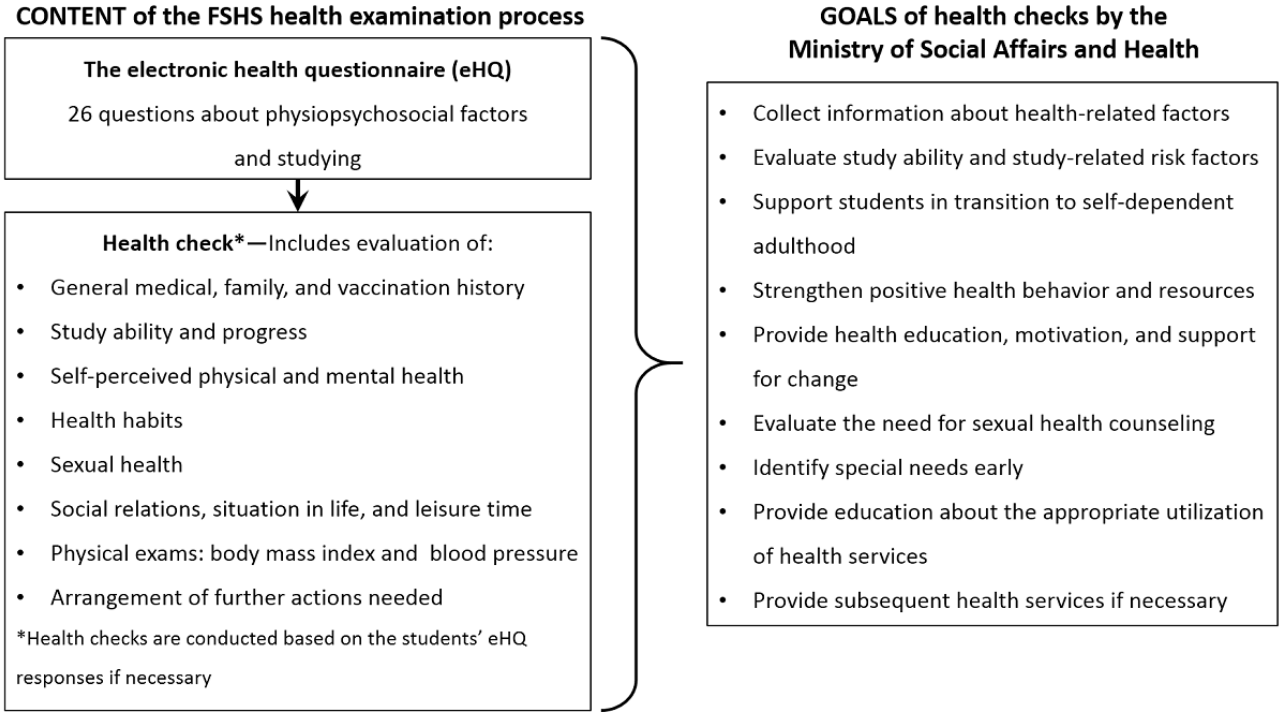


The eHQ consists of 26 questions about physical and mental health, social relations, and studying (see Multimedia Appendix 3). It includes questions about self-rated health, long-term diseases, and recurrent symptoms. Health habits, such as exercising, eating habits, sleeping, and substance abuse, including the Alcohol Use Disorders Identification Test (AUDIT), are reported [33]. Mental health-related questions cover, for example, questions about usual state of mind and loneliness. Most of the questions are adapted from validated questionnaires or from Finnish population surveys. However, the eHQ as a whole has not been validated.

The invitations to answer the eHQ were sent in clusters via email during the 2011-2012 academic year. To fill the eHQ, the students signed into a separate program protected by strong electronic identification [34]. The students who were referred to a health check were responsible for making the appointment themselves. Responding to the eHQ and attending the health check were voluntary for students. In the study, we will compare eHQ respondents with nonrespondents, and attendees to the health check with nonattendees, in terms of the research questions.

The general goals of the health checks are defined by the Ministry of Social Affairs and Health, whereas the content of the checks is undefined (see Figure 3) [6,17]. Therefore, FSHS has defined the content of the health checks for university students (see Figure 3).

Figure 3. The content of the health examination process defined by the Finnish Student Health Service (FSHS) and the goals of health checks in student health care according to the Ministry of Social Affairs and Health.



Data Sources

The data have been obtained from three nationwide registers: the eHQ register, the medical records of FSHS, and the *Higher education achievement register* (VIRTA) owned by the Ministry of Education and Culture [35].

The response data to the annual eHQ accumulate within the eHQ register, which is a separate part of the medical records of FSHS. The register is owned and managed by FSHS. The response data have been obtained for the 2011-2012 academic year.

The FSHS's medical records include systematic documentation on the students' medical history and care at FSHS. The study data include the following: (1) primary reasons for the encounters, (2) primary diagnoses, (3) number of encounters, and (4) profession of the health care professional involved in the encounter for the 2011-2017 period. The outcome variables *mental health problem* and *health check attendance* are derived from the medical records data. Mental health problems are identified based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and the International Classification of Primary Care, Second edition (ICPC-2) classifications [36,37].

VIRTA is the Higher education achievement register of the national data warehouse for higher education. The register includes, for example, records of graduations of all Finnish higher education institutions. The information about students' graduations has been obtained for the 2011-2017 period. The outcome variable *graduation* was obtained from the VIRTA data.

The data have been linked using Finnish personal identity codes. All Finnish citizens and permanent residents have personal identity codes administered by the Population Register Centre [38]. The code is individual to its holder and remains unchanged throughout the holder's lifetime [38].

Statistical Analyses

To describe the data, the frequencies, percentages, and medians with interquartile ranges will be calculated. For the preliminary analysis, chi-square tests will be employed to detect the associations between the categorical variables. Further, the normally distributed data will be analyzed with *t* tests and analyses of variance. In the cases where data are not normally distributed, the Mann-Whitney U test and the Kruskall-Wallis test for detecting the differences between the groups will be utilized. Multiple comparisons will be performed with the Bonferroni method.

In research questions 1, 2, and 4 a-c, multiple logistic regression will be the main analysis method to account for the associations between explanatory and outcome variables. The outcome variables in the regression analyses will be *graduation*, *having a mental health problem*, and *attending the referred health check*. The main explanatory variables will be students' responses to the eHQ. In addition, demographic factors (ie, age, sex, and field of study) will be accounted for.

In research questions 3 and 4 d, the use of FSHS health care services will be analyzed with clustering analysis to detect the patterns of how the students are using the services. The patterns will then be analyzed with the explanatory variables in order to find the associations between service use and other variables.

Comparisons in the study will be made between eHQ respondents and nonrespondents, health check attendees and nonattendees, graduates and nongraduates, and students who have and do not have mental health problems.

The analyses will be carried out using IBM SPSS Statistics for iOS and Windows, version 25.0 or later (IBM Corp), and R, version 3.6.1 (The R Foundation), with suitable packages [39].

Results

Schedule

As of August 2019, the data collection and processing are complete and statistical analyses are in progress. Preliminary results are expected in autumn 2019. Further publications are expected in 2020, and two PhD theses are expected to be completed by the end of 2022 (see Figure 1).

Ethics and Governance

The study is being conducted under the guidelines of the Finnish National Board on Research Integrity [40]. The study has been ethically reviewed by the Ethics Committee of the Tampere Region (reviews 2/2017 and 23/2017). The review was affirmative.

The study has been evaluated and authorized by the Finnish National Institute of Health and Welfare, which authorizes the research use of confidential data in Finland (Dnro THL/1364/5.05.00/2017) [41]. The study has received permission from the FSHS to conduct research. All 13 Finnish universities have given permission for their part to use the Higher education achievement register. A risk assessment and data protection plan has been delivered to the Finnish office of the data protection ombudsman.

Discussion

This study is the first to assess the usage of a health questionnaire in screening students for health checks. In addition, the study explores the eHQ in identifying the students who have mental health problems and the effects of attending the health check.

The strengths of the study are its high-quality nationwide register data with good coverage and the high percentage of completed questionnaires from the respondents. The register data enable the assessment of the whole cohort of university entrants with a relatively long follow-up. Conducting register-based studies in Finland is feasible due to the unique identity codes that enable data linkage between the registers and individual-level analyses [42].

The limitations of register-based studies, in general, should be considered. Even though it has been found that Finnish administrative registers are of high quality, missing or incorrectly recorded data are always a possibility [42]. In this study, the medical records might include missing or false data due to the possibility of human error. In addition, it might also be counted as a limitation that the eHQ is not a validated questionnaire.

It is valuable to study primary health care practice with respect to resource allocation and conducting evidence-based processes. The health examination process of FSHS consumes public resources and the need for resources will increase significantly in the near future. The services of FSHS will expand to also cover the students of universities of applied sciences (approximately 140,000 students) from the beginning of 2021. This means FSHS will provide student health care services for all higher education students in Finland (approximately 250,000 students). Hence, the number of students to whom the health examination process is provided will approximately double. It is essential to obtain evidence regarding FSHS's processes to allocate resources effectively.

The main practical implication of this study is the development of the statutory health examination process for higher education students in Finland. Students are especially interested in, and well capable of, using new digital applications. Therefore, the development of the health examination process will focus on digital solutions, for example, the robotization of the eHQ. This study provides information about the functionality of the process, which is needed for further digitalization. Furthermore, we believe the findings will support both health care and the university administration in understanding, more profoundly, the health and welfare requirements of university students.

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Authors' Contributions

SP and NS designed the study, collected and processed the data, and wrote the manuscript with equal contributions. KK and MK significantly contributed to the design of the study and revised the manuscript. RA significantly contributed to the statistical design and revised the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

KK retired from FSHS in 2017; FSHS has not supported the study financially.

Multimedia Appendix 1
The continuum of preventive health care services in Finland.
[PDF File (Adobe PDF File), 62 KB - resprot_v9i1e14535_app1.pdf]

Multimedia Appendix 2
Study ability: the definition of the concept.
[PDF File (Adobe PDF File), 72 KB - resprot_v9i1e14535_app2.pdf]

Multimedia Appendix 3
The electronic health questionnaire (eHQ) questions.
[PDF File (Adobe PDF File), 49 KB - resprot_v9i1e14535_app3.pdf]

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Abbreviations

AUDIT: Alcohol Use Disorders Identification Test
eHQ: electronic health questionnaire
FSHS: Finnish Student Health Service
ICD-10: 10th revision of the International Statistical Classification of Diseases and Related Health Problems
ICPC-2: International Classification of Primary Care, Second edition
VIRTA: higher education achievement register

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Protocol

The Canadian Partnership Against Cancer Rectal Cancer Project: Protocol for a Pan-Canadian, Multidisciplinary Quality Improvement Initiative to Optimize the Quality of Rectal Cancer Care

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Abstract

Background: Over the last 2 decades, the use of multimodal strategies, including total mesorectal excision (TME) surgery, preoperative chemotherapy, multidisciplinary case conference, pelvic magnetic resonance imaging, and pathologic assessment using Quirke method, has led to significant improvements in oncologic outcomes for patients with rectal cancer. Although the literature supports claims on the effectiveness of these multimodal strategies, the uptake of these multimodal strategies varies considerably among centers, suggesting that the best evidence is not always implemented into clinical practice.

Objective: This study aims to perform a quality improvement initiative to (1) identify existing gaps in care for these multimodal strategies and (2) implement knowledge translation (KT) interventions to close these gaps to optimize quality of care for patients with rectal cancer across high-volume centers in Canada.

Methods: Process indicators for the selected multimodal strategies to optimize rectal cancer care will be selected and prospectively collected for all patients with stages 1 to 3 rectal cancer undergoing TME surgery. KT interventions, including audit and feedback, opinion leaders, and community of practice, will be implemented to increase the uptake of these clinical strategies.

Results: The uptake of the process indicators over time and the effect of the uptake of the process indicators on short- and long-term oncologic outcomes will be evaluated for each multimodal strategy.

Conclusions: This quality improvement initiative will identify existing gaps in care for the selected multimodal strategies and implement KT interventions to close these gaps. The results of this study will inform further efforts to optimize rectal cancer care.

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KEYWORDS

rectal cancer; quality improvement; knowledge translation

Introduction

Over the last 2 decades, the increasing use of multimodal strategies has resulted in significant improvements in oncologic outcomes. Although some of this may be attributed to the widespread adoption of total mesorectal excision (TME), multimodal strategies, including the addition of preoperative chemoradiotherapy, have led to further decreases in local recurrence rates and are currently recommended for stage 2 and stage 3 diseases [1-6]. Furthermore, improved pretreatment staging with pelvic magnetic resonance imaging (MRI) has increased the appropriate assignment of preoperative chemoradiotherapy and has assisted with surgical planning by predicting the status of the circumferential resection margin (CRM) status [7,8]. Similarly, pathologic assessments, including the status of the CRM and completeness of the TME, are important quality and prognostic indicators [9,10]. Finally, a multidisciplinary cancer conference (MCC) has been introduced to enhance interdisciplinary communication and coordinate, deliver, and monitor the ideal treatment for each patient [2,6,11].

Although these multimodal strategies have been shown to be effective in the literature, are recommended in published guidelines, and are mandatory components of the Commission on Cancer National Accreditation Program for Rectal Cancer [5,12-14], the implementation of these multimodal strategies varies considerably across centers in North America and Europe [15-20]. This unwarranted variation in the uptake of these multimodal strategies suggests that the best evidence is not always implemented into clinical practice and represents a significant quality gap for patients and providers [21]. To date, there has been little systematic investigation to evaluate the impact of knowledge translation (KT) interventions to reduce variation and optimize the quality of care for patients with rectal cancer.

The Canadian Partnership Against Cancer (CPAC) Rectal Cancer Project is a multiyear, multifaceted quality improvement initiative that will be conducted at 8 high-volume rectal cancer centers across Canada. The objectives of this initiative are to (1) identify existing *evidence to practice* gaps for multimodal care of rectal cancer, including pretreatment MRI, MCC, appropriate use of preoperative radiotherapy, TME surgery, and pathologic assessment using the Quirke method and (2) initiate KT interventions to close these gaps to ensure that all patients with rectal cancer receive optimal and high-quality care.

Methods

Prestudy Needs Assessment

Before developing our study protocol, our investigative team conducted a survey to assess the uptake and variation of uptake of multimodal strategies for the treatment of rectal cancer at 8 high-volume centers across Canada. An email survey was sent to a senior surgeon at each of these centers, and they were asked to indicate their center's current practices for each of the multimodal strategies shown in Table 1. These modalities included routine use of (1) the Quirke method for pathologic assessment, (2) the College of American Pathology (CAP) checklist for a pathologic report, (3) a synoptic operative report, (4) MCC for all patients with rectal cancer, (5) pretreatment MRI for all patients with rectal cancer, (6) specified MRI protocol for rectal cancer, and (7) a synoptic MRI report. The response rate of the survey was 100% (8/8).

The results of this survey showed that there was a significant variation in the uptake of these multimodal strategies across the 8 Canadian centers (Table 1). Most of the hospitals had not formally implemented the Quirke method, and the use of the CAP checklist was variable. Only 2 centers routinely presented patients with a new diagnosis of rectal cancer at MCC, and only 1 center formally documented this MCC decision in the patient chart. Although all centers reported routine use of MRI for local staging of rectal cancer, only 2 centers reported using a standard MRI protocol and synoptic MRI report. No center had implemented all the multimodal strategies, and those that have implemented 1 or 2 of these strategies had seemed to have done this without complete fidelity to optimal practice. On the basis of these survey results, our investigative team felt that it was reasonable to proceed with our quality improvement initiative.

Table 1. Prestudy survey assessing uptake of multimodal strategies at 8 high-volume centers.

Multimodal strategy	Hospital							
	1	2	3	4	5	6	7	8
Quirke protocol	N[a]	N	?[b]	N	Y[c]	Y	N	N
College of American Pathology checklist	?	Y	Y	Y	Y	Y	N	Y
Synoptic operative report	Y	Y	N	Y	N	N	Y	Y
Rectal cancer Multidisciplinary Cancer Conference	N	N	Y	N	Y	N	N	N
Routine use of MRI[d]	Y	Y	Y	Y	Y	Y	Y	Y
MRI protocol	N	N	N	N	Y	Y	N	N
MRI synoptic report	N	N	N	N	Y	Y	N	N

[a]N: no.

[b]?: unable to determine.

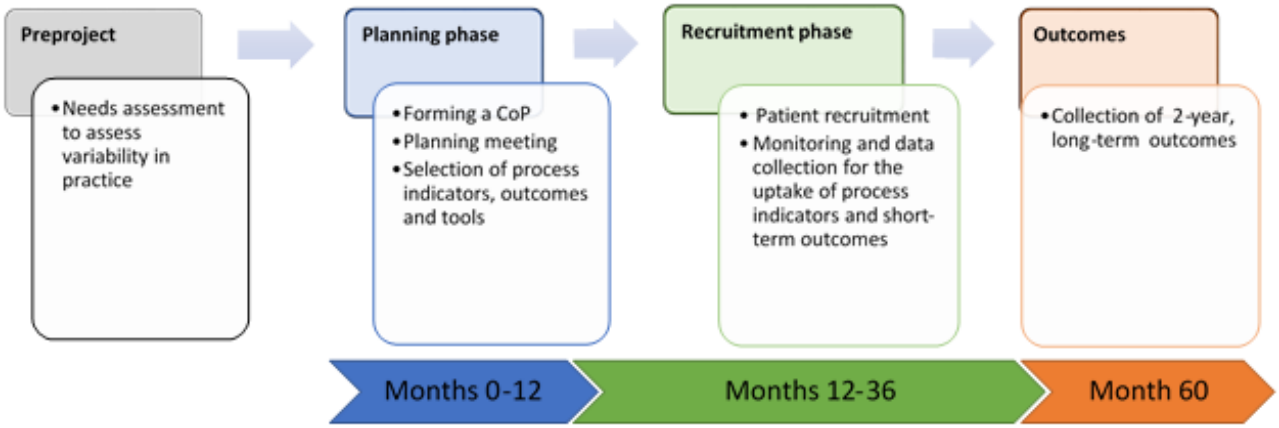
[c]Y: yes.

[d]MRI: magnetic resonance imaging.

Study Overview

This initiative will be conducted at 8 high-volume rectal cancer centers across Canada and will consist of 2 phases. The first phase is a planning phase that will last 1 year, and the second phase is a recruitment phase that will last 2 years. During this phase, process indicators for the selected multimodal strategies will be collected and monitored, and KT interventions will be conducted to increase the uptake of these process indicators. An overview of the study is provided in Figure 1. Before the start of the study, research ethics approval and data sharing agreements will be obtained.

Figure 1. Study overview. CoP: community of practice.

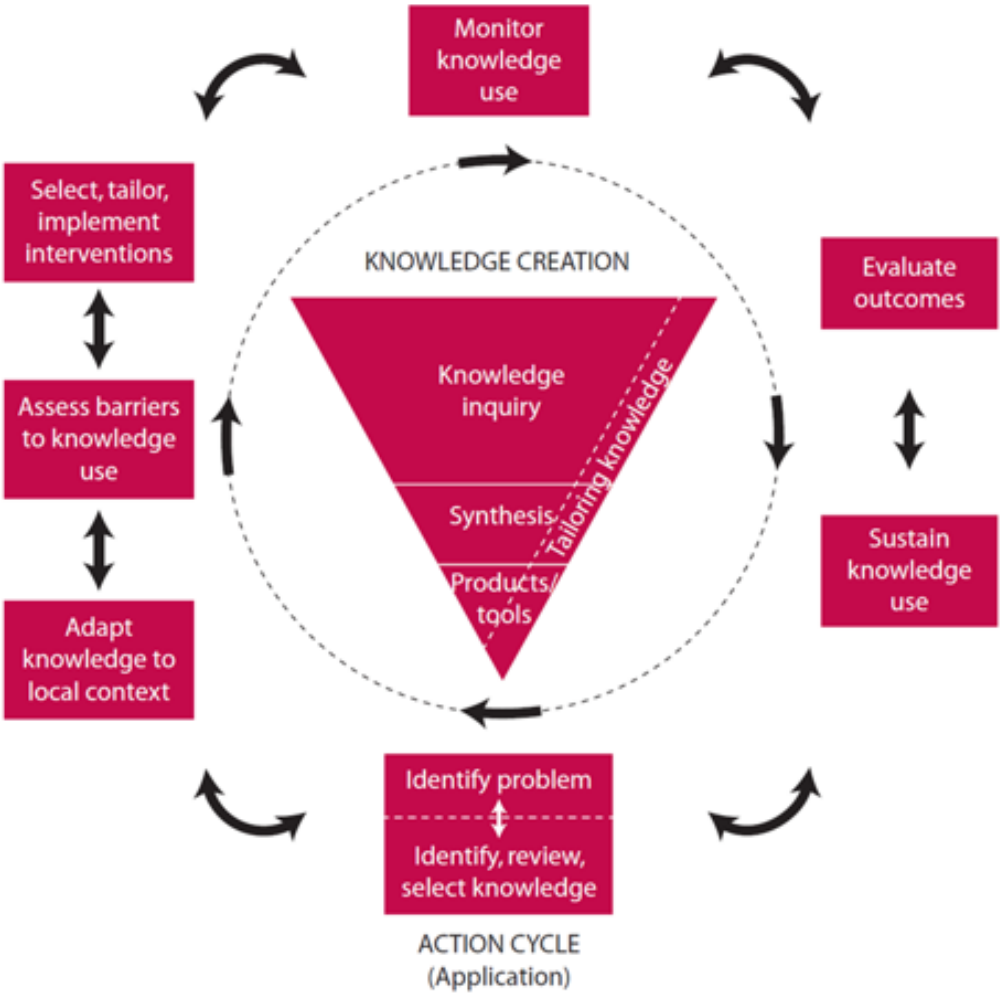


Conceptual Framework

The conceptual framework for this initiative is the Knowledge to Action (KTA) cycle (Figure 2) [22]. The KTA cycle consists of a knowledge creation funnel and an action cycle. Knowledge creation is conceptualized by an inverted funnel with a vast number of knowledge pieces present in the knowledge inquiry process that are then reduced in number through knowledge synthesis and then an even smaller number of tools or products to facilitate the implementation of the knowledge.

The action cycle is represented by the activities needed for knowledge application. The action cycle is conceptualized as a dynamic process in which all phases in the cycle can influence one another and can also be influenced by the knowledge creation process. The action cycle often starts with an individual or group identifying a problem and the knowledge relevant to solving this problem.

Figure 2. Knowledge to Action cycle.



Knowledge Translation Interventions

KT refers to iterative, multistep processes that involve appraisal of the current quality of care to identify *evidence to practice* gaps, implementation of KT interventions to address these gaps, and outcome measurement to evaluate the effect of these employed interventions [23-26]. For this initiative, the main KT interventions will be a community of practice (CoP), audit and feedback, and opinion leaders.

A CoP is defined as "a group of people who share a concern, a set of problems, or a passion for a topic, and who deepen their knowledge and expertise in an area by interacting on an ongoing basis," and, more recently, CoPs have emerged as a promising form of KT intervention [27,28]. Through their collaborative and informal structure, it is proposed that CoPs reduce professional and organizational boundaries by facilitating the dissemination of explicit and tacit knowledge among members, reducing professional isolation, and encouraging group innovation [28,29]. The utility of CoPs has been demonstrated in several health care settings, where they have been used to improve compliance with evidence-based guidelines [30].

Audit and feedback is a widely used strategy to improve health care practice and has been shown to be an effective strategy to promote behavior change among physicians [31]. Improvements from audit and feedback have been attributed to the intrinsic effects of friendly competition among participants, self-regulation based on performance goals, and the Hawthorne effect [31]. Specific to rectal cancer care, several European studies have demonstrated improvements in survival and quality of care after implementing national rectal cancer audits, including those without comparative feedback [32,33].

Physician leaders act as role models and opinion leaders to effect behavior change in other physicians. Physician leaders have been shown to increase compliance with implementation guidelines and help to ensure that changes are sustained after implementation is complete [34-36].

Participating Centers

A total of 8 high-volume rectal cancer centers across Canada will participate in this initiative and represent a convenience sample. At each center, there will be a designated site lead who will be in charge of managing the project locally at their institution.

Planning Phase (Year 1)

During the planning phase of the study, our investigative team will assemble a pan-Canadian, multidisciplinary CoP and organize an in-person planning workshop with the CoP to finalize the study protocol.

The investigative team will form the CoP by inviting a colorectal surgeon at each of the 8 sites to be the site lead and act as a champion for the study at their institution. Each of these surgeons will be asked to invite a radiologist, radiation oncologist, medical oncologist, and pathologist from their respective centers to be a member of the CoP and site lead at their center for their respective specialty.

The CoP members will be invited to participate in an in-person planning workshop to finalize the study protocol. This will involve a modified Delphi method with the CoP to select process indicators and outcomes to measure the uptake of the multimodal strategies to optimize rectal cancer care, including (1) pretreatment MRI, (2) MCC, (3) appropriate use of radiotherapy, (4) TME, and (5) pathologic assessment using the Quirke method. Before the workshop, a survey will be circulated to the CoP with suggested process indicators and outcomes for each of the multimodal strategies, and the CoP members will be asked to rate each of these process indicators and outcomes on a categorical scale from 1 to 5 based on clinical importance. The CoP members will also be encouraged to provide additional process indicators and outcomes on the survey. At the workshop, the survey results and best available evidence for each of the suggested process indicators and outcomes will be presented. This will be followed by a moderated multidisciplinary discussion and an anonymous vote to include or exclude each of the suggested process indicators and outcomes. All the suggested process indicators and outcomes in which 90% or more of the CoP vote to keep will be used as the final set of process indicators and outcomes for the study. Following the selection of the process indicators and outcomes, the CoP will discuss specific tools that may be used to capture the selected process indicators and outcomes. The goal of this discussion will be to identify specific tools that are already being used successfully at the participating centers and to modify these as necessary for the purpose of the study. Therefore, at the end of the workshop, the study framework with recommended process indicators, outcomes, and tools will have been finalized by the CoP. The suggested process indicators and tools included in the preworkshop survey are shown in Table 2. The suggested short-term oncologic outcomes included in the preworkshop survey are completeness of TME, CRM status, and lymph node retrieval. The suggested long-term oncologic outcomes included in the preworkshop survey are local recurrence, distant metastasis, overall survival, and disease-free survival at 2 years.

The site leads at each participating center will be responsible for presenting the final study protocol to their colleagues at a study launch. At the study launch, the site leads will also obtain feedback from their colleagues regarding facilitators and barriers to implementation at their institution. Although the final process indicators and outcomes will not be modifiable, the site leads will be encouraged to modify the recommended tools to facilitate the implementation of the multimodal strategies at their center locally based on feedback from their colleagues.

Table 2. Suggested process indicators and tools.

Multimodal strategy	Suggested process indicators	Suggested tools
All patients with rectal cancer should have a pretreatment MRI[a]	Performance of pretreatment MRI and MRI report includes *T-category, N-category, and circumferential margin status*	Synoptic MRI report
All patients with rectal cancer should have their case presented at MCC[b]	Presentation of case at MCC and MCC report generated for all cases	Synoptic MCC report
All patients with rectal cancer should receive high-quality TME[c] surgery	Completeness of TME documented in operative note and preoperative stoma marking	Synoptic operative report
All rectal cancer specimens should have pathologic assessment using the Quirke method	Use of the Quirke method	Quirke method gross specimen checklist and College of American Pathologist checklist
All patients with locally advanced rectal cancer should receive neoadjuvant CRT[d]	CRT for all patients with stages 2 and 3 rectal cancer and peer review of radiotherapy treatment plan	—[e]

[a]MRI: magnetic resonance imaging.

[b]MCC: multidisciplinary cancer conference.

[c]TME: total mesorectal excision.

[d]CRT: chemoradiotherapy.

[e]No tool identified.

Recruitment Phase (Years 2 and 3)

The recruitment phase of the study will consist of capturing the selected process indicators and outcomes for all patients with a new diagnosis in a consecutive and prospective manner at each center.

Patient Sample

Eligible patients will include those with a (1) new diagnosis of stage 1 to 3 biopsy-proven rectal adenocarcinoma; (2) located 15 cm or less from the anal verge; and (3) undergoing curative-intent TME surgery at the participating center. Patients with stage 4 rectal cancer or not requiring TME surgery will be excluded. On the basis of center volumes, it is expected that each center will recruit 50 to 100 rectal cancer patients per year;

therefore, data will be collected for 600 to 800 patients with rectal cancer over the recruitment period. Participating physicians will be responsible for identifying potential patients for the study, and at each site, study coordinators will obtain informed consent. Before the start of the recruitment phase, Research Ethics Board approval and data sharing agreements will be obtained from all participating sites.

Data Collection

A dedicated research coordinator at each site will collect process indicators and short-term oncologic outcomes for each patient, and the research coordinator will abstract these data into a Web-accessible database designed for the study. The hard copies of deidentified patient data, including MRI reports, MCC reports, operative reports, and pathology reports, will also be collected for quality assurance and central review. Moreover, 2 years following the completion of patient recruitment, the long-term oncologic outcomes will be collected for each patient.

Every 3 months, an interim report will be generated for process indicators and short-term outcomes for the entire cohort as well as each individual center. Results will be anonymized for all hospitals outside the home hospital, and a total of 7 reports over the recruitment period will be generated. Each site will be encouraged to identify gaps in care at their center and work together to develop local strategies to close gaps in care. The CoP will participate in a teleconference after each reporting cycle to discuss the reports, evaluate each other's progress, identify barriers to success, and discuss strategies to overcome these barriers. After the first year of recruitment, a second, in-person meeting is planned. At this meeting, high-performing hospitals will be asked to present their practices and implementation strategy to the other sites, and the sustainability of the multimodal strategies will be discussed.

Data Analysis

For the final data analysis, each process indicator will be reviewed and presented graphically using standard quality improvement tools including statistical process control and run charge to identify change trends. To account for the lack of independence in the outcome measurements (ie, patients clustered within centers), generalized estimating equations models will be used to evaluate group differences for the indicators over time and between centers. Center-specific evaluation of selected outcomes over time will employ standard statistical analysis, such as logistic regression. Incorporated in all analyses will be an evaluation of the appropriateness of statistical technique and assumptions. Both short- and long-term oncologic outcomes will be reported, and Kaplan-Meier curves for disease-specific and overall 2-year survival will be generated.

The final analysis will evaluate the effect of the uptake of the process indicators on short- and long-term oncologic outcomes.

Results

The CPAC is funding this study. Data collection and central review are currently ongoing and will be completed by December 2019.

Discussion

Principal Findings

The CPAC Rectal Cancer Project is a multiyear, multifaceted KT initiative that aims to identify existing *evidence to practice* gaps in rectal cancer care and to implement KT interventions to close these gaps with the overall goal to optimize the quality of care and outcomes for patients with rectal cancer. The results of this study will be highly relevant, as they will not only provide insight into the current status of rectal cancer care but also evaluate the effectiveness of targeted KT interventions to optimize care and provide data for the development of national benchmarks.

There are several unique features of this proposed study. First, an integrated KT approach is employed in both the planning and recruitment phases of the study through the use of the CoP. It is expected that by involving the CoP or knowledge users early in the planning process of the study, the results will be more relevant and more likely to be used in clinical practice by the CoP members and their colleagues. The CoP is also expected to increase stakeholder *ownership* and *engagement* with the study and increase the likelihood of successful implementation of the multimodal strategies and long-term sustainability. Another important attribute of the CoP is that it is multidisciplinary, and this is expected to foster more meaningful interdisciplinary discussions, collaboration, and sharing of best practice across specialties. In this regard, we plan to have the process indicators and outcomes selected by all the members of the CoP.

Following the completion of the study, our group will have unique patient-level, process indicator, and outcome data, and we will be able to use these data to set national and multidisciplinary benchmarks for optimal rectal cancer care in Canada. We will also be able to recommend successful KT interventions that will provide the opportunity to scale this approach out to other centers. Finally, there will be standardized procedures and protocols at the 8 participating centers, and the CoP will be able to continue to collaborate and conduct future trials with a coordinated infrastructure.

Some of the limitations of this study are as follows. First, all the participating centers are high-volume academic centers and may not be generalizable to other practice settings or be representative of rectal cancer care on a national level. Second, as this study is focused on the uptake of the process indicators, the study may be relatively underpowered to detect significant differences for both short- and long-term oncologic outcomes. Finally, the sustainability of the study and planning for sustainability of the multimodal strategies following completion of the study will be critical.

Conclusions

The CPAC Rectal Cancer Project is a quality improvement initiative to identify existing *evidence to practice* gaps in rectal cancer care and implement KT interventions to close these gaps to optimize the quality of care for patients with rectal cancer in Canada. The multidisciplinary CoP is a unique feature of this study and is expected to increase the successful implementation

and sustainability of the multimodal strategies for optimal rectal cancer care. The results of the study will be highly relevant, as they will show the current uptake of multimodal strategies for optimal rectal cancer care and the effectiveness of targeted KT interventions to improve the uptake of these multimodal strategies.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer Review Funding Reports from Canadian Partnership Against Cancer.
[PDF File (Adobe PDF File), 1027 KB - resprot_v9i1e15535_app1.pdf]

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Abbreviations

CAP: College of American Pathology
CoP: community of practice
CPAC: Canadian Partnership Against Cancer
CRM: circumferential resection margin
KT: knowledge translation
KTA: Knowledge to Action
MCC: multidisciplinary cancer conference
MRI: magnetic resonance imaging
TME: total mesorectal excision

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Original Paper

A Context-Specific Digital Alcohol Brief Intervention in Symptomatic Breast Clinics (Abreast of Health): Development and Usability Study

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Abstract

Background: Potentially modifiable risk factors account for approximately 23% of breast cancer cases. In the United Kingdom, alcohol consumption alone is held responsible for 8% to 10% of cases diagnosed every year. Symptomatic breast clinics focus on early detection and treatment, but they also offer scope for delivery of low-cost lifestyle interventions to encourage a cancer prevention culture within the cancer care system. Careful development work is required to effectively translate such interventions to novel settings.

Objective: The aim of this study was to develop a theory of change and delivery mechanism for a context-specific alcohol and lifestyle brief intervention aimed at women attending screening and symptomatic breast clinics.

Methods: A formative study combined evidence reviews, analysis of mixed method data, and user experience research to develop an intervention model, following the 6 Steps in Quality Intervention Development (6SQuID) framework.

Results: A Web app focused on improving awareness, encouraging self-monitoring, and reframing alcohol reduction as a positive choice to improve health was found to be acceptable to women. Accessing this in the clinic waiting area on a tablet computer was shown to be feasible. An important facilitator for change may be the heightened readiness to learn associated with a salient health visit (a teachable moment). Women may have increased motivation to change if they can develop a belief in their capability to monitor and, if necessary, reduce their alcohol consumption.

Conclusions: Using the 6SQuID framework supported the prototyping and maximized acceptability and feasibility of an alcohol brief intervention for women attending symptomatic breast clinics, regardless of their level of alcohol consumption.

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KEYWORDS

cancer; information seeking behavior; health risk behaviors; secondary prevention; alcohol drinking; health knowledge; attitudes; practice; health promotion; health literacy

Introduction

Background

Breast cancer is the most common type of cancer worldwide, and its incidence is rising [1]. The World Health Organization considers that sufficient knowledge is available to prevent 30% to 50% of cancer cases globally and that "prevention offers the most cost-effective long-term strategy for the control of cancer" [2]. In the United Kingdom, the proportion of breast cancer cases attributable to lifestyle factors is as follows: insufficient physical activity—2%, overweight or obesity—8%, and alcohol consumption—between 8% [3] and 10% [4]. Alcohol increases the risk of breast cancer in a dose-dependent fashion, even from low-risk drinking levels, with an estimated relative risk of 1.09 for 10 g/day [5]. Observational evidence shows that alcohol consumption may also increase the risk of recurrence of breast cancer in survivors [6,7]. New UK clinical guidelines advise this group to observe an upper limit of 5 units per week [8].

Systematic reviews of alcohol interventions indicate that, outside of regulatory interventions, alcohol brief interventions (ABIs) demonstrate the greatest effectiveness and cost effectiveness [9-11], with small reductions in alcohol consumption (20g/week) that can be sustained for at least a year [12,13]. Despite this, ABIs remain relatively underutilized across health care systems. In England, fewer than 7% of "increased-risk" drinkers recall receiving advice from their general practitioner on their alcohol consumption in the past year, compared with 50% of smokers who recalled receiving tobacco cessation advice [14].

The use of "teachable moments" is increasingly advocated to encourage modification of lifestyle determinants of cancers [15-17], but more research is required as to how best to situate health prevention interventions into current health systems. In England, over 540,000 women annually attend UK National Health Service (NHS) symptomatic breast clinics [18] as part of a rapid referral (2-week wait) system to prevent delay in diagnosis. Because fewer than 8% of women attending are found to have breast cancer [19], and health promotion information is not offered to those without a diagnosis, in prevention terms, the majority do not currently benefit from attending the clinic.

Objectives

Previous research has criticized the premature trialing of ABIs in new environments, with recommendations that "applications of brief intervention to novel settings should begin with foundational research and developmental studies" [20]. This paper describes the development of a context-specific ABI aimed at women attending symptomatic breast clinics, using the 6 Steps in Quality Intervention Development (6SQuID) [21], a framework commonly employed in the development of public health interventions.

Methods

Framework

The 6SQuID framework [21] is intended to improve the design of public health interventions and, consequently, their effectiveness. This study synthesized information from 4 sources of data (reviews, empirical data from the target population, theory and concept mapping, and iterative content appraisal and design) to complete these steps in the breast health setting (Table 1).

Table 1. The 6 steps of the Quality Intervention Development framework as applied in the development of Abreast of Health (adapted from the study by Wight et al [21]).

Step and data provenance	Methods
1. Define and understand the problem and its causes	
Attitudes literature (E[a])	Scoping review
Scoping study [22] (E)	Scoping review
2. Clarify which causal or contextual factors are malleable and have greatest scope for change	
Risk attitude literature (E)	Scoping review and theory mapping
Scoping study [22] (E)	Scoping review and theory mapping
Review of existing apps (N[b])	Scoping review and theory mapping
3. Identify how to bring about change: the change mechanism	
Behavior change technique review (E)	Theory and concept mapping
4. Identify how to deliver the change mechanism	
Behavior change technique review (E)	Concept mapping
User testing (N)	Agile prototyping
5. Test and refine on small scale	
User testing (N)	"Think aloud" and "teach me back" cognitive interviewing
6. Collect sufficient evidence of effectiveness to justify rigorous evaluation/implementation	
To be addressed in future publication (N)	—[c]

[a](E): existing data from the public domain.

[b](N): new data generated during this study.

[c]Not applicable.

Reviews

The academic and gray literature were reviewed iteratively in 3 different areas relevant to the intervention (Multimedia Appendix 1):

1. Knowledge and social attitudes to alcohol among women (particularly in the United Kingdom) and among health care staff—this included information on knowledge of alcohol volumes, effect of alcohol on health, and confidence in managing alcohol-related health risks.
2. Knowledge and social attitudes in relation to modifiable risk factors for cancer—particular attention was paid to interaction with social determinants of health, including health literacy, socioeconomic status, and social deprivation.
3. Findings from existing reviews on behavior change mechanisms and techniques for reducing alcohol consumption—in addition to reviews from the Cochrane library, we focused on systematic and narrative reviews of features of digitally delivered ABIs [23-27].

Mixed Method Study With the Target Population

A mixed method study was undertaken to complement evidence from the literature reviews, with data from the target environment: symptomatic breast clinics and an NHS Breast Screening Programme unit in Southampton, United Kingdom. A total of 205 women attending appointments were recruited to take part in (1) a survey of knowledge of risk factors for breast cancer and alcohol beverage content and (2) 5 focus groups. Moreover, 33 health professionals took part in a similar survey, of whom 8 also participated in semistructured interviews. The full detail is reported separately [22], but it will be referred to here as part of the intervention development process.

Theory and Concept Mapping

As part of 6SQuID steps 3 to 4, relevant theories and behavior change constructs were reviewed and mapped onto harmonized constructs from 2 systematic collations of health psychology theories commonly used in meta-analyses. These were (1) the 26 mechanisms of action [28] consolidating and extending the preexisting Theoretical Domains Framework [29] and (2) the 93 behavior change techniques (BCTs) from the BCT Taxonomy v1.1 [30].

Iterative Content Appraisal and Design

The structure and content (both textual and visual) of the intervention prototype were designed by JMAS, PDM, and CKP in an Agile approach [31] between December 2016 and April 2017. This method relied on rapid prototyping and testing of small components using short cycles:

1. The research team scoped, reviewed, and appraised existing alcohol information leaflets, Web, and mobile phone apps. This involved mapping BCTs and appraising the language, tone, and focus of different approaches to consolidate a view of the most adapted content. A particular focus was placed on identifying features that were deemed difficult

to understand, that were insufficiently relevant, or that could be perceived by some women as scary and/or judgmental. Similarly, features that appeared most helpful at implementing target mechanisms of change were also noted.

2. A total of 10 women recruited from symptomatic breast clinics were invited to test and comment on a range of existing health apps in 1 focus group, adding to findings from the team's own analysis.
3. The research team sketched the visual layout of small components of the intervention.
4. Immediate comments and reactions on early versions of wording and visual features of these components were invited from 161 women recruited from symptomatic breast clinics. Participants took part in face-to-face cognitive interviews, which invited them to "think aloud" and "teach back" information gathered while testing the prototype to the researcher [32,33].

New findings were discussed by the research team on a weekly basis, setting objectives for the next data collection cycle the following week. Conclusions from these activities were mapped to a particular component of the emerging prototype intervention and recorded on a Kanban board (using the Trello software) [34] together with lists of actions, to incorporate them in the design work at every iteration of the weekly cycles.

All participants were recruited from the women attending the symptomatic breast clinics at Southampton General Hospital on referral from their primary care physician. All participants were approached in the waiting room, and having given consent, they either participated at that time and/or agreed to take part in a focus group/testing session at a later date. Activities (2) and (3) above were approved by Health Research Authority Research Ethics Committees as part of 2 independent studies (references: 17/LO/0953 and 18/SC/0120).

Results

Steps 1 to 2: Causal and Contextual Factors of the Target Problem

Having identified alcohol consumption as a potentially modifiable lifestyle cause of breast cancer, we undertook a broad review of underpinning factors (Multimedia Appendix 1). Table 2 gives a thematic summary of dominant themes of social and psychological determinants of knowledge, attitudes, and behavior around alcohol consumption.

Key findings were that although 60% to 72% of women attending breast screening appointments or symptomatic breast clinics drink alcohol, only 20% of women were aware that it was a risk factor for breast cancer [22,35-60]. Despite efforts from public campaigns informing the population of the effects of alcohol on long-term health, recent studies still demonstrate that the UK population recognizes these far less than the social harms of alcohol. This focus on risks associated with "binge" drinking (high-intensity, single-occasion alcohol use) can dim the awareness of the effects of consuming alcohol in lesser quantities across a sustained period. A recent UK–based qualitative study by Khadjesari et al [38] examined attitudes to alcohol and the government's low-risk drinking guidelines (recommendation not to drink more than 14 (UK) units a week on a regular basis, maintaining several drink-free days per week) [37] among adults attending primary care facilities. The authors argued that the narrow public understanding of risks focused on the effects of high-intensity consumption of alcohol reduces the perceived relevance of low-risk drinking guidelines and contributes to participants' belief that the 14-unit threshold is unnecessarily low.

From steps 1 to 2, we concluded that the greatest scope for change resides in increasing awareness of alcohol's role in promoting chronic conditions such as cancer, even at low levels. This interacts with other behavioral predictors listed in Table 2, some of which are situated in the cancer context. For example, attitudes and beliefs such as cancer predeterminism and fatalism affect engagement with prevention behaviors [57,58] and the perceived relevance of information of lifestyle risk factors.

Table 2. Thematic summary of social and psychological determinants of knowledge, attitudes, and behavior around alcohol consumption.

Domain	Evidence
Knowledge: low alcohol literacy	Only 20% of women in breast clinics [22] identified alcohol consumption as a risk factor for breast cancer, a similar proportion as in the general population [35,36]. This lack of awareness is singled out as an obstacle in promoting low-risk drinking by the UK Chief Medical Officers [37]. Some common beliefs about alcohol and cancer are incorrect, for example: that alcohol only becomes a health risk in "problem drinkers" or people who are alcohol dependent; red wine being the only type of alcohol causing cancer; conversely, red wine/moderate alcohol intake being good for health; physical exercise mitigating the effects of heavy drinking [38].
Knowledge: low alcohol numeracy	Individuals do not always accurately recall the frequency, volume, and concentration of alcohol they drink [39,40]. Improving numeracy and encouraging monitoring of alcohol intake within primary care have been proposed by some [41,42] as a population prevention strategy.
Social role and identity of health professionals	In addition to lacking in time and relevant training on lifestyle interventions, health care staff may not believe it is part of their clinical role to discuss lifestyle factors in relation to modifiable risk factors for cancer [43-46]. Evidence also points to health professionals lacking in awareness of the causes of cancer, relevant lifestyle guidance, and the appropriate advice to give [43,47,48], and it points to lacking confidence that information will motivate women to change behaviors [43,47-49], sometimes hindered by the health care professionals' own lifestyle choices [50]. Clinicians perceive a lack of patient interest in the subject [48] and tend to underestimate evidence on the fact that changing behaviors affect breast cancer risk [43,47-49].
Beliefs about capability and readiness to learn	Patients are more concerned by genetic determinants rather than modifiable risk factors for breast cancer [51]. Previous research has found some skepticism and defensiveness toward health promotion messages related to alcohol [52,53]. In some individuals, health literacy levels may be an obstacle to processing and making decisions based on the information given [54]. Many lack skill or confidence in taking practical steps to reduce alcohol consumption [54,55].
Health beliefs: cancer predeterminism and fatalism	A proportion of the population believes that incidence of cancer is purely down to "fate" or known genetic causes. "Cancer fatalism" is thought to have a negative impact on health behaviors, including screening uptake. Evidence suggests that it is more prevalent among women from black and minority ethnic backgrounds and that beliefs that cancer is predetermined are strongest among women: (1) born outside the United Kingdom, (2) whose main language is not English, or (3) exhibiting lower levels of health literacy [56]. Fatalistic beliefs are correlated with lifestyle [57], and these mediate the relationship between health literacy and information seeking [58].
Exposure to fear appeal messages	Alcohol and cancer are health themes in which public health campaigns have traditionally appealed to fear processes, seeking impact by evoking a strong emotional response. Alcohol harm reduction video advertisements, in particular, tend to have a negative emotional tone (74%) and focus on short-term risks (53%), with only 18% focusing on how to adapt lifestyle to improve long-term health [59]. This contributes to a subtext, which may trigger fear by association, even when unintended.
Perceived relevance of alcohol prevention	Generalist alcohol brief interventions are rarely tailored to individuals' drinking behavior. We found that many leaflets contain messages and recommendations that are aimed at higher-risk drinkers; therefore, these are not relevant to many recipients' level of alcohol consumption or lifestyles. These messages may, therefore, be easily dismissed by the majority of readers as irrelevant [38].

Step 3: Mechanisms of Action

Beyond the need to increase knowledge of the long-term health effects of alcohol (commonly invoked as a necessary mechanism of action to promote behavior change) [28], attitudes toward the behavior and perceived susceptibility/vulnerability play a role. From existing reviews of behavior change mechanisms and techniques, we explored the role of emotions and perceived susceptibility/vulnerability in mediating or moderating alcohol behavior change.

The teachable moment model [61] posits that some health events facilitate behavior change by affecting subjects' perception of personal risks, by evoking an affective response (such as a worry), which challenges their health-related beliefs to the point of promoting behavior change. However, this effect could be moderated by other processes in situations perceived as threats to life (eg, a potential cancer diagnosis). Under the assumption that a symptomatic breast referral raises the level of fear or perceived vulnerability, the extended parallel process model by Witte et al [62] anticipates one of two main responses: participants either accept related health messages (danger control processes) or reject them (fear control processes).

Danger control processes predict an enhanced "readiness to learn," which we define as the propensity to absorb information on health risks, reflect on its meaning, and use it in relation to everyday lifestyle choices. An ABI could capitalize on danger control processes by establishing an association between alcohol and the risk of breast cancer and redirecting the individual's attention toward achievable methods of reducing alcohol consumption.

Conversely, an ABI could fail by triggering fear control processes, by exacerbating fatalistic thoughts in women attending clinic who believe that cancer risk is largely predetermined and beyond their control. Such beliefs are known to be more prevalent in populations with limited health literacy [56]. If fear control processes dominate, recipients of the ABI may be inclined to discard lifestyle advice in an effort to manage or control their fear of cancer.

Data from our focus groups indicated that although fear control processes occur among women attending breast clinics (eg, "information overload," avoidance of health literature), the desire to learn about modifiable risk factors is also present [61,63,64]. Studies by Anderson et al [65] have shown that the anxiety generated by a breast mammogram, far from constituting

an obstacle to health promotion, can be used for opportunistic large-scale lifestyle interventions. Adapting the content of the intervention so as to minimize fear control processes is thus the main avenue to activating the potential efficacy of a teachable moment.

In addition to the findings from our reviews, qualitative evidence we collected [22,64] suggested that an intervention would need to enhance the perception that, out of all cancer risk factors, alcohol is one of the most easily modified, and it is necessary to emphasize the health and well-being *gains* of adopting and/or maintaining a lower level of alcohol consumption. Framing low-risk alcohol consumption levels in terms of "health gains" [66], using positive language, may be particularly important in the areas of cancer and alcohol use, where health promotion has been dominated by fear appeal techniques (eg, campaigns on missing the early signs of cancer or against drink driving). As individuals targeted by the proposed intervention will be influenced by their previous exposure to primarily fear-based messages, we specifically monitored the meaning early testers gave to health promotion messages embedded in the prototype intervention.

From step 3, we concluded that the intervention is most likely to succeed if it provides reassurance that alcohol is a controllable determinant of cancer and that it promotes positive benefits of limiting alcohol use for long-term health and well-being.

Step 4: How to Deliver the Change Mechanism

Our previous work identified that the most feasible and scalable mode of delivering a lifestyle intervention in clinics was a Web app accessed by women in the clinic waiting area on a tablet computer [22]. In addition to circumventing the health care professional's lack of time and confidence in delivering lifestyle brief interventions, preliminary user testing confirmed that electronic delivery was acceptable and brought advantages in terms of privacy.

Within the constraints set by a Web app, and with the help of the third review, we identified candidate BCTs to deliver the following mechanisms of action (see Table 3):

- Improving knowledge of the health benefits of low-risk drinking;
- Increasing skills in relation to estimating the alcohol content of beverages;
- Changing attitudes to, and beliefs about consequences of, alcohol consumption; and
- Capitalizing on perceived susceptibility/vulnerability heightened by the symptomatic breast clinic attendance to increase motivation while emphasizing personal control and belief in the capability to reduce cancer risk.

The 4 BCTs employed with the highest degree of fidelity across the prototype were as follows: provision of information on health consequences of alcohol, feedback on behavior, discrepancy between current behavior and goals, and social comparison. Other techniques, for example, self-monitoring or instructions on how to perform the behavior, informed the design of prompts or suggestions deeper in the application interface available to those who were interested in exploring them rather than being delivered procedurally by the interface to all users.

Table 3. Behavior change techniques and features identified for prototyping.

Behavior change techniques (taxonomy number)	Prototype features
Information about health consequences (5.1)	• Information on alcohol's dose-response association with breast cancer and the absence of a safe threshold • Information on the proportion of breast cancer cases attributable to alcohol in the United Kingdom • Information about benefits of low-risk drinking beyond lower risks of breast cancer (other types of cancers, mental health, dementia, liver, etc) • "Myth busting" quiz on risk factors for breast cancer
Feedback on behavior (2.2) and discrepancy between current behavior and goal (1.6)	• Assessment of current alcohol consumption in units per week • Personalized feedback based on the UK Chief Medical Officers' low-risk drinking guidance [37] • Automated suggestion of 1 of 3 goals in line with the same guidance [37], as a function of the current pattern of alcohol consumption measured by the app: (1) low-risk drinkers: maintain current low-risk drinking; (2) low-frequency and high-intensity drinkers: have no more than 5 units of alcohol in any 1 day; (3) increased-risk drinkers: reduce alcohol consumption by a specified number of units per week (to reduce their consumption to under 14 units/week), with equivalent amount presented in number of wine glasses
Social comparison (6.2)	• Personalized feedback of current alcohol consumption compared with (1) other women in England and (2) other women in the clinic
Framing/reframing (13.2)	• Frame alcohol as an easily controllable risk factor for breast cancer • Focus messages on risk reduction by changing behavior rather than risk promotion by current behavior (gain framing) • Frame alcohol as any other health risk factor by embedding alcohol within broader information on lifestyle determinants of health: physical activity, diet, and weight • Offer ways to reduce alcohol consumption and promote them as simple and easy steps • Emphasize choice, presenting change as an easy option, with advice on how to cut down
Self-monitoring of behavior (2.3)	• "Top tips": recommend keeping a diary of alcohol intake with a mobile phone app (hyperlink to National Health Service drinks tracker app) or a paper diary (hyperlink to a diary template)
Credible source (9.1)	• "Myth busting" quiz challenging common misunderstandings on risk factors believed to promote breast cancer • Breast Cancer Now charity logo and endorsement • National Health Service branding of the app (requested by women, to be implemented subject to relevant authorizations) • Delivery of the intervention within the clinic waiting room, endorsement by health care staff
Instruction on how to perform a behavior (4.1); behavior substitution; and problem solving (1.2)	• "Top tips": examples of techniques to reduce alcohol consumption on social occasions, by setting goals, self-monitoring, and involving relatives • "Top tips": advice on choosing beverages with lower alcohol content and/or smaller volume; alternating drinks with glasses of water • Drink calculator: information on beverage sizes and alcohol content in UK units • Hyperlinks to further resources: drinking diary template, Public Health England drink tracker app, "Soberistas," and "Club Soda"

Information About Health Consequences (Behavior Change Technique 5.1)

Information related to consequences for the risk of breast cancer was designed to convey the dose-dependent nature of the association between alcohol and breast carcinogenesis, emphasizing that no "safe" threshold exists for alcohol consumption in relation to breast cancer risk. The material designed by the team is adapted from an existing information leaflet [67] developed by a partner charity (Breast Cancer Now) on the basis of extensive qualitative research.

Feedback on Behavior (Behavior Change Technique 2.2), Discrepancy Between Current Behavior and Goal (Behavior Change Technique 1.6), and Social Comparison (Behavior Change Technique 6.2)

As women are often unsure about their alcohol risk levels (Table 2), study participants indicated that personalized feedback needed to be the first step of the intervention. Therefore, we assessed a range of questionnaires to assess current alcohol consumption or risk level. Testing of existing mobile phone and Web apps in the focus group confirmed that women wished to position themselves on a risk gradient to identify the scale of change they needed to undertake. We found that stratification tools that included items measuring social risks of alcohol were off-putting (eg, the items on injuries or feelings of guilt in the Alcohol Use Disorders Identification Test [68]). Such items triggered perceptions associated with substance "abuse," which diverted attention from dose-dependent processes putting them

at risk of chronic medical conditions. Therefore, we chose a short consumption-focused 3-item questionnaire, the Extended Alcohol Use Disorders Identification Test-consumption items ("Extended AUDIT-C"), and we are currently validating an algorithm that estimates average weekly alcohol consumption based on these 3 items.

Framing/Reframing of Alcohol (Behavior Change Technique 13.2)

The content of the intervention sought to reframe alcohol as one of the more controllable lifestyle risk factors for chronic illness (Table 3). We aimed to do the following:

- Offer a new perspective on low-risk drinking as a positive choice (gain framing) made to improve future health prospects
- Challenge binary stereotyping of alcohol use opposing "safe drinkers" and "alcoholics/boozers"; instead, represent the risks of drinking as a continuum. The language describing alcohol risks was kept as neutral as possible to adapt to a wide audience, and we excluded references to addiction or social harms of alcohol [38].

Some BCTs were potentially unhelpful in the context of the teachable moment within our target health settings because of their potential to trigger fear control reactions. In particular, we did not wish to enhance the *salience of health consequences of alcohol drinking* (BCT 5.2) or evoke *anticipated regret* (BCT 5.5) as the situational context of the breast clinic already made potential consequences of breast cancer tangible and memorable.

Finally, we identified other features likely to mediate the efficacy of the intervention, which required consideration as part of the iterative design and testing stage. As the usability of an electronic intervention is a predictor of engagement [69], we paid attention to women's evaluation of its quality and discoverability (the extent to which women were able to find content on the app without being told it existed). We allowed the users to assess the alcohol content of their own preferred alcoholic drinks, and we sought to make "top tips" easy to navigate to enable participants to focus on specific information of interest to them.

Step 5: Iterative Design, Testing, and Refining of a Prototype Intervention

Following a phase of testing, with cycles of refinement of the prototype with 161 women in clinics, the final prototype consisted of the following:

1. An initial assessment of alcohol consumption, smoking, height, and weight.
2. Personalized feedback on alcohol intake integrated with other risk factors: A feedback page presents the estimated number of units per week, and drinking risk level, assisted by a graphic visualizing alcohol risk levels based on the UK Chief Medical Officers' guidance [37] (Multimedia Appendix 2). Individuals can compare their own drinking risk level with: the Department of Health low-risk drinking guidelines; drinking risk levels of women nationally; the proportion of other women attending the same clinic who drink at a similar risk level. To reduce stigma, this feedback is integrated with more succinct personalized feedback on benefits of not smoking; success rates of quit attempts; and ranges of healthy weights corresponding to the person's height, with a button linking to health promotion content on physical activity and diet. The study participants improved the wording of the personalized feedback wherever it proved confusing or off-putting (eg, feedback aimed at low-frequency but high-intensity alcohol consumption was rephrased from "drinking large quantities" to "having no more than 5 units" on any single day).
3. An overview page linking to other health promotion information, including the following:
    - A myth-busting quiz testing knowledge on modifiable risk factors for breast cancer, including alcohol.
    - Information on the dose-response association between breast cancer and alcohol.
    - An interactive drink calculator providing alcohol units and calories of standard drinks as well as larger volumes (eg, bottles). This was refined to help participants add up, over any period, how many units of alcohol they may be consuming; how many kilocalories these drinks contain; food equivalents (in hamburgers and biscuits); and metabolic equivalents in minutes of tasks such as running, swimming, or housework.
    - Example goals for maintaining low-risk drinking or reducing alcohol consumption.
    - Specific information pages on the following: weight management, physical activity, diet, and smoking. A section on breast symptoms initially designed and tested was removed to refocus content on lifestyle promotion.

Discussion

Principal Findings

This study applied a rigorous intervention development framework, drawing on a suite of reviews of the risk factor literature, attitudes toward modifiable risk factors for cancer, and digital health interventions. We involved women attending breast clinics in the design, prototyping, and testing of a context-specific digital ABI in breast health settings with a potential to reach over 540,000 women per year in England alone, at very low costs, and where little information is currently provided in relation to modifiable risk factors for breast cancer. Coined as "teachable moments" in the cancer prevention literature [15], breast appointments constitute a privileged opportunity to raise awareness of potentially preventable causes of breast cancer. This assumes the provision of relevant, acceptable, and effective health promotion messages delivered with the highest level of fidelity.

The mechanisms of actions identified in this paper and our reviews of their evidence base suggest potential to achieve small reductions in alcohol consumption. Several moderators of the mechanisms of change for this intervention have been identified: acceptability to women, particularly those whose anxiety makes them potentially averse to health-related information; usability of the Web app delivering the intervention; and engagement with the subcomponents of the digital interface. The next phase

of research will evaluate the feasibility, acceptability, and usability of the intervention in clinics with the target population and produce the necessary evidence on how to optimize the effect of such moderators.

Comparison With Prior Work

The design of the proposed intervention differs from that of other digital ABIs, which focus either on student populations or longer-term engagement with mobile phone or Web apps [13,70]. In a clinical setting characterized by a high throughput and a narrow window for engagement, our development has focused on designing content that engages with the user as quickly as possible and is relevant to the widest range of women attending. This is a marked difference from other precedents in the United Kingdom such as Down Your Drink [71], which enrolled participants from primary care into a 6-week program through a Web-based account. Our intervention is designed to promote the take-up of other resources for longer-term engagement, where required. Effective engagement with such resources (eg, a mobile phone drink tracker) is likely to constitute a key mediator of the intervention's effect.

Limitations

This prototype intervention was developed in a single site in Southampton, United Kingdom. Feasibility and acceptability remain to be demonstrated in other sites, with different population demographics. The proposed intervention is also designed around the characteristics of the UK cancer detection model, and it may require adaptation to other health systems.

Conclusions

Breast cancer is the most common type of cancer in women, and alcohol is one of the most feasible risk factors to moderate for the prevention of breast cancer [3]. Symptomatic breast clinics constitute a context in which targeted health improvement interventions could take place. Unlike other ABIs, the proposed intervention aims to be acceptable and feasible to deliver to all women who attend symptomatic breast clinics, irrespective of their level of alcohol consumption. Despite extensive research on ABIs, current evidence is predominantly restricted to increased-risk drinkers. It also provides little data on the maintenance of the effects of digitally delivered ABIs beyond 12 months [13]. The effectiveness of the proposed intervention thus requires further research.

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Conflicts of Interest

ERC declares honoraria, advisory board meetings, and support to attend educational meetings from the following: Roche, Astra-Zeneca, Lilly, Nanostring, and Pfizer.

Multimedia Appendix 1
Scope of literature reviews.
[DOCX File , 16 KB - resprot_v9i1e14580_app1.docx]

Multimedia Appendix 2
Archive of five views of the prototype web application.
[ZIP File (Zip Archive), 523 KB - resprot_v9i1e14580_app2.zip]

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Abbreviations

6SQuID: 6 steps in quality intervention development
ABI: alcohol brief intervention
BCT: behavior change technique
NHS: National Health Service
NIHR: National Institute for Health Research

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Protocol

Quality of Inpatient Tuberculosis Health Care in High-Burden Resource-Limited Settings: Protocol for a Comprehensive Mixed Methods Assessment Study

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Abstract

Background: The quality of care for tuberculosis (TB) is deficient in high-burden countries and urgently needs improvement. However, comprehensively identifying the required improvements is challenging. Providing high-quality TB care is an important step toward improving patients' quality of life and decreasing TB morbidity and mortality. Effective tools for assessing the quality of TB services using international standards and guidelines can identify existing gaps in services and inform improvements to ensure high-quality inpatient TB services.

Objective: This study aimed to develop evaluation instruments for defining the quality of provision of TB services.

Methods: To assess quality of services in the largest TB hospital in Armenia, we developed instruments based on the Joint Commission International Accreditation Standards for Hospitals, International Standards for TB Care, TB Laboratories Bio-Safety Standards, and the World Health Organization framework for conducting TB program reviews. A mixed methods approach was utilized, triangulating quantitative (checklists) and qualitative (in-depth interviews) results. A scoring system and strengths, weaknesses, opportunities, and treats analysis was applied to detail results for each of the 122 standards assessed. A scaling approach was used to present overall performances of inpatient services for eight patient-centered functions and five organization management functions.

Results: Overall, 40 in-depth interviews and 91 checklists (21 observations, 16 policy papers, 20 staff qualification documents, and 34 medical records) were developed, utilized, and analyzed to explore practices of health care professionals, assess inpatient treatment experience of patients and their family members, evaluate facility environmental conditions, and define the degree of compliance to standards.

Conclusions: The effective comprehensive evaluation instruments and methods developed in this study for quality of inpatient TB services support the implementation of similar effective assessments in other countries. It may also become a platform to develop similar approaches for assessing ambulatory TB services in resource-limited countries.

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KEYWORDS

tuberculosis; standard of care; health services; research design

Introduction

Background

In 2014, the 67th World Health Assembly set a goal for the year 2035: The number of tuberculosis (TB) deaths will reduce by 95%, the TB incidence rates will reduce by 90% as compared with those in the year 2015, and no family will "face catastrophic costs due to tuberculosis" [1]. The same report identified a stubborn persistence of the burden of TB disease in resource-limited countries, exasperated by multidrug resistant (MDR)-TB. Multidrug resistance threatens effective TB control and is a major threat to global health security. However, the effective management of MDR-TB is limited by health service barriers [1]. Approximately 39% of the estimated TB cases and 75% of the estimated MDR-TB cases globally were either undiagnosed or underreported in 2017, indicating deficiencies in the quality of TB diagnostic and treatment services [2-4].

To achieve the goal of reducing the burden of TB worldwide, the special challenges of MDR-TB in high-burden resource-limited countries such as Armenia have provided impetus for new recommendations, moving from a focus on expanding coverage of free TB diagnostic and treatment services to a focus on quality of services [5]. Provisions to achieve high-quality TB health care are essential steps toward improving TB medical practice and patient outcomes, leading to decreases in TB disease incidence [6,7]. The World Health Organization (WHO) defines high quality of health care as a patient-centered conjunction of six dimensions: effectiveness, efficiency, accessibility, acceptability, equitability, and safety. Best practices address all these dimensions [8].

Standards Measuring Quality of Inpatient Services

The internationally adopted Joint Commission International (JCI) Accreditation Standards for Hospitals are evidence-based standards to measure the quality of services provided in hospitals in order to improve performance and outcomes of hospitals [9]. The assessment of service quality provided in hospitals is conducted through utilization of functions, standards, and measurable elements [9]. Functions consist of various standards, and the standards consist of measurable elements. Measurable elements measure the degree of compliance of hospital performance to their respective standards. Compliance to standards are, in turn, used to evaluate overall hospital performance for the respective function [9].

The Quality Improvement Handbook for TB and MDR-TB Programs identifies three perspectives on the quality of TB care: the perspectives of patients, service providers, and health facility managers [10]. Service providers' perspective of quality [11,12] includes clinical competence, confidence, being respectful, educating patients, application of TB management core principles, team working ability, motivation, and proper documentation of treatment outcomes [13,14]. Facility managers' perspective includes offering services that satisfy patients and community, succeeding on performing TB monitoring indicators, and assuring recognition of their health facility by other stakeholders [10]. The International Standards for TB Care instrument addresses these perspectives, which are utilized to measure the quality of care for TB patients [7].

Assessments of quality of TB health care have typically relied heavily on quantitative assessment methods, including survey instruments, checklists using simulations, checklists for direct observations in the health care facility, and chart reviews or audits [5]. However, quantitative assessments alone provide an incomplete profile of the quality of health care facility services and do not fully address underlying factors influencing quality [5,15]. Qualitative assessments such as semistructured in-depth interviews and focus groups have long been touted for answering quality of health care questions that quantitative methods are ill suited to answer [15], including questions on how health care services are actually operating [5,15]. Qualitative assessments are better at extricating reasons for questionable clinical practices and providing further clarification on how patients and caregivers experience and perceive their health care [15]. However, these qualitative assessment methods are infrequently used to assess the quality of health care [16]. They are especially absent in resource-limited high-burden countries for assessing the quality of TB health services, where there is a heavy reliance on quantitative assessment methods alone [16-20]. In addition, a large majority of the quality assurance tools for resource-limited settings are designed for national TB programs or for national- or district-level services and are not applicable to individual TB hospitals [19].

Study Rationale

The most comprehensive understanding of the quality of health care and underlying factors influencing quality requires a combination of both quantitative and qualitative assessment methods, a *mixed methods* approach [21,22]. Mixed methods better inform the design and development of more successful interventions to improve the quality of health care [23,24]. Yet, no previous published literature integrated both qualitative and quantitative assessments to evaluate the quality of inpatient TB health care in resource-limited high-burden settings. We designed and applied a mixed methods assessment based on the WHO best practices for a comprehensive evaluation of TB inpatient health care services. This assessment was designed to inform systematic feasible improvements in quality and address the two pillars of integrated patient-centered care, and it intensified research and innovation of the Global End TB strategy [25]. This study aimed to develop evaluation instruments using international experience and different assessment tools for defining the quality of care in the largest TB inpatient facility in Armenia.

Methods

Study Design and Instruments

For a larger, more comprehensive, valid evaluation of the quality of diagnostic and treatment services of the largest TB hospital of the National Tuberculosis Control Center (NTCC) in Armenia, we used a mixed methods study design. We integrated qualitative and quantitative methods by triangulating results from all data collection instruments and methods [26].

We developed the study instruments based on suitable JCI Standards for Hospital Accreditation, International Standards for TB Care, TB Laboratories Bio-Safety Standards, and WHO Framework for Conducting TB Programs Review [9,27]. JCI

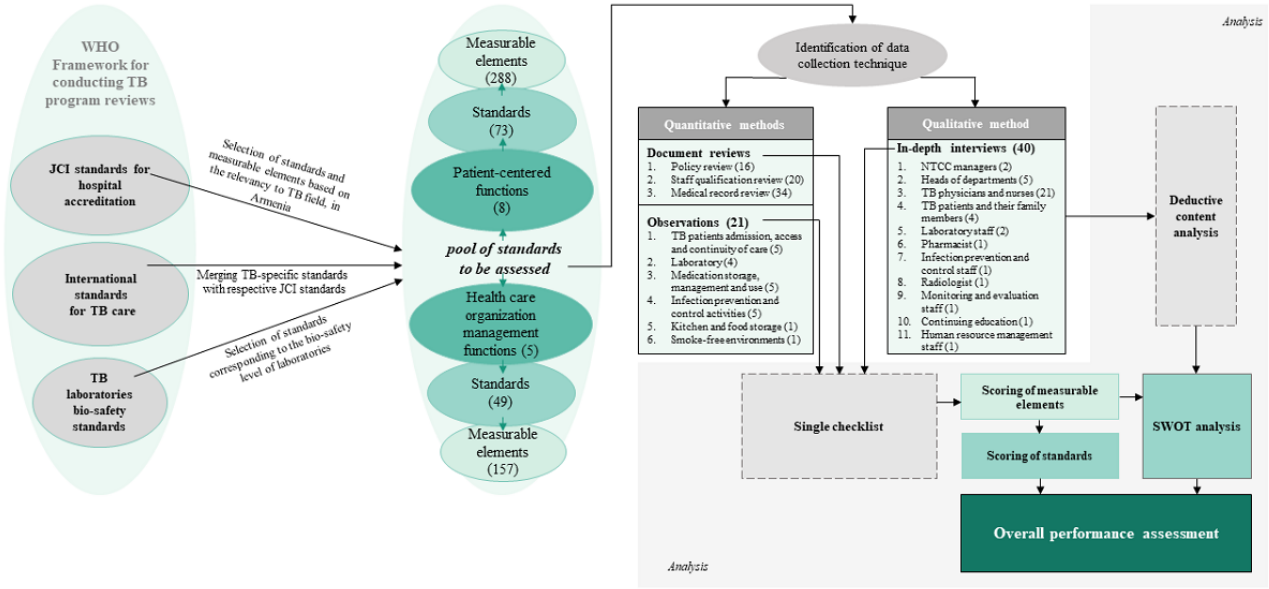
standards and measurable elements were incorporated into the study instruments when appropriate for the assessment (Figure 1). These standards were divided into two main sections consisting of eight patient-centered functions, including the TB-tobacco control function [28] (using the WHO recommendations for integration of TB and tobacco control measures [29]), and five health care organization management functions. All these functions have their specific standards, and each of these standards consist of several measurable elements (Multimedia Appendix 1).

The study instruments include document review checklists for policy review, staff qualification review, and medical records; observation checklists for TB patients' admission, access and continuity of care, laboratory services, medication storage management and use, infection prevention and control, and kitchen and food storage; and in-depth interview guides for 11 groups of key informants (Figure 1). The JCI and WHO standards or measurable elements were used to develop open-ended questions for the in-depth interview guides. All the study instruments were developed in English and translated into Armenian. The quantitative checklists were pretested before data collection; the qualitative guides were continuously improved, as needed, during the process of data collection.

The Institutional Review Board of the American University of Armenia approved the study for compliance with locally and internationally accepted ethical standards (protocol number: AUA-2016-002).

All participants were informed of their rights; all those who chose to participate provided verbal informed consent. Audio recording and observations were possible only with permission of participants; if a participant did not want to be audio recorded, only written notes were taken.

Figure 1. Flowchart for data management and analyses. JCI: Joint Commission International; NTCC: National Tuberculosis Control Center; SWOT: strengths, weaknesses, opportunities, and threats; TB: tuberculosis; WHO: World Health Organization.



Document Review

Policy documents were reviewed to understand the formal documents that regulate the hospital's daily practices in relation to TB treatment and diagnosis. Reviewed documents included organizational charter of the NTCC, internal disciplinary rules of the organization, and internal regulations of different structural units. We also reviewed several guidelines and national regulations, such as hand-hygiene guidelines, waste and expired materials' disposal guidelines, methodological guides for TB infection control, and the national standards for TB treatment and diagnosis.

The staff's qualification document review was designed to evaluate compliance of relevant professional experience, qualifications, and credentials required for job duties and responsibilities of the staff.

Medical records review included reviews of medical records and TB treatment cards of patients with TB admitted for TB inpatient treatment at the NTCC 2 months before the assessment. We selected 2 months before the assessment to have adequate time to review the full range of medical records per patient (medical history, TB treatment card, and MDR-TB treatment files). After discharge, patients' TB treatment cards are transferred to TB outpatient centers. All clinical departments that did not admit new TB patients during the data collection period were asked to provide all records they had from 2016.

Observations

Observations were designed to explore several environmental conditions and daily practices of health care providers in TB treatment and diagnosis using standardized checklists. To evaluate the quality of diagnostic laboratory services, we observed daily practices in both bacteriological or

microbiological and clinical laboratories of the hospital, considering the degree of compliance with the WHO biosafety standards of TB laboratories [30] and the radiology department. We used a standardized checklist to assess smoking practices and strategies in order to eliminate indoor smoking based on the observation of behaviors of health care providers and patients or family members.

In-Depth Interviews

The study team identified key informants from clinical departments and administrative units (based on experience and expertise on inpatient care) by using purposive sampling to optimize information acquisition and convenience sampling for those willing to participate, given the optimal utilization of available resources. All stakeholders of inpatient TB services were included to ensure validity. In-depth interviews included 11 key informant groups or sampling units to protect their confidentiality and provide *data triangulation* [26]: (1) NTCC managers, (2) heads of departments, (3) TB physicians and nurses, (4) patients with TB and their family members, (5) laboratory staff, (6) pharmacists, (7) infection prevention and control staff, (8) radiologists, (9) monitoring and evaluation staff, (10) continuing education staff, and (11) human resource management staff. They were further categorized as (1) administration, (2) health care providers, and (3) patients with TB and their family members. TB health care providers were physicians and nurses with professional experience of working in the inpatient unit of the NTCC. To ensure full coverage, at least one representative from each inpatient department participated in the study. Participating TB patients (their family members) had completed their intensive phase of TB treatment in the NTCC hospital and were in the continuation phase of treatment in outpatient TB centers. For patients from the children's TB department, only adult caregivers were contacted to participate. To recruit patients with TB, we collaborated with physicians from the TB outpatient center who made the initial contact with patients to share their contacts with the research team, and after they agreed, they passed the patients' contact information to the research team.

Data Management

The quantitative assessment checklists (legal and staff qualification documents review, medical records, and observations) data were entered in a Microsoft Excel 2013 worksheet for further analysis.

The qualitative in-depth interview data were analyzed utilizing deductive content analysis with a structured matrix [31-33]. The research team used a predefined structure of initial coding, which comprised the measurable elements of the selected standards (Figure 1). After verbatim transcription of the data, two researchers reviewed all transcripts and started the analysis using *investigator triangulation*. *Data triangulation* was applied across the different data sources [26].

To integrate qualitative and quantitative results to measure compliance to the standards, we developed a single checklist comprising all assessed standards with their measurable elements. Using this checklist, we applied integrated *methodological triangulation* across both quantitative and qualitative results [26].

Next, we developed a scoring system, setting the maximum score for each standard to 10. Applying weighted scores to measurable elements within each standard, we calculated the score of the assessed standards by summing the scores of their measurable elements. The number of measurable elements for each standard ranged from 2 to 10 (average=4), depending on the standards' complexity. We based our evaluation of compliance to the NTCC's daily practices on the obtained scores (scored from 0 to 10) for each assessed standard.

After developing the coding scheme and the scoring system, we conducted a strengths, weaknesses, opportunities, and threats (SWOT) analysis, grouping all the findings into SWOT for each of the 122 standards [34]. The findings include both a scoring table and a SWOT analysis for each of the standards. The scoring table and SWOT analysis were supported by direct quotes from respondents, which reduced the influence of biases of the study team and enhanced the findings for improved communication to a wider audience (Multimedia Appendix 2).

Furthermore, to measure the overall performance of inpatient services of the NTCC in meeting the 13 assessed functions, we calculated the *function mean score*. We calculated this score based on a scoring system we developed that identifies the level to which standards of each function were met. The score ranges were defined using the SD calculated from the mean [33], with the minimum score equal to 0 and the maximum score equal to 10. These numeric values were further defined as a function scale, with categories of *not met* (0), *minimally met* (0.1-3.3), *partially met* (3.4-6.6), *satisfactory met* (6.7-9.9), and *fully met* (10). Regarding data on meeting the standards, we have converted the scores to corresponding percentage (Multimedia Appendix 2).

Results

Document Review

Overall, 16 different internal policy papers and national regulations were reviewed to complete the policy review checklist. We used the policy review checklist to assess the presence or absence of certain policies and procedures that are recommended internationally. The staff's qualification documents review utilized 20 personnel files, including descriptions of positions of all employees from all departments and the staffing plan of the organization for which standardized checklists were utilized. The medical records review included 34 medical records and TB treatment cards of patients with TB and utilized standardized checklists (Figure 1).

Observations

Applying the standardized checklists, we conducted 21 observations in the hospital and in its vicinity (Figure 1).

In-Depth Interviews

Overall, 40 in-depth interviews of key informants were conducted: NTCC managers (n=2), heads of departments (n=5), TB physicians and nurses (n=21), TB patients and their family members (n=4), laboratory staff (n=2), pharmacist (n=1),

infection prevention and control staff (n=1), radiologist (n=1), monitoring and evaluation staff (n=1), continuing education staff (n=1), and human resource management staff (n=1; Figure 1).

Data Management

The calculated scores of the 122 assessed standards and their SWOT analysis contributed to understanding the details and the extent to which inpatient TB services in Armenia comply with local and international standards. The scaling approach, which was applied to evaluate the overall performance of inpatient services for its 13 functions, helped visualize existing gaps in patient-centered and organization management levels of the system and share findings with a wider audience.

Discussion

Principal Findings

Improving the quality of TB health services is possible through adherence to international standards adapted for the local resource-limited context. Modern mechanisms of patient safety and quality assurance in inpatient and diagnostic facilities will result in sustained improvements in operations and improved quality of care provision and will create a safer environment for patients with TB including those with drug-resistant TB. The suggested protocol for quality assessment could help identify gaps in quality of care and patient safety; addressing those gaps could strengthen *the response of health systems in providing accessible, affordable, and acceptable services with patient-centered approaches* in line with the *WHO Roadmap to prevent and combat drug-resistant TB in the European region* [35].

Conclusions

National TB programs in other countries (beside Armenia) can use similar innovative mixed methods and instruments to determine compliance of their TB care systems with the internal policies and procedures and national and international guidelines to improve TB care.

Moreover, this approach of inpatient assessment of TB services can be applied for developing and adopting mechanisms for ambulatory assessment of TB services, providing resource-limited national TB programs with a tool to comprehensively measure compliance of TB services with the international standards.

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Authors' Contributions

NT, ZG, LM, and VP designed the study. NT, ZG, and LM implemented the study activities. NT and BC drafted the manuscript. NT, ZG, LM, BC, and VP reviewed, commented on, and approved the manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standards of patient-centered and health care organization management functions to evaluate the quality of inpatient diagnostic and treatment services.
[DOCX File , 155 KB - resprot_v9i1e13903_app1.docx]

Multimedia Appendix 2
Examples of strengths, weaknesses, opportunities, and threats and overall performance analyses.
[DOCX File , 34 KB - resprot_v9i1e13903_app2.docx]

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Abbreviations

JCI: Joint Commission International
MDR: multidrug resistant
NTCC: National Tuberculosis Control Center
SWOT: strengths, weaknesses, opportunities, and threats
TB: tuberculosis
WHO: World Health Organization

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Protocol

Developing an Evidence-Based Nursing Handover Standard for a Multi-Site Public Hospital in Switzerland: Protocol for a Web-Based, Modified Delphi Study

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Abstract

Background: Poor communication processes create opportunities for errors when caregivers fail to transfer complete and consistent information. Inadequate or nonexistent clinical handovers or failures to transfer information, responsibility, and accountability can have dire consequences for hospitalized patients. Clinical handover is practiced every day, in a multitude of ways, in all health care settings.

Objective: The goal of this study is to build a consensus, evidence-based nursing handover standard for inpatients during shift changes or internal transfers between hospital wards. The study will be based on papers published by Slade et al.

Methods: This protocol describes a modified Delphi data-collection survey involving a targeted panel sample of 300 nurse experts. A multi-round survey will select an anonymous panel from a multi-site public hospital in Switzerland. Each survey stage will be described and will build on the previous one. The study will end with a focus group discussion involving a randomly selected panel to explain why items for the evidence-based clinical nursing handover standard were accepted or not accepted. An item must achieve a consensus of ≥70% for inclusion.

Results: The present study's expected outcome is a consensus-built, evidence-based nursing handover standard for inpatients during shift changes or internal transfers between the wards of a multi-site public hospital in Switzerland.

Conclusions: This survey will enable us to develop an evidence-based nursing handover standard for use during shift changes and internal inpatient transfers in a multi-site public hospital in Switzerland.

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KEYWORDS

modified e-Delphi survey; consensus; nursing; shift; nursing handover; standard; inpatient transfers; evidence-based practice; multi-site hospital

Introduction

The Rationale for an Evidence-Based Nursing Handover Standard

The complexity of health care and its communication processes continues to challenge health care professionals, institutions, and organizations. Poor communication processes create opportunities for errors when caregivers fail to transfer complete and consistent information [1]. Clinical handover is practiced every day, in a multitude of ways, in all health care settings [2,3]. Clinical handover of patients relates to, and is defined as [4]:

> *The transfer of professional responsibility and accountability for some or all aspects of care for a patient, or group of patients, to another person or professional group on a temporary or permanent basis.*

The literature identifies three basic components of good practice in nursing handover styles: bedside, verbal, and nonverbal. Handovers at bedside are located at the patient's bedside, which promotes patient and nurse face-to-face interaction and encourages patients' verbal participation, thus making the patient central to the information exchange process [5,6]. Verbal communication is in an office setting, where the nurse responsible for a group of patients exchanges relevant, documented information. Nonverbal communication is in an office setting, where nurses inform themselves by reading the patient's health record, which includes progress notes, medication charts, observation charts, and nursing care plans. However, there is also taped communication, which is in an office setting where the nurse in charge collects the relevant information and records it onto an audiotape so that the oncoming shift can listen at a convenient time.

Inadequate or nonexistent handovers, or failures to transfer information, responsibility, and accountability can have direct consequences for patients [7]. They can result in delays to diagnosis, treatment, and care, tests being missed or duplicated, and subsequent incorrect operationalization of care plans or drug follow-up [8]. Current nursing handover practices in a multi-site hospital in Switzerland are highly variable, unreliable, and differ across medical specialties. This can lead to discrepancies in the content and accuracy of the information provided. Previous studies have revealed multiple barriers to communication within health care organizations, including hierarchy, gender, ethnic background, primary health care education, and differences in communication styles [9,10]. These inconsistencies in communication cause considerable risks to patient safety and care [11]. Health care institutions have recently sought to discover specific risks and contributing factors that cause difficulties in handover communications [12]. An internal survey of health care professionals in a multi-site public hospital in Switzerland concerning the culture of safety in patient care in 2017 revealed that almost two-thirds of the health care professionals (nurses, physicians, and allied health care professionals) considered the quality of information transmission to be poor and at-risk to patient safety [13]. Experimental studies have shown that information is poorly retained if verbal or handwritten handovers are transferred across multiple shifts [14].

Validated root causes for communication failures at handover include: institutional cultures which fail to promote successful handovers (eg, lack of teamwork and respect), differing expectations between information givers and receivers, ineffective communication methods (whether verbal, recorded, bedside, or written), poorly timed or nonsynchronous physical transfers and patient handovers, insufficient time allocated to successful handovers, interruptions to handovers, lack of standardized procedures for conducting successful handovers, inadequate staffing to accommodate successful handovers at certain times of the day or week, and a lack of patient participation during the handover [15-17].

The web-based, modified Delphi (e-Delphi) survey proposed in this study will target the development of standardized solutions to those risks, to be followed by the development and implementation of factors to improve the effectiveness of communication during transitions of care [18]. It has been suggested that standardizing the content and processes involved in patient handovers (eg, shift reports) ensures consistency in the exchange of critical information and is an effective means of improving communication and thus patient safety [19,20]. Although there is a lack of detail about what the specific content necessary for handover communication should be, standardizing processes (eg, presenting the patient) could be a starting point for selecting the content (eg, patient name, age, and current condition). Effectively addressing the challenges of transferring information in complex care environments requires that specific information on each topic be incorporated into two-way communication [21]. The literature reveals little empirical evidence of a link between effective information transfer during handovers and patient safety [22].

Rationale for a Web-Based, Modified Delphi Study

Delphi studies are a recognized method for building consensus around an issue where little knowledge or agreement previously existed [23]. The Delphi method is a framework for a forecasting process based on the results of multiple rounds of questionnaires sent to a panel of experts. This approach uses [24,25]:

> *Structured anonymous communication between experts to gather consensus perspectives about an issue or topics that can then be used to inform decision-making or to agree about methods of functioning.*

Inadequate communication during nursing handovers increases the risk of adverse events because incomplete, inaccurate, or omitted data create ambiguities between the sender and the receiving health care professionals.

The web-based, modified Delphi study involves rounds of web-based questionnaires for which experts are asked to provide their opinions on particular topics [26]. Initially, this is done independently, but in subsequent rounds, the experts are made aware of the group's opinions when making their decisions, to reach consensus. The key features of e-Delphi methods are that they are iterative and anonymous, which is particularly beneficial for a multi-site hospital with different medical

specialties. Anonymity and the web-based format encourage participation and opinion-sharing by a large set of panel members, and they thus prevent dominant individuals from controlling discussions, which is important within hierarchical environments such as health care institutions. We will use a Delphi panel approach to find a consensus on data gaps and the most appropriate study design for constructing a standard evidence-based tool.

Higher numbers of handovers pose greater risks to patients, although little is known regarding the precise mechanisms by which handovers undermine care. Some studies have highlighted information management at shift changes as being particularly vulnerable to error [14,22,25,27]. Handover strategies should recognize the interconnectedness of the different categories and the themes of administrative, clinical, and medical information from the outset. The general themes of clinical nursing handover standards cover a range of factors which come together to define the degree of smoothness and patient safety involved in those handovers [28-30]. Handovers are an essential component in the continuity of care [31]. During the patient journey, such transitions in care are notably vulnerable periods [32]. Transferring the responsibility of care to another practitioner introduces the potential for an error to occur should all the relevant information not be communicated accurately and efficiently [33]. The information transferred may be inaccurate, lack clarity, or be incomplete, which increases the risk of potentially harmful errors [34,35].

Study Purpose

The purpose of this study is to outline a proposed protocol for an e-Delphi survey to construct a consensus, evidence-based nursing handover standard for inpatients during shift changes or internal patient transfers between the wards of a multi-site public hospital in Switzerland. The study has not yet been conducted.

Methods

Design

This protocol describes a multi-round survey of an anonymized panel selected from a multi-site public hospital in Switzerland to find a consensus for an overall, evidence-based nursing handover standard for nursing shift changes and internal inpatient transfers. In the absence of a standardized reporting protocol for a modified e-Delphi survey, this protocol referred to publications by Keeney et al [36], Burchell et al [37], Slade et al [38,39], and Cole et al [23].

Setting and Population

The study will be conducted in a multi-site public hospital, located in a southern part of Switzerland, and serving a population of about 340,000 [13]. It recorded almost 40,000 individual hospitalizations in 2017 and is composed of two hospital centers in two linguistically and culturally different regions [13]. Each hospital center includes standard medical hospitalization wards to cover its mission of universal public health care.

The research sample population will be composed of a panel of 300 eligible nurse experts drawn from the institution's staff lists of clinical nurse specialists and nurse supervisors. They are all highly qualified, experienced, and recognized within their departments. In agreement with the two hospital centers' directors, all eligible nurse experts will be invited to participate in the e-Delphi survey.

Eligibility and Recruitment of the Web-Based, Modified Delphi Panel of Nurse Experts

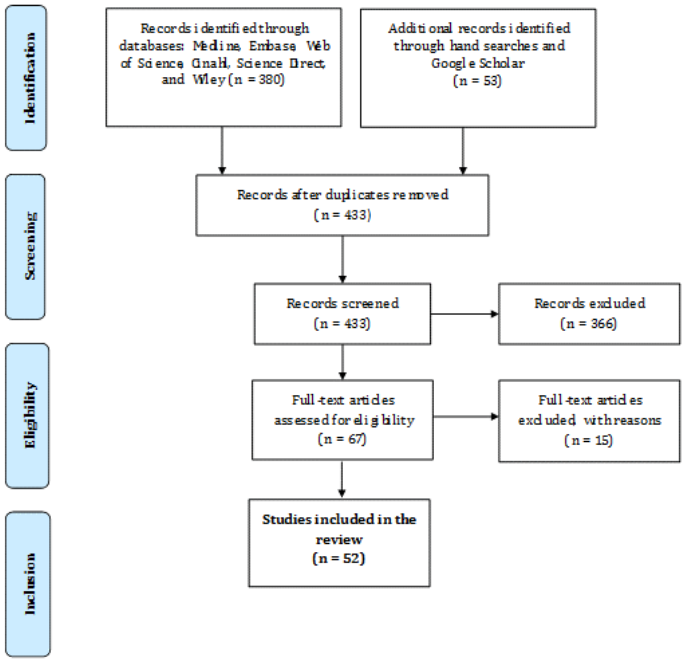
In our application of the e-Delphi method, the term expert includes people with significant work experience as health care professionals. The investigators will invite professionally active nurse experts from the domains of general medicine, surgery, geriatrics, rehabilitation, gynecology, obstetrics, pediatrics, emergency department medicine, intensive care, anesthesia, and psychiatry to join the panel. The inclusion criteria will be: (1) to have worked in their current specialty for at least three months before the launch of the data collection process; (2) to have been employed as a registered nurse clinical educator, a student-success coach, or a nurse supervisor; and (3) the capacity, willingness, and time to participate in the expert panel and the communication skills to understand and answer clinical statements effectively.

Literature Review to Design the Components of the Web-Based, Modified Delphi Survey

A literature review was conducted to map the components needed for an evidence-based, clinical nursing handover standard. A comprehensive scoping review of all the components of effective, evidence-based nursing handovers has been conducted, as have research group discussions on the necessary content for those handovers (see Figure 1 and Textbox 1) [40]. In collaboration with a medical librarian and using predefined search terms, we conducted a comprehensive scoping literature search for published articles in the following electronic databases, from inception until September 30, 2018: Medline via PubMed (from 1946), Embase (from 1947), CINAHL (from 1937), the Web of Science (from 1900), Science Direct, and Wiley. We conducted a hand search of the bibliographies of all relevant articles and completed this with a search for unpublished studies using Google Scholar.

Inclusion criteria for our literature search were that the article described the definition, content (structure), and implementation of a nursing handover standard. The search accepted study designs that were either uncontrolled trials, trials with a comparison group (uncontrolled, pre-post historical controls), or observational studies. Publications could be in English, French, or German, but they were excluded if they focused on interprofessional handovers, transitions from hospital to home, primary care settings, or they were study protocols. The search syntax consisted of the search themes joined using the Boolean terms "AND" and "OR". The following descriptor terms and free keywords were included: "shift-to-shift hand-off," "hand-off," "handover," "sign-out," "shift change," "shift change report," "inter-shift report," "shift-to-shift report," "transition of care," AND "nursing; nursing care; nursing quality; nursing safety; inpatients; hospital; hospitalization." Figure 1 presents the search strategy's results.

Figure 1. Search strategy for the retrieval of the necessary components of a nursing handover standard.



Textbox 1. Relevant components of an evidence-based nursing handover standard for inclusion in the e-Delphi survey.

Culture and attitude for good handover practices:

- Respectful and collaborative attitude
- Proactive listening
- Positive, factual language adapted to patients, situations, and professionals
- Confidentiality
- The handover environment

Handover preparation, including coordination and sources of information:

- Clinical assessment before the handover
- Use different sources of information
- Updated patient records
- Reconsider and reanalyze information

Handover phases, including communication of patient-specific information

- Mnemonic techniques to guide communication and format content chronologically
- Face-to-face handovers with the opportunity to ask questions
- Information technology to support data access to the patient's complete history and health status
- Patient records ensuring the traceability of decisions and follow-up
- Information technology to support data updates
- Flexible information technology to support adaptations for each specialized ward
- Handovers at the patient's bedside at the risk of reduced confidentiality
- Handovers at the patient's bedside for understanding their values and preferences

A minimum dataset should be transmitted:

- Summary of the patient's hospitalization history and care planning
- Assessment of the disease
- Prognosis of health status
- Allergies
- Reanimation status
- Medication treatment
- Laboratory results
- Vital signs
- Patient's activities and planned examinations

Knowledge Synthesis for the Selection of Items for the Nursing Handover Standard

The investigators reviewed the above findings at two meetings and selected the relevant components of an evidence-based nursing handover standard to be included in the Delphi panel survey. Textbox 1 presents the main components of an evidence-based nursing handover standard retrieved in the comprehensive scoping review.

Web-Based, Modified Delphi Survey Administration

Each round of the e-Delphi survey will be communicated through SurveyMonkey, which is a secure, commercial, web-based platform that ensures anonymous survey participation. The collected data will be stored in Switzerland, protected with high-end firewalls, and treated confidentially. All the eligible nurse experts and potential members of the expert panel will be sent a personalized link to fill out each round of the survey. Although a personalized link is used to access the survey, personal information will not be stored, and contact details will be removed from the completed survey. The survey's predetermined percentage of agreement to qualify as consensus was established at 70% for all the items in the e-Delphi process' different rounds [36].

Rounds in the Web-Based, Modified Delphi Process

The e-Delphi data collection process will be composed of three rounds. Item management and answers from each round will be downloaded into the SPSS 25.0 software package for analysis

(IBM Corp, Armonk, New York, United States). These enabled the development of a structured questionnaire linking all the possible components with item statements on which should be included in the handover standard. Participants will give their opinions on whether items should be included by using a five-point Likert scale ranging from strongly agree to strongly disagree. One open-ended question at the end of the questionnaire will ask:

> *What topic, not yet mentioned in these statements, should also be integrated into the handover standard?*

The questionnaire will be translated into French and German and trialed with three or four clinical experts not involved in this e-Delphi survey.

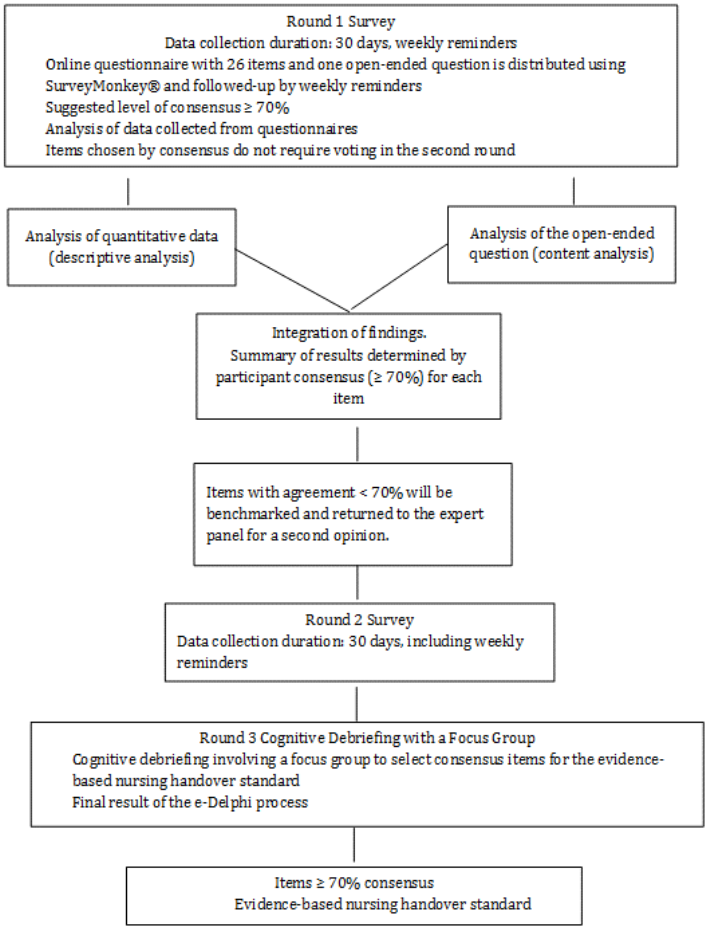
In the first round, the potential panel of experts will be asked to respond to a selection of items (Textbox 1). This will involve distributing the structured questionnaire by email to the selected sample of potential participants, including a cover letter describing the study's aim and instructions on how to fill in the questionnaire. Respondents will be able to use an open text field (with the open-ended question) to explain their choices or suggest items not listed in the first round, but which they believe are important. Finally, the panel will also report their sociodemographic and professional characteristics, including age, professional role, and years of experience. An email reminder will be sent out every week after launching the e-Delphi process. The first round will close after 30 days, and the returned data will be analyzed.

The second round will only involve those statements for which no consensus agreement was found in the first round, plus new statements which have arisen from the panel's suggestions in response to the open question. A cover letter explaining this, and with further instructions for round two, will be sent with the questionnaire. A weekly reminder will be sent out. The second round will end after 30 days, and the returned data will then be analyzed. The second round's expected outcome will be a final selection of items about which the panel agreed. Moreover, if the items generated by the open question did not find any consensus in the second round, they will be resubmitted in the third round.

The third and final round will end with a focus group cognitive debriefing made up of 8-10 randomly selected, but highly involved, nursing experts. Cognitive debriefing is the process by which the results of a survey are actively discussed among representatives of the target population [41].

Numerous qualitative methods have been used to capture caregivers and clinicians' perspectives of important changes in daily practice. Patrick et al considered that the cognitive debriefing technique could be used in a Delphi study [42]. As Patrick et al outlined, the cognitive debriefing process is structured around and usually focused upon the assessment of a specific clinical output, and it incorporates direct questions about the understandings, relevance, and comprehensiveness of the measures leading to that output [42]. They will explain and validate the consensus items to be used in the standard for evidence-based nursing shift handovers and patient transfers within our multi-site public hospital in Switzerland (Figure 2). The focus group guide will be pretested before the start of the focus group.

Figure 2. Planned e-Delphi survey data-collection process to design an evidence-based nursing handover standard. e-Delphi: web-based, modified Delphi.



Data Analysis

The analysis of responses from each round will be done iteratively and independently. The investigators will supplement their quantitative analyses with a thematic analysis of the text of the open-ended question to better understand disagreements and include suggestions [38].

The proposed study will be carried out using the SurveyMonkey online questionnaire website, and all the items will be translated into French and German. Data will be extracted into an Excel (Microsoft, Redmond, Washington, United States) spreadsheet and then imported into SPSS statistical software, version 25. The population of panel experts will be described using descriptive statistics such as frequencies, distributions, and leading trends. The data collected on a 5-point Likert scale will be recoded as dichotomous variables: disagreeing with the statement will include the strongly disagree, partially agree, and no opinion responses, and agreeing with the statement will include the partially agree and strongly agree responses. Consensus agreement on inclusion by the nurse experts versus no consensus on inclusion will be calculated by using the sum of the distribution of the agree/disagree responses for the item. As there is no standard definition of consensus for Delphi studies [43], we have chosen a consensus level of ≥70% of responses selecting the item for inclusion in the handover standard [36]. Items that do not reach the required level of consensus in round one will be reconsidered in round two. Appropriate exact tests will be used to compare means and percentages if participant anonymity can be ensured. Analyses for internal validity will be carried out by three or four experienced nurse experts who were not included in the proposed study and who will be contacted by email and asked to examine the questionnaire items' clarity, wording, and understandability before the modified e-Delphi study is launched.

Ethical Considerations

Ethical approval has been obtained from the Human Research Ethics Committee of the Canton Vaud (CER-VD) (2019-00925). The study will ensure the anonymity of its panel of nurse expert participants as well as the standards of good research practice mentioned in the Declaration of Helsinki [44].

Results

The present study's expected outcome is a consensus-built, evidence-based nursing handover standard for inpatients during shift changes or internal transfers between the wards of a multi-site public hospital in Switzerland. The first round's expected outcomes will be the selection of numerous items about which the panel agreed and a list of items about which it could not find a consensus. The second round's expected outcomes will be a final selection of the items about which the panel was in agreement and a list of items about which no

agreement could be found (ie, topics rejected for inclusion in the handover standard). The third round of the e-Delphi process will be a cognitive debriefing involving a focus group discussing the consensus/no consensus items in the nursing shift handover and patient transfer standard.

Discussion

Primary Findings

The significant number of nurse experts involved in the proposed e-Delphi survey determined our use of an electronic data collection method. However, different data collection methods for Delphi surveys, such as using face-to-face interviews or focus groups with and without patients, have been previously documented in the literature [36,45,46]. The study's potential for introducing significant benefits to the patient handover and transfer contexts lies in its combined use of clinical and applied research skills to meet a patient safety issue. Indeed, the study will have a direct impact on future patient safety, quality of care, and the continuum of care. It will enable the front-line nursing staff of a multi-site public hospital in Switzerland to coconstruct their consensus on the content necessary for an internal, evidence-based nursing shift handover and patient transfer standard. In addition to the items to be included in the nursing shift handover standard, the proposed study will seek a consensus about information flows and patients' involvement in their nursing handovers. The proposed study's findings will be a substantial contribution to the hospital's overall strategy for continually improving the quality and safety of care using evidence-based practices [47]. The investigators' choice of the e-Delphi method maintains the principles of offering an equal voice to all professional stakeholders. As Klee et al and McFarlane mentioned, a consensus handover standard is a way to change the daily practice of all the nurses involved in a hospital's nursing processes, and it is not uniquely limited to those survey participants who accepted the items for the standard [48,49].

The proposed study design is not without potential pitfalls. One significant challenge was the selection of the items for the nursing handover standard. The investigators' choices were based on a comprehensive scoping review. Nevertheless, it is possible that specific important topics, which may be effective in our settings and context, were overlooked or excluded. A second challenge will be ensuring a representative selection of nurse experts, considering the particularly heterogeneous characteristics of their training and clinical expertise (management versus clinical experts). The investigators will seek to make the sample as representative by identifying diverse perspectives, but it should be acknowledged that the opinions of the nurse experts selected are unlikely to capture every possible viewpoint. Involved nurse experts will ensure that item rating is carefully considered, and the response rates remain high. Input will be maximized by limiting the number of questions asked in each round. The focus group will enable a better understanding of why nurse experts did or did not select specific items by giving them a voice and assessing their experience of an e-Delphi study. Procedures will be established to minimize participation by ineligible staff, including the active promotion of the study within the hospital and direct invitations to certain potential participants, via established, official staff lists.

Finally, certain items may not reach the desired level of consensus, even after three rounds. However, by conducting the e-Delphi survey, the investigators will have developed a better understanding of the importance of accurately and effectively transmitting relevant information between nurses during shift changes and internal patient transfers, and they will be better prepared and positioned to anticipate any potential barriers to implementation.

Future additional research will be considered, such as an implementation study of the handover standard tool in the different acute wards, a before-after study after the introduction of the evidence-based nursing handover tool, and a qualitative study of perceptions of nurses and patients about the introduction of a standard handover tool in daily practice.

Conclusion

The results of the proposed e-Delphi study will characterize the perceived requirements for an evidence-based nursing handover standard. However, the methodology of this e-Delphi survey in a multi-site public hospital in Switzerland should not be considered generalizable for building clinical nursing handover standards for other hospitals. Nevertheless, the approach presented here could be thought of as good clinical research practice for surveying a large sample and may be transferable to other settings where the input of experts in a particular field is required to coconstruct methods of safely transmitting information between health care professionals.

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Authors' Contributions

All the authors contributed to the design and development of this study protocol and to the drafting of the manuscript. They all approved the final version and have agreed to be held accountable for all aspects of the work.

Conflicts of Interest

None declared.

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Abbreviations

e-Delphi: web-based, modified Delphi

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Protocol

Testing the Effectiveness of Enhanced Alcohol Warning Labels and Modifications Resulting From Alcohol Industry Interference in Yukon, Canada: Protocol for a Quasi-Experimental Study

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Abstract

Background: Alcohol warning labels are a promising, well-targeted strategy to increase public awareness of alcohol-related health risks and support more informed and safer use. However, evidence of their effectiveness in real-world settings remains limited and inconclusive.

Objective: This paper presents a protocol for a real-world study examining the population-level impact of enhanced alcohol warning labels with a cancer message; national drinking guidelines; and standard drink information on attention, processing, and alcohol-related behaviors among consumers in Canada. Postimplementation modifications to the original protocol due to interference by national alcohol industry representatives are also described.

Methods: This quasi-experimental study involved partnering with local governments in two northern Canadian territories already applying alcohol warning labels on alcohol containers for sale in liquor stores. The study tested an 8-month intervention consisting of three new enhanced, rotating alcohol warning labels in an intervention site (Whitehorse, Yukon) relative to a comparison site (Yellowknife, Northwest Territories) where labelling practices would remain unchanged. Pre-post surveys were conducted at both sites to measure changes in awareness and processing of label messages, alcohol-related knowledge, and behaviors. Liquor store transaction data were collected from both sites to assess changes in population-level alcohol consumption. The intervention was successfully implemented for 1 month before it was halted due to complaints from the alcohol industry. The government of the intervention site allowed the study to proceed after a 2-month pause, on the condition that the cancer warning label was removed from rotation. Modifications to the protocol included applying the two remaining enhanced labels for the balance of the intervention and adding a third wave of surveys during the 2-month pause to capture any impact of the cancer label.

Results: This study protocol describes a real-world quasi-experimental study that aimed to test the effectiveness of new enhanced alcohol warning labels as a tool to support consumers in making more informed and safer alcohol choices. Alcohol industry interference shortly after implementation compromised both the intervention and the original study design; however, the study design was modified to enable completion of three waves of surveys with cohort participants (n=2049) and meet the study aims.

Conclusions: Findings from this study will directly inform alcohol labelling policies in Canada and internationally and provide further insight into the alcohol industry's attempts to disrupt research in this area. Additional unimpeded real-world evaluations of enhanced alcohol warning labels are recommended.

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KEYWORDS

alcohol warning labels; alcohol policy; alcohol; cancer; national drinking guidelines; standard drink labels; alcohol industry

Introduction

Alcohol poses significant public health and safety problems in Canada, which are especially severe in its northern territories [1,2]. Harms and economic costs of alcohol consumption are increasing nationally and were recently estimated at CAD $14.6 billion per annum, greater than all other psychoactive substances including tobacco. Per capita alcohol costs were at least double the national average in the north. In 2016, alcohol was responsible for 14,800 deaths (including 4275 from cancer), 87,000 hospital admissions, and 139,000 productive years of life lost in Canada [2]. Despite the extent of this harm, there are low levels of awareness of health risks from alcohol, particularly cancer risk [3], and of national low-risk drinking guidelines (LRDG) among Canadians [4-6].

Alcohol warning labels are a promising strategy for increasing public awareness of alcohol-related health risks and supporting safer consumption [7,8]. They are a unique intervention providing critical information both when alcohol is purchased and during consumer use. Alcohol warning labels also have a broad reach, as nearly all drinkers are exposed to labels; those who consume alcohol more heavily are exposed more often and are thus most likely to recall these messages [9,10]. Based on studies of tobacco warning labels, key label elements include a relatively large size and font, full color graphics or images, personally relevant and direct messages, and prominent placement on packages [11-13]. Implementing rotating messages to prevent a wear-out effect over time and having accompanying education campaigns also increase the effectiveness of warning labels in the context of tobacco and alcohol [11,14].

Alcohol warning labels are currently mandated on alcohol containers in 47 countries worldwide, although not in Canada—with the exception of two northern jurisdictions applying labels by local directives. However, to date, labels used internationally are small, are not prominently displayed on containers, and virtually all contain text-only messages with vague statements and minimal graphics [15,16]. There is increasing evidence of concerted efforts by the global alcohol industry to embed alcohol in the fabric of society and minimize or misrepresent information presented to the public on alcohol-related harms [17,18], suggesting that the existence of such few instances of labels following best practice guidelines may not be accidental. In 2010, Thailand was set to introduce a series of labels that included graphic images representing alcohol harms in a similar style to those used successfully on tobacco packages. However, significant push back from trade organizations representing major alcohol-producing countries prevented the labels from being implemented [19]. More recently, alcohol suppliers in the United Kingdom negotiated a private deal with the government, allowing an additional 30-month "grace period" before commencing implementation of mandatory health messaging on alcohol products, a requirement introduced in 2016, and which included listing newly lowered national drinking guidelines; the public was only informed of the deal 22 months into the grace period and the outdated higher drinking guidelines still remain on many products [20].

The majority of evaluations that have tested the effectiveness of existing alcohol warning labels have focused on the mandatory label introduced in the United States in 1989 [9,21,22]. The US label, which states that drinking alcohol while pregnant can cause birth defects and that consumption of alcohol impairs ability to drive a car and operate machinery and may cause health problems, is text-only with no requirements for color, message rotation, or prominent placement on alcohol containers. Not surprisingly, effects of this label were limited mainly to situational preventive behaviors (not drinking before driving, not driving after drinking), sparking conversations about drinking and pregnancy and interventions by collaterals to prevent someone else from drunk driving, with the heaviest drinkers reporting the highest recall of label messages [9,22]. Lab-based and smaller-scale qualitative studies conducted in Canada and elsewhere revealed that consumers were open to prominently displayed alcohol warning labels that included a health message such as a cancer warning [23-25], standard drink information, and LRDG [6,23,25]. When tested in Canada, the drinking guidelines and standard drink information helped consumers more accurately calculate the number of standard drinks in a bottle and better track their consumption in relation to the LRDG [6,23].

There is a dearth of evidence measuring the effectiveness of enhanced alcohol warning labels that follow best practice recommendations, especially those that include integral information for consumers such as alcohol-related harms including risk of cancer and information to facilitate safer drinking patterns. Accordingly, the primary objective of this study is to test, in a real-world setting, if labelling alcohol containers with a cancer message, standard drink information, and national drinking guidelines supports more informed and safer alcohol use and has a population-level impact on alcohol consumption. Specifically, our research questions include the following: (1) What is the effect of enhanced alcohol warning labels relative to usual labelling practice (comparison site) on noticing labels and recall of label messages; processing label messages; knowledge of alcohol-related health risks, national drinking guidelines, and the concept of a standard drink; and

self-reported drinking behaviors? (2) What is the population-level effect of enhanced alcohol warning labels on alcohol consumption relative to usual labelling practice (comparison site)? In this paper, we present the original protocol of this controlled pre-post quasi-experimental study and describe how the study design was modified postimplementation in response to efforts by representatives of the national alcohol industry in Canada to disrupt the study.

Methods

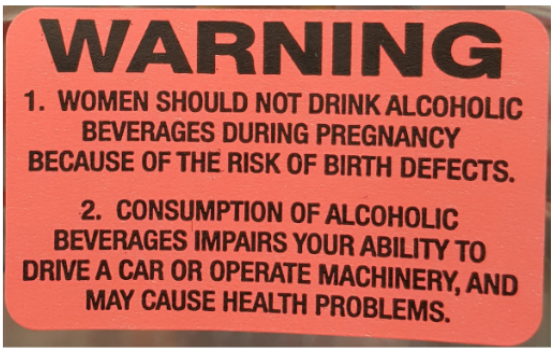
Setting

This study was conducted in two capital cities (Whitehorse, Yukon, and Yellowknife, Northwest Territories) located in two of Canada's three vast and sparsely populated northern territories. Whitehorse (population=28,225 as of 2016) and Yellowknife (population=19,569 as of 2016) are appropriate matched sites for a number of reasons: They have similar government-run alcohol distribution systems that account for almost all off-premise alcohol sales in both cities and comparable per capita alcohol sales, population size, ethnic diversity, age, education levels, and income profiles [2,26-29]. Whitehorse has one mid-sized government-run liquor store and a handful of private stores or licensed premises such as bars or hotels that can sell off-sales; there are five small government-run agency stores located in five small communities across Yukon. Yellowknife has limited off-sales available from licensed premises and two government-run agency stores; there are five small agency stores located in five small communities across the rest of the territory. Further, both territories have had exposure to alcohol warning labels since 1991 when application of a postmanufacture label on containers cautioning consumers about drinking while pregnant (with an additional warning about alcohol and driving and general health risks in Northwest Territories) became mandatory by territorial directives (Figures 1 and 2). No other jurisdictions in Canada currently require alcohol warning labels.

During the development of the study, the research team approached provinces and territories with an invitation to participate in the labelling experiment. The government-run Yukon Liquor Corporation, responsible for the sale and distribution of alcohol in the territory, accepted and agreed to participate in the study as the intervention site. The single flagship liquor store in Whitehorse presented an ideal and practical intervention site and offered maximum exposure to the new labels with well-established labelling procedures already in place. The Northwest Territories' government-run Liquor Commission agreed to act as a comparison site, which involved making no changes to labelling practices at their two Yellowknife retail liquor stores during the intervention period.

Figure 1. Alcohol warning label on alcohol containers in Yukon prior to the intervention (2.3 cm x 2.8 cm).

Figure 2. Alcohol warning label on alcohol containers in the Northwest Territories prior to and during the intervention (3.0 cm x 5.0 cm).



Ethics Approval and Consent to Participate

This study received ethics approval from the Research Ethics Board at Public Health Ontario (identification number: 2017-010.04) and the Human Research Ethics Board at the University of Victoria (Protocol 17-161) and obtained the relevant research licenses required in Yukon and Northwest Territories. Written, informed consent was obtained from all

study participants prior to completing the survey, and participants were also provided with a letter of information about the study.

Alcohol Warning Label Intervention

The labelling intervention involved rotating three new evidence-informed enhanced alcohol warning labels (Figures 3-5) on all alcohol containers (with the exception of select local and single-serve beer and single-serve cider, ~3% of total sales) in the intervention site liquor store for an 8-month period. Intervention labels were applied in store by trained liquor store staff, using specialized label-application guns. Consistent with evidence for effective labelling initiatives [11,14,30], a social marketing and awareness campaign including in-store signage, handouts, a website, toll-free helpline, and radio spots that incorporated the three label messages was planned to run parallel to the timeframe of the intervention.

The design of the enhanced intervention labels was directly informed by the results of a between-group experiment testing the efficacy of the label content, format and size [23], and focus groups among residents across Yukon to further refine the label design and gauge consumer acceptability of the labels [25]. The labels were also reviewed during extensive consultations with international experts and local public health and community stakeholders in Yukon. As per territorial government regulations, all label messaging was required to be presented in both English and French, Canada's two official languages. To address resulting label-size considerations, the final messages were presented on three separate rotating labels.

As shown in Figures 3-5, the three new enhanced alcohol warning labels improved on the existing label in the intervention site in a number of ways: They were larger in size, used a bright yellow background and red border, and incorporated graphics along with the three distinct health messages. The first label (Figure 3) stated that alcohol can cause cancer, which is an evidence-based statement [31-37], specifically mentioning breast and colon cancers, two prevalent cancers in Canada [1,38]. The second label (Figure 4) presented Canada's LRDG for men and women [39] using an infographic, and the third label (Figure 5), also using an infographic, provided consumer information on how many standard drinks are contained in different size and strength alcoholic beverages [40]. Standard drink labels with the most common alcohol strengths were developed for standard size wine (750 mL, 12% and 15%), spirits (750 mL, 40% and 60%), beer (355 mL, 5% and 7.5%) and cider (2 L, 7%) containers; a standard drink in Canada contains 13.45 mg of pure alcohol.

Study Design and Data Sources

A pre-post quasi-experimental study with the comparison site was designed to test the impact of the 8-month labelling intervention. No randomization was applied as full voluntary cooperation, and participation of the intervention site was required for implementation of the alcohol warning labels intervention. The study included two data sources from both the intervention and comparison sites: (1) surveys with cohort participants, and (2) aggregated liquor store-level sales data (Figure 6). Pre-post surveys included a split-panel design with a panel cohort nested within two repeated cross-sectional data collections to assess participant responses. Wave 1 surveys were conducted in the intervention and comparison sites in May/June 2017, 4 months before the label intervention was to be implemented in the intervention site in November 2017. Wave 2 surveys were scheduled for both sites in May/June 2018, 8 months after the label intervention was implemented in the intervention site. Contact information provided by participants at Wave 1 allowed for email recruitment at Wave 2 using a time-limited online survey. All survey periods continued for 6 weeks, the survey was approximately 18 minutes in length, survey measures were consistent across waves and sites, and participants received a gift card to a national coffee store chain or an Interac electronic transfer as remuneration in appreciation of their time.

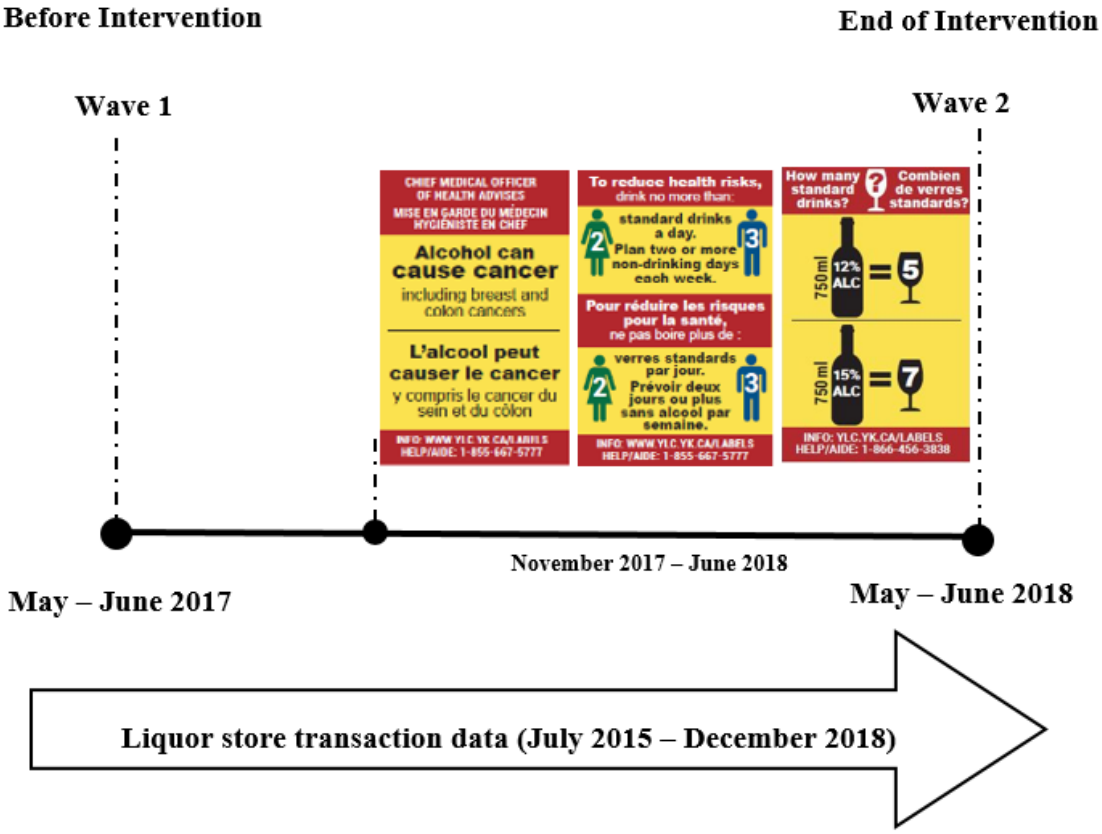
Figure 3. Intervention alcohol warning label: Cancer warning (5.0 cm x 3.2 cm).

Figure 4. Intervention alcohol warning label: Low-risk drinking guidelines (5.0 cm x 3.2 cm).

Figure 5. Intervention alcohol warning label: Standard drink information - example for 750 mL wine (5.0 cm x 3.2 cm).

Arranged by prior agreement with governments in both the intervention and comparison sites, aggregated product-level liquor store sales data spanning the months before, during, and after implementation of the intervention labels were also obtained. Analyses of sales data were designed to estimate the impact of the labels on population-level alcohol consumption, specifically the total volume, type, and strength of alcohol purchases in liquor stores before, during, and after the intervention. Alcohol sales data are a robust and standard measure for tracking target population alcohol intake over time and for cross-jurisdictional comparisons, as purchases are predictive of consumption [41].

Figure 6. Original study design and timeline.



Surveys

Survey Recruitment and Procedures

In Wave 1, surveys were conducted with liquor store customers in the intervention and comparison sites over a 6-week period from May to June 2017. Trained research assistants were stationed in liquor store lobbies from Monday to Saturday in both sites; all stores were closed on Sundays. Recruitment in the intervention site took place each day during opening hours of the store between 10 AM to 6 PM and during extended Friday opening hours between 10 AM to 8 PM. Store opening hours in the comparison site were between 11 AM to 11 PM each day, and recruitment took place between 12 PM and 8 PM; recruitment hours in the comparison site were carefully selected to cover peak sale periods equivalent to those in the intervention site. Customers were systematically selected to participate in the survey upon exiting the liquor store using a standard intercept technique of approaching every person that passed a preidentified landmark in the liquor store. Eligibility for the survey was established through a screening tool: Participants had to be aged ≥19 years (the legal drinking age in both sites), have consumed at least one alcoholic drink in the past month, be residents of the intervention or comparison site cities, not currently self-report being pregnant or breastfeeding, and have purchased liquor at the store that day. Eligible participants were required to read and sign consent forms prior to starting the survey. The survey was completed independently in English on a 10-inch tablet with no interviewer assistance; the majority of the population was English speaking at both sites. Because the main objectives of the study were to assess the extent to which consumers notice, understand, and use alcohol warning labels when purchasing and consuming alcohol, per agreement of the human subjects committees, the purpose of the study was only partially disclosed to the participants to avoid influencing participant responses.

In May 2017, a small feasibility study was conducted with 20 participants at the liquor store at the intervention site. The study tested all aspects of the survey including recruitment, measures, and data collection protocol. Prior to the feasibility study, cognitive interviewing was conducted with a convenience sample of participants as a pretest to assess survey interpretation and comprehension.

Survey Measures

Survey measures were adapted from those used in previous evaluations of the alcohol warning labels used in the United States, of Canadian food labelling systems, and of tobacco warning labels to collect data on both the existing and new enhanced alcohol warning labels [13,24,25,27-29,42,43]. Select primary and secondary outcomes are listed in Table 1.

Table 1. Select primary and secondary outcomes.

Outcomes and question	Response options
Primary	
Noticing labels	
"In the past 6 months, have you seen any warning labels on bottles or cans of beer, wine, hard liquor, coolers, or ciders?"	No/Yes/Don't know/Prefer not to say
Label recall	
"In the past 6 months, what messages have you seen on the warning labels on bottles or cans of beer, wine, hard liquor, coolers, or ciders? (Please list all messages you have seen on labels.)"	Open-ended text field/Don't know/Prefer not to say
Label processing	
"In the past 6 months, how often, if at all, have you read or looked closely at/thought about/talked about with others the warning labels on bottles or cans of beer, wine, hard liquor, coolers, or ciders?"	Never/Rarely/Sometimes/Often/Very often/Don't know/Prefer not to say
Self-reported behavior change due to labels	
"In the past 6 months, has the amount of alcohol you are drinking changed as a result of the warning labels on bottles or cans of beer, wine, hard liquor, coolers, or ciders? Are you drinking:	Less/Same amount/More/Don't know/Prefer not say
Self-reported alcohol-drinking behaviors	
"During the past 6 months, how often did you drink alcoholic beverages?"	Less than once a month/Once a month/2 to 3 times a month/Once a week/2 to 3 times a week/4 to 6 times a week/Every day/Don't know/Prefer not to say
"During the past 6 months, on those days when you drank alcohol, how many drinks did you USUALLY have?"	Enter number of drinks: Open-ended numeric field/Don't know/Prefer not to say
Sex-specific alcohol consumption on a single occasion	
"During the past 6 months, how often have you had 4 or more (if male participant)/3 or more (if female participant) drinks on one occasion?"	Never in the past 6 months/Less than once a month/Once a month/2 to 3 times a month/Once a week/2 to 5 times a week/Daily or almost daily/Don't know/Prefer not to say
Secondary	
Alcohol-related health risks	
"Based on what you know or believe, can drinking alcohol cause breast cancer/liver disease/the flu/[when pregnant] harm to a fetus?"	No/Yes/Don't know/Prefer not to say
Awareness of national drinking guidelines	
"Were you aware of Canada's Low-Risk Drinking Guidelines before today?"	No/Yes/Don't know/Prefer not to say
Knowledge of standard drink measurements	
"How many 'standard drinks' are in this bottle of [preferred drink type]?" (image of their preferred drink type shown on tablet screen)	Enter number of drinks: Open numerical field/Don't know/Prefer not to say
Self-reported use of label information	
"If the number of standard drink were displayed on bottles and cans of alcoholic drinks, like the one shown on the screen, would you ever use this information to help yourself or someone else stay within the daily drink limit advised by in the low-risk drinking guidelines?"	No/Yes/Don't know/Prefer not to say
"To what extent, if at all, would labels with low-risk drinking guidelines on bottles and cans of alcoholic beverages make you think about the number of drinks you consume?"	Not at all/Not much/Neutral/Somewhat/Very much/Don't know/Prefer not to say
Support for alcohol labelling and other alcohol-related policies	
"Cans and bottles of alcoholic beverages should be labelled with low-risk drinking guidelines/the number of standard drinks per container/warnings describing the link between alcohol and diseases, such as cancer."	Strongly disagree/Disagree/Neutral/Agree/Strongly agree/Don't know/Prefer not to say

Participants were informed that a "drink" refers to 341 mL of beer, 5 oz of wine, and 1.5 oz of spirits. Sociodemographic variables were assessed using survey items adapted from national surveys in Canada, and health literacy was assessed by the validated 6-item New Vital Sign measure [4,44]. Additional

response options including *Don't know* and *Prefer not to say* were also presented across all survey questions.

Sample Size Calculation

Target sample sizes of 406 per condition per wave was calculated prior to the study to provide 80% power to detect a minimum difference of 8% in the proportion of "Yes" or correct responses to the cognitive processing outcomes with a two-tailed test, where a=.05. The final sample size was inflated by 10% up to 450 participants per condition to account for missing data on key measures. Estimates were based on data from the evaluation of the alcohol warning labels used in the United States [9].

Survey Analyses

Similar to previous evaluations of label interventions, variables such as awareness and recall of label messages and knowledge of related health risks were assessed as binary outcomes (0=No/Don't know vs 1=Yes). Volume of alcohol consumption was calculated as the mean number of drinks consumed per week in the past 6 months. For baseline (Wave 1) data, logistic regression analyses were performed to examine the relationship between select primary and secondary outcome measures and sociodemographic factors; adjusted odds ratio and corresponding 95% CI of the outcomes for sociodemographic factors was estimated [45]. Generalized estimating equation models using a binomial distribution with logit link function were used to examine the longitudinal effects of the alcohol warning labels intervention on all secondary outcome measures across the three waves. Generalized estimating equation models can account for a mix of within-subject correlation that arises from the cohort participants being asked the same questions over multiple survey waves plus the replenishment sample [46]. The large overlap in the cohort sample across waves implies that observations were not and cannot be treated as independent. Difference-in-difference terms with an interaction between wave and site were added to each model to assess the changes in outcomes across survey waves and between sites. Sociodemographic variables and other covariates, such as time in sample, were also included in all models. All analyses were conducted using SAS 9.3 (SAS Institute Inc, Cary, North Carolina).

Liquor Store Sales Data

Sales Data

Product-level liquor store sales data, provided by the Yukon government alcohol monopoly, included all retail and wholesale purchases in the Whitehorse liquor store and the five liquor stores in the surrounding areas (Dawson, Faro, Haines Junction, Mayo, and Watson Lake) from July 2015 to December 2018. These data were aggregated by units and volume sizes; beverage category (beer, wine, spirits, coolers, and cider); percent alcohol/volume (eg, <4%, 4%-5.4%, 5.5%-6.9%, ≥7% for beer); site; and month. Liquor store sales data provided data at the store level and did not include individual-level customer data or financial information. Overall, this provided 28-month baseline and 14-month follow-up data, enabling estimation of seasonal effects and secular sales trends for control in analyses. Multilevel regression analyses of pooled six time series alcohol data also controlled for regional effects. The Northwest Territories' sales data were included in the analysis as an additional control. Total monthly alcohol sales for the Northwest Territories, including the two liquor stores in Yellowknife, were retrieved from the Northwest Territories Bureau of Statistics for the same time period [47]. Per capita alcohol consumption was estimated for individuals aged ≥15 years in Yukon and Northwest Territories for each monthly period by dividing the total liters of ethanol sold by the population aged ≥15 years as per data from Statistics Canada [24]. Dollar values were adjusted by consumer price index (CPI) using territory-specific CPI data from Statistics Canada [48].

Socioeconomic and Demographic Data

Several socioeconomic and demographic data by site and time period were obtained to produce per capita alcohol consumption estimates and socioeconomic variables in order to examine and control for their potential confounding effects [49-53]. These data included population data in Yukon [54] and Northwest Territories [55], income and CPI data [56-62], and land data [63].

Liquor Store Sales Data Analyses

Multilevel regression models [64] were used to analyze pooled monthly per capita retail alcohol sales in six areas (one single liquor store in Whitehorse, Dawson, Faro, Haines Junction, Mayo, and Watson Lake) in Yukon to examine the effect of alcohol warning labels on per capita alcohol consumption among people aged ≥15 years, adjusting for the potential confounding effects of annual household income, the proportion of young people aged 20-29 years, the proportion of men, the proportion of Indigenous populations, annual trends and seasonal variations, and temporal and regional autocorrelation. Separate models were created to examine specific effects of the labels by beverage type. Per capita alcohol consumption variables were log transformed to remove skewness in their distributions. The number of days in each month was used as a weighting variable; the number of days varied by month and the labels were initially applied starting mid-month. Estimates of monthly per capita alcohol consumption in the Northwest Territories based on official sales data for the same time period were used as an additional separate control in the models.

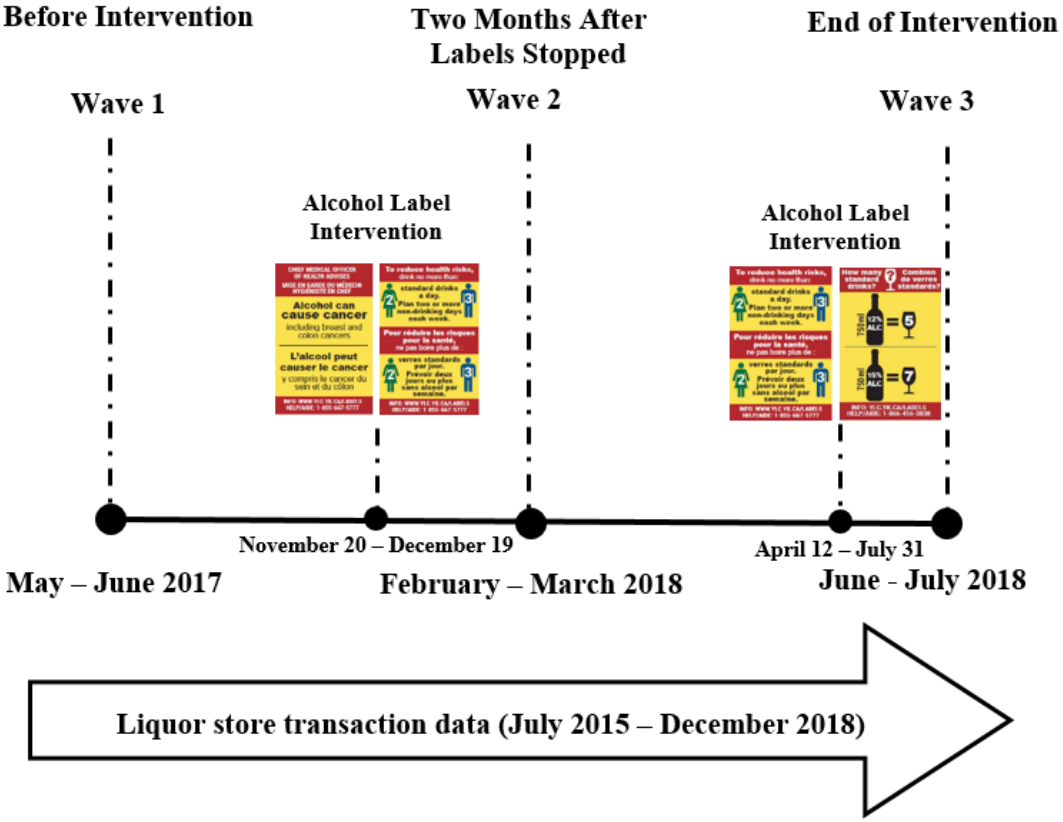
Results

Postimplementation Modifications to Study Design

Postimplementation modifications were made to the study design due to interference from Canadian alcohol industry trade associations. On December 19, 2017, 4 weeks after the intervention launched on November 20, the Yukon Liquor Corporation paused all application of the new enhanced labels for nearly 4 months due to complaints from the national industry representatives [65]. On February 15, 2018, the Yukon Government granted permission for the intervention to proceed for the remainder of the study period on the condition that the cancer warning label be rotated out permanently [66,67]. Based on remaining label stock, an estimated 47,000 cancer warning labels and 53,000 LRDG labels were applied to alcohol containers during the first month. On April 12, 2018, label

application resumed in the intervention site, starting with the LRDG labels and followed by the standard drink labels on May 28, 2018; application continued until July 31, 2018 (Figure 7). An estimated 117,000 LRDG and 92,000 standard drink labels were applied during that period. Yukon's original alcohol warning labels cautioning about drinking during pregnancy were not applied to containers at any point during the intervention period.

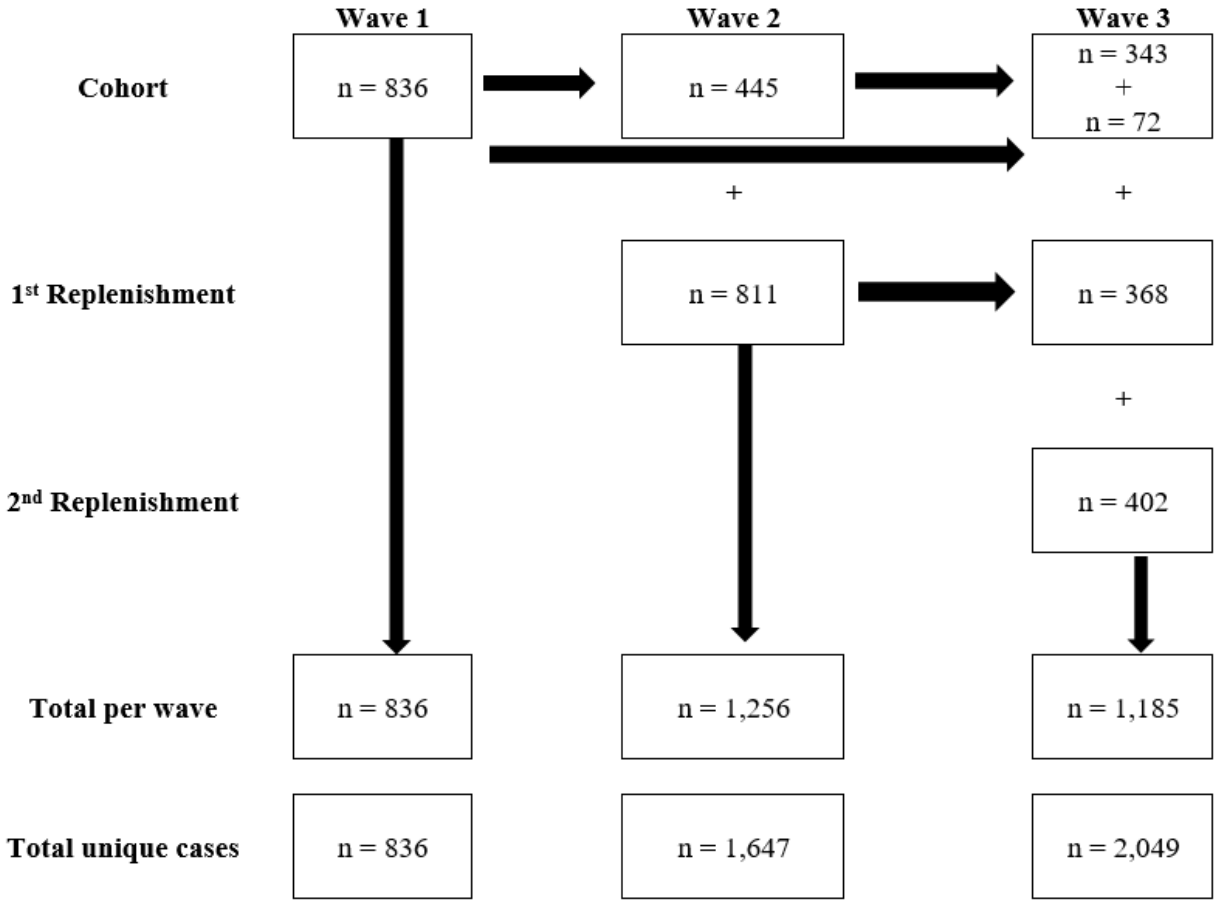
Figure 7. Modified study design and timeline.



Study Implementation

The baseline (Wave 1) surveys were completed over a 6-week period in May and June 2017. The study team was granted permission to conduct an extra wave of surveys (Wave 2) in both the intervention and comparison sites for a 6-week period in February-March 2018 to capture any effect of the cancer label. The third and final wave of surveys (Wave 3) was conducted for 6 weeks at both sites between mid-June and the end of July 2018 (see Figure 8 for sample sizes across waves). In total, 2049 participants were eligible and completed a survey in at least one of the three survey waves. Overall, response rates were 8.9% at the intervention site and 8.0% at the comparison site [68], which were low but consistent with previously published studies using similar intercept techniques [69-71]. Cooperation rates of 97.6% at the intervention site and 95.5% at the comparison site were achieved across survey waves. Overall, 53.2% (445/836) participants were retained in Wave 2 and 47.5% (783/1647), in Wave 3. Participants who were lost to follow-up between waves were more likely to be younger; male; have lower education, income, and literacy; consume high or unknown levels of alcohol; and be at the comparison site (Multimedia Appendix 1). A number of components of the social marketing and awareness campaign were implemented during the intervention period. These components included an initial media release about the alcohol warning labels, a toll-free helpline number, and an informational website hosted by the Yukon Liquor Corporation that offered additional resources such as more detailed LRDG and standard drink information [72]. The Yukon Liquor Corporation was not able to implement the other planned elements of the campaign during the intervention period, including promotional materials such as a "drink counter" fridge-magnet notepad, in-store posters, and related radio spots by the Chief Medical Officer of Health.

Figure 8. Structure of the survey cohort showing attrition and replenishment across waves.



Discussion

Principal Results

This study presented a rare opportunity to conduct a quasi-experiment with high internal and external validity and the potential to provide real-world evidence to directly inform alcohol labelling policies in Canada and internationally. Moreover, it provided a unique opportunity to collaborate with northern governments in Canada to test a population-level intervention among an understudied, high-priority northern population that has a higher prevalence of alcohol intake and alcohol-related harms relative to the rest of Canada [2]. This research was the first study in Canada and one of the few internationally to examine the effects of best-practice alcohol warning labels and determine if these labels are an effective population-level intervention for increasing awareness of alcohol-related harms as well as reducing alcohol consumption. Unimpeded, it had the potential to make a unique contribution to the evidence and provide critical information to develop and refine communication approaches and alcohol-labelling policies.

As found previously, there are difficulties associated with introducing or testing alcohol warning labels in real-world settings, largely as a result of alcohol industry interference or pushback and increasing reluctance from governments [19,20]. In this study, representatives from the national alcohol industry in Canada raised their objections to the alcohol warning labels intervention with government officials immediately following the launch. Records of email communication with the Yukon Liquor Corporation illustrate the industry representatives' ongoing attempts to discredit the research team and distort the evidence linking alcohol and cancer [73]; a letter of complaint was sent to one of the study leads' university administration (Multimedia Appendix 2); and freedom of information requests for all communications related to the study for the research team and the territorial liquor corporations in Yukon and Northwest Territories were submitted. The industry's opposition is understandable: They fear that strong warning labels will shrink their market and erode profits. In this case, their stated concerns included legislative authority for applying labels to containers, trademark infringement, and defamation and damages related to warning labels affixed to "brand-owner products" without consent [65]. However, it quickly became clear that the cancer warning label, in particular, was eliciting the strong response, which is consistent with broader industry positions on this type of health messaging [17,65]. To enable the intervention to proceed, the government partner ultimately modified their participation in the study to avoid what was understood as a risk of a lawsuit (however groundless) against the jurisdiction if they continued to apply the cancer label [67,74]. The threat of litigation is a deterrence tactic similar to what has been used previously by the tobacco industry, often resulting in protracted and expensive cases [75].

After the study was halted in December 2017, the research team actively engaged with the media to document the alcohol

industry's attempts to stop the study and highlight the threats of litigation being directed against Yukon. The territorial government's decision to resume participation in the study can largely be attributed to unwavering support from several prominent public health and government officials and academics both in Yukon and across Canada as well as wide public interest due to the national and international media coverage [74,76]. The research team's partnership with the government-run liquor corporation that had developed over a number of years during the planning of the study also greatly facilitated the ability to expedite modifications to the study design in response to the unplanned interruption and maintain as much of the integrity of the original protocol as possible.

Limitations

Although a significant limitation of the study is the postimplementation modifications that were required as a result of the alcohol industry's attempts to stop the study and some related media coverage, findings from the subsequent waves of postintervention data will provide an indication of the extent to which the new enhanced alcohol warning labels impacted key outcomes. One benefit of the industry interference was that it provided detailed clarification on the potential industry response to enhanced alcohol warning labels and an example of how the intervention was modified to ensure successful completion of the study. Additional study limitations include participants being recruited using nonprobability methods, precluding the findings from being representative estimates of broader alcohol-consumer populations, and use of self-report surveys that may be subject to social-desirability bias. Analysis of liquor store sales data from both sites is a strength of this study and will provide objective evidence of changes in population-level alcohol consumption. Finally, some elements of the planned social marketing and awareness campaign were not launched during the intervention period; thus, the comprehensiveness of the educational strategy was not fully realized.

Implementation of stronger policies and safeguards to prevent alcohol industry interference with scientific scholarship are recommended, so that further unimpeded, real-world testing and implementation of enhanced, best-practice alcohol warning labels can proceed in the future. Incorporating proactive media engagement with messaging around potential industry responses to alcohol warning label initiatives as part of the research design may help protect future studies from industry interference.

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Authors' Contributions

EH, TS, JZ, and DH designed the study. EH obtained the funding for the study. KV, EH, and NS-M prepared the manuscript with the contribution of SS, DH, TG, TS, JZ, AW, and JM. All authors read and approved of the final manuscript.

Conflicts of Interest

TS received research funds and travel expenses from both the Swedish (Systembolaget) and Finnish (ALKO) government retail alcohol monopolies for the conduct of research into the impacts of their policies on alcohol consumption and related harm. TG's research has been partially supported by the National Alcohol Beverage Control Association (NABCA). None of the other authors report any conflicts.

Multimedia Appendix 1
Participant flow diagram across waves.
[PNG File , 53 KB - resprot_v9i1e16320_app1.PNG]

Multimedia Appendix 2
Letter of complaint from alcohol industry sent to the University of Victoria.
[PDF File (Adobe PDF File), 40 KB - resprot_v9i1e16320_app2.pdf]

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Abbreviations

CPI: consumer price index
LRDG: low-risk drinking guidelines

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Protocol

The Impact of Hearing Impairment on the Life Trajectories of Aboriginal Children in Remote Australia: Protocol for the Hearing Loss in Kids Project

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Abstract

Background: Previous studies have reported a high prevalence of chronic otitis media (OM) and hearing impairment (HI) in Aboriginal children in the Northern Territory (NT) of Australia. Children affected by these disorders are believed to be at increased risk for adverse outcomes in early childhood development, school attendance, academic performance, and child maltreatment and youth offending. However, to date, there have been no studies quantifying the association between HI and these outcomes in this population.

Objective: This study will investigate the association between HI and the 5 outcomes in Aboriginal children living in remote NT communities.

Methods: Individual-level information linked across multiple administrative datasets will be used to conduct a series of retrospective observational studies on selected developmental and school outcomes. The predictor variables for all studies are the results from audiometric hearing assessments. The outcome measures are as follows: Australian Early Development Census results, representing developmental readiness for school, assessed around 5 years of age; Year 1 school attendance rates; Year 3 school-based academic performance, assessed in the National Assessment Program—Literacy and Numeracy; incidence of child maltreatment events (including both notifications and substantiated cases); and incidence of a first guilty verdict for youth offenders. Confounding and moderating factors available for the analysis include both community-level factors (including school fixed effects, socioeconomic status, level of remoteness, and housing crowdedness) and individual-level factors (including maternal and perinatal health and hospital admissions in early childhood).

Results: The study commenced in 2018, with ethics and data custodian approvals for data access and linkage. This has enabled the completion of data linkage and the commencement of data analysis for individual component studies, with findings expected to be published in 2019 and 2020.

Conclusions: This study will provide first evidence of the impact of OM-related HI on the developmental, educational, and social outcomes of Australian Aboriginal children. The findings are expected to have significant implications for policy development, service design, and resource allocation.

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KEYWORDS

data linkage; hearing impairment; indigenous population; child development; primary schools; academic achievement; child maltreatment; juvenile delinquency

Introduction

Background

Children's experiences during infancy and early childhood are critical to their health and educational and socioemotional well-being throughout their life course [1-5]. Through this period of rapid development, children are particularly sensitive to influences from their living environment [1,6]. At this age, the ability to hear is crucial to children's normal development, as children learn to speak and communicate by imitating the sounds they hear, and hearing impairment (HI) is likely to reduce children's exposure to sounds and voices and hamper their language development [7]. Consequently, delayed or impaired language learning can adversely affect children's physical health, as well as social and emotional development [7-9].

Otitis media (OM) and the associated HI among Australian Aboriginal children has been extensively researched [10-19]. Community surveys conducted in Aboriginal children living in remote communities have consistently reported extremely high prevalence of OM, as high as 90% in some reports, which has persisted through decades of clinical and public health interventions [14,18-20]. Studies have also found that OM affects Aboriginal children early in life, is more severe, and persists for longer [7,10,21], with prevalence peaking at the young age of 5 to 9 months [15]. Among the affected children, if OM is left untreated or not treated adequately, it often progresses to chronic suppurative OM (CSOM) and tympanic membrane perforation, with mild to moderate conductive hearing loss [22-24]. The impact of HI on language development may be compounded in Aboriginal children, when English is a second or third language, but school-based teaching relies on English [22,25-28]. In this setting, it may be reasonably expected that OM-related HI may directly or indirectly impact children's readiness for school and subsequent participation and performance at school, as well as their ongoing social and behavioral development through childhood and adolescence.

Although there is an abundance of the literature showing the correlations among child maltreatment, youth offending, early childhood development, school performance, and school attendance [29-33], to date, there has been no population-level investigation into the impact of HI on the long-term developmental, educational, and social outcomes of Aboriginal children. Furthermore, studies investigating the impact of OM (or its associated HI) on various aspects of early childhood development, including cognitive development, speech and language development, and educational outcomes, have produced equivocal results [7,34-36]. Several reasons have been proposed for such an inconclusiveness [22,34-37]. First, there are limitations in study design. Many studies have relied on surveys and have therefore been restricted by the inherent limitations of this design, as well as limited statistical power. On the other hand, the negative associations of OM with effusion (OME) and children's later language development found in some prospective and randomized clinical trials still need to be verified with large-scale studies that can provide more precise population-level estimates. Second, the majority of these studies used clinical diagnoses of OM, such as OME [38] or chronic OM [39,40] as the independent variable, rather than a direct assessment of hearing. The uncertainty surrounding the presence and degree of HI when OM is used as the predictor variable compromises the validity of the findings. Third, many studies have not controlled for known confounding or moderating variables, such as maternal education and socioeconomic status [41-44]. Finally, there has been a lack of population-level audiometric assessment data to report population-level outcomes.

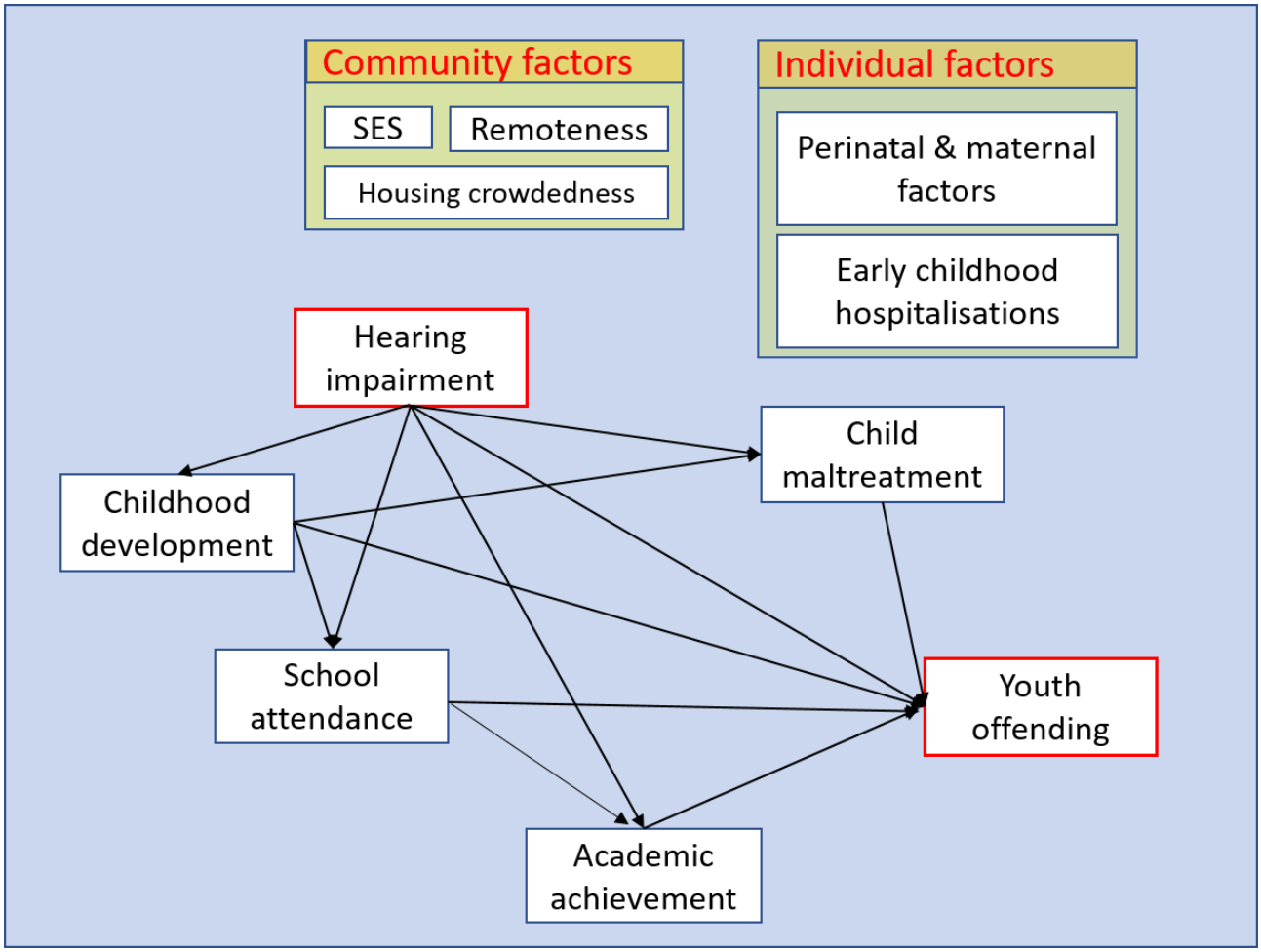
Objectives

To address this research gap, the Hearing Loss in Kids (HeLoKids) Project aims to apply a life-course epidemiological approach [45] to investigate the association between HI and developmental, educational, and social outcomes in Aboriginal children living in remote Northern Territory (NT) communities. By using linked administrative datasets containing longitudinal unit-record data for health, education, child protection, and youth justice systems, as well as hearing assessment results, this study is able to examine the selected outcomes while controlling for a wide range of potential confounders and moderators, as illustrated in the conceptual model in Figure 1.

Specifically, the study will undertake a series of studies that test the following hypotheses:

1. HI is independently associated with poorer developmental outcomes at the time of entry into full-time school (aged about 5 years).
2. HI is independently associated with lower school attendance rates in Year 1 (aged about 6-7 years).
3. HI is independently associated with poorer academic achievements in Year 3 (aged about 8 years).
4. HI is independently associated with higher risk of child maltreatment.
5. HI is independently associated with higher risk of youth offending.

Figure 1. Conceptual diagram indicating the pathways of influence of hearing impairment on life trajectories and the interplay between them (SES: socioeconomic status).



Methods

Setting

The NT is located in the north and central part of Australia, with an area of 1,352,176 square kilometers. It has the smallest total population among Australian states and territories, with an estimated resident population of 247,300 in 2018 [46], and the highest proportion of Aboriginal people in the total population (about 30%, compared with 3% for Australia) [47]. The NT also has the highest proportion of the total population living in remote and very remote areas (40.4% in 2017), as measured using the Accessibility and Remoteness Index of Australia (ARIA+) [48,49]. NT Aboriginal people have also been reported to be socioeconomically disadvantaged, as measured with the Socio-Economic Indexes for Areas, based on aggregated Australian population census data on social and economic status [50]. In addition to the high prevalence of OM, NT Aboriginal children have lower school attendance and retention, lower academic achievement, higher rates of reported child maltreatment, and higher rates of youth offending than their non-Aboriginal counterparts [51-55].

Design and Linkage Process

The HeLoKids Project will be conducted as a series of retrospective observational cohort studies to examine the association between HI and a range of developmental, educational, and social outcomes. These studies will utilize administrative datasets held within an extensive repository of deidentified unit-level information for NT children, which has been incrementally developed since 2009 [56]. SA NT DataLink (a South Australia [SA] and NT partnership) [57] completed the linkage of datasets collated in the repository. The data linkage process involves individual data custodians preparing a dataset containing identifying information only and then forwarding the dataset to SA NT DataLink. SA NT DataLink then combines the datasets from multiple custodians and links records for the same individual, which are present in the various datasets, and creates an anonymized project-specific linkage key for each individual. SA NT DataLink then adds the linkage key to the original datasets and returns each dataset to the respective data custodian. The data custodian creates a research dataset by combining the linkage keys with approved research variables and removing identifying information. The research dataset, created by each custodian, is then forwarded to the research team. The research team is able to use the linkage keys to merge information on individuals from multiple datasets to create the datasets necessary for analysis.

Remote Hearing Assessment Dataset

The Remote Hearing Assessment (RHA) dataset contains middle ear examination and audiometric assessment information collected by the NT Outreach Hearing Health Program [58].

This program is an Australian Government funded specialist ear and hearing health outreach service, available to all NT Aboriginal children and young people, aged under 21 years, most of whom live in remote communities.

The NT Outreach Hearing Health Program uses pure tone audiometry to assess children's hearing ability and determine the type (sensorineural, conductive, mixed, or indeterminate) and level of hearing loss. The level of hearing loss of an ear is calculated by taking the average of the thresholds of hearing (as deviation from normal threshold, in decibels Hearing Level—dB HL) for 3 frequencies: 500 Hz, 1000 Hz, and 2000 Hz. The results for each ear are classified as either normal or 1 of 4 ordinal categories of hearing loss, namely mild (16-30 dB HL), moderate (31-60 dB HL), severe (61-90 dB HL), and profound (91 dB HL or greater). This relatively conservative classification of hearing loss was chosen over the more widely used World Health Organization classification, as it is deemed more suitable for children aged under 15 years [58,59]. Further details on this classification of hearing loss are available elsewhere [58]. The clinical assessment for each ear is also recorded and classified under the following categories: acute OM (AOM), AOM with perforation, CSOM, dry perforation, Eustachian tube dysfunction, increase in middle ear pressure, OME, normal, and others.

The dataset provided to this study includes information collected from 2007 to 2015, for over 8000 children and young people aged between 0 and 21 years, which is about 22% of the NT Aboriginal population in this age group. Children and young people access these services through referral by primary care services. From January 2013, access to these services was prioritized according to clients' need for service. This means that the children and young people whose records are captured in the RHA dataset are not a random sample of the general population, and the information is likely to be biased toward those with abnormal middle ear examination and hearing difficulties.

The Study Cohort

The study cohort comprises NT-born Aboriginal children, with hearing assessment results in the RHA dataset and with a residential location classified as *remote* or *very remote* on the basis of ARIA+ [48]. Further inclusion and exclusion criteria will vary among the component studies of this study, depending on the respective requirements. In principle, as the data analysis will be based on a complete-case analysis, only children with data in the selected dependent, outcome, and control variables will be included. Children who have had surgical treatment for OM before the age of 4 years will be excluded, as the surgery could alter the impact of HI during the early childhood period. This will be done by searching in another linked administrative dataset, the NT Hospital Separations Dataset, and excluding children admitted before the age of 4 years, with any diagnosis code plus any procedure code related to OM and its treatment (Table 1).

Table 1. Otitis media—related hospital admission diagnoses and surgical procedures used to exclude children who had received surgical treatment, with International Classification, 10th Revision-Australian Modification codes.

ICD-10AM[a] Code	Diagnosis/procedure
Diagnosis	
H65	Nonsuppurative otitis media
H66	Suppurative and unspecified otitis media
H72	Perforation of tympanic membrane
Procedure	
41527-00	Myringoplasty, transcanal approach
41530-00	Myringoplasty postaural or endaural approach
41533-01	Myringoplasty with atticotomy
41542-00	Myringoplasty with ossicular chain reconstruction
41551-00	Mastoidectomy by intact canal wall technique with myringoplasty
41554-00	Mastoidectomy by intact canal wall technique with myringoplasty and ossicular chain reconstruction
41560-00	Modified radical mastoidectomy with myringoplasty
41560-01	Radical mastoidectomy with myringoplasty
41563-00	Modified radical mastoidectomy with myringoplasty and ossicular chain reconstruction
41563-01	Radical mastoidectomy with myringoplasty and ossicular chain reconstruction
41626-00	Myringotomy, unilateral
41626-01	Myringotomy, bilateral
41632-00	Myringotomy with insertion of tube, unilateral
41632-01	Myringotomy with insertion of tube, bilateral
41635-01	Excision of lesion of middle ear with myringoplasty
41638-01	Excision of lesion of middle ear with myringoplasty and ossicular chain reconstruction
41789-00	Tonsillectomy without adenoidectomy
41789-01	Tonsillectomy with adenoidectomy
41801-00	Adenoidectomy without tonsillectomy
90114-00	Other procedures on eardrum or middle ear

[a]International Classification, 10th Revision-Australian Modification.

Dependent Variables

For this study, the term "hearing loss" (HL) is used for a single ear to refer to a certain degree of loss of hearing ability, whereas "hearing impairment" (HI) is used for an individual's state of hearing loss in both ears. The dependent variables used across all component studies will be HI, and its values will be derived from the hearing assessment data contained in the RHA dataset. It will be an ordinal variable comprising the following categories:

- Normal hearing: normal audiometry results in both ears.
- Unilateral hearing loss: normal in one ear and any degree of hearing loss in the other.
- Mild HI: mild hearing loss in the better hearing ear.
- Moderate-or-worse HI: moderate-or-worse hearing loss in the better hearing ear.

Although OM tends to develop early in life in NT Aboriginal children and be persistent and often asymptomatic [19,21], a child may not have a hearing assessment until the child is older, when both the diagnosis of OM and hearing assessment become easier. As a result, a proportion of children may not be tested until after the outcome event for the study. There are also a proportion of children with multiple records of hearing assessment in the RHA database. For the purpose of this study, we assume the results for the first hearing assessment of a child, at any age, are representative of the long-term hearing level for that child.

Outcome Measures

This study aimed to investigate the impact of HI on the 5 aspects of life-course trajectory, listed in the following sections.

Early Childhood Development and School Readiness

The Australian Early Development Census (AEDC) is a cross-sectional national census of all children at the time of school entry, and it has been conducted triennially since 2009 [60]. The AEDC involves classroom teachers assessing children, aged about 5 years, across 5 domains of early childhood development, associated with readiness for school learning,

namely physical health and well-being, social competence, emotional maturity, language and cognitive skills (school based), and communication skills and general knowledge. The score for an AEDC domain is marked on a scale of 0 to 10, with higher scores indicating higher levels of development. A score falling below the 10th percentile of the national AEDC population indicates a *developmentally vulnerable* result on that domain [61].

Data on the outcomes of early childhood development will be accessed from the AEDC dataset, one of the linked administrative datasets used in this study. The AEDC data available for this study contain data from the censuses held in 2009, 2012, and 2015. The first type of outcome variables is directly available in the AEDC dataset and are the dichotomous results of developmental vulnerability for individual domains and the summary measure of *being developmentally vulnerable on two or more domains* (DV2). Children assessed as vulnerable on 2 or more domains are considered to be at higher developmental risk, and they generally require additional support to progress through early schooling.

The second type of outcome variables is the domain scores, which are continuous variables. These outcome measures will be used because of the fact that a high proportion of children in our study cohort have been assessed as *vulnerable*, using the dichotomous outcome variables [61], and the use of continuous domain scores is anticipated to be more sensitive in detecting differences among groups. We will use the scores for individual domains in domain-specific analysis and the sum of the scores of the 5 domains as a general indicator of children's overall readiness for school learning.

School Attendance in Year 1 of Primary School

The outcome measure for this component will be children's annual school attendance rate for Year 1 (aged approximately 6-7 years). Year 1 is chosen, as it is the first year of compulsory school attendance in the NT and as, in the study population, school attendance rates decrease with increasing year level. The data source will be the School Attendance dataset, provided by the NT Department of Education, which contains records of enrollment and daily attendance status for students studying in NT Government schools for the period 2005 to 2016. The school attendance outcome will be expressed as the number of school days attended per year, with approximately 200 school days available per year.

Academic Performance in Year 3 of Primary School

The outcome measure for children's academic performance in early years of primary school will be taken from the National Assessment Program–Literacy and Numeracy (NAPLAN) dataset. NAPLAN is an annual national assessment program, which commenced in 2008, and is undertaken by all students in Australia in years 3, 5, 7, and 9 (aged approximately 8, 10, 12, and 14 years, respectively) [62]. NAPLAN includes separate tests for numeracy, reading, writing, and language conventions (which include spelling, grammar, and punctuation). The test contents are developed to include specific considerations for Indigenous education, English as a second language, and special needs education [63]. The tests are designed to assess students' understanding of the core elements of the national curriculum and to assist schools and teachers to identify students who may not have learned the skills required to progress academically. The raw score for each test is converted into a scaled score out of 1000. Data were available from 2008 to 2016. The outcome measures for this study will be the scale scores for the 5 NAPLAN domains for Year 3. The selection of Year 3 optimizes the study cohort by avoiding both the declining school attendance and declining participation in NAPLAN assessments in later years.

Child Maltreatment

The data source for this study is the NT Government Child Protection dataset, which is a statutory data collection of child maltreatment—related contacts with child protection services. The research dataset will include information on all notifications (reports), substantiated cases, and episodes of out-of-home care. The outcome measures for this study will be the cumulative incidence of first notification of child maltreatment and the cumulative incidence of first substantiated case of child maltreatment. The time to event will be calculated from date of birth to the earliest of the following: date of each event of interest, date of death, the last observed date in the linked datasets, or the designated end of follow-up date for the study. Data are available from 1999 to 2017.

Youth Offending

The Youth Justice dataset was provided by the NT Department of the Attorney-General and Justice, and this contains records of youth offending in the NT. The outcome measure for this study will be the cumulative incidence of first episode of a proven guilty offence within the youth justice system. The starting point for follow-up will be the 10th birthday, which is the minimum legal age of criminal responsibility, and the follow-up time will be calculated to the date of first offence or censored at the date of death, the last observed date in the linked datasets, or the set endpoint for follow-up of this study. Data are available for the period 1997 to 2017.

Control Variables

The selection of control variables will vary between studies and the availability of the relevant variables in the linked datasets. We will draw reference from published literature in selecting control variables known to have confounding or moderating effects on the association being investigated. Individual-level control variables will be retrieved from the linked health, education, child protection, and justice datasets, including maternal and perinatal factors from the Perinatal Registry dataset (a statutory collection containing information for all births in the NT), as well as hospital admission diagnoses from the NT Hospital Separation Dataset. Community-level factors will include relative level of geographic remoteness (as measured with ARIA+), housing crowdedness (as measured with average household size and average persons per bedroom in the community), and socioeconomic disadvantage (as measured with the Index of Relative Socio-Economic Disadvantage) [48,50,64]. Aggregated data on these factors will be combined with the linked administrative datasets, using the relevant

location variable for each study (either community of residence or school location).

Statistical Analysis Plan

For each component study, statistical analyses will start with descriptive statistics to examine the distribution of key demographic, control, predictor, and outcome variables in the study cohort. The approach of complete-case analysis will be adopted in regression analysis. As this approach may lead to exclusion of participants with missing data, we will include comparisons of the study cohort and those excluded from analysis using suitable statistical methods (z-test, *t* test or chi-square analysis) to assess the differences between the 2 groups. When the groups are found to be statistically different on any number of included variables, we will include discussion of the implications of these differences on the validity of the study's findings.

The dependent variable, HI, is structured as an ordinal variable, and we anticipate a *dose-response* relationship between the levels of HI and the outcome variables. In all regression analyses, the investigation of associations will use *normal hearing* as the reference category.

The study investigating the impact on AEDC outcomes will use logistic regression for dichotomous outcomes and linear regression on continuous ones. In the studies investigating the impact of HI on Year 1 attendance rates and NAPLAN results, multivariate linear regression models will be fitted to estimate the association between HI and the school-based outcome measures, and the models will include school-fixed effects to control for the average observed and unobserved differences in schools and students of the schools. In the studies examining the association between HI and child maltreatment and between HI and youth offending, multivariate survival analysis will be used by fitting Cox proportional hazard models.

In these component studies, a parsimonious model building strategy will be adopted in the regression modeling process. Univariate regression analysis will first be carried out to select variables with *P* value<.25. These and all possible 2-way interaction terms will be fitted in the multivariate regression model–building process. Variables deemed to be key confounders or moderators selected on the basis of past studies will be retained throughout the model-building process.

The final part of the study will investigate the interplay of key early childhood factors known to be associated with youth offending. It will examine how and to what extent the outcome of youth offending in NT Aboriginal children is shaped by the health, developmental, educational, and social factors investigated in this study, including HI, AEDC outcomes, Year 1 attendance rates, Year 3 NAPLAN results, and child maltreatment. The analysis will also examine the influence from key demographic factors relevant to children's family and school learning circumstances. Structural equation modeling (SEM), using path analysis methods, will be utilized to quantify the relative impact of these factors on the outcome of youth offending. Distributional assumptions will be assessed to identify any outliners. The model will examine the direct pathway through which HI is associated with youth offending; it will also include the indirect pathways by which AEDC outcomes, Year 1 school attendance, and Year 3 NAPLAN results act as mediators in the direct pathway. In the SEM analysis, the *maximum likelihood with missing values* convergence method will be used to relax the requirement for each child to have complete data, as it is expected that the number of children will be reduced after linking multiple datasets. Relevant model fit indices will be reported for each pathway, including *P* value, model chi-square, goodness of fit index, p of close fit, comparative fit index, the root-mean-squared error of approximation, and the standardized root mean square residual. All statistical analyses will be performed using Stata for Windows, Version 15 (StataCorp).

Results

The study commenced in 2018. Ethics clearance and data custodian approvals for data access and linkage have been obtained. This has enabled the completion of data linkage and the commencement of data analysis for individual component studies. Findings are expected to be submitted for publication in peer-reviewed journals in 2019 and 2020.

Discussion

Principal Findings

The availability of the RHA dataset for data linkage with a wide range of health, education, child protection, and youth justice datasets has provided an unprecedented opportunity for investigating the impact of HI on life-course trajectory of Aboriginal children and young people. The hearing assessment results obtained through pure tone audiometry for a large cohort of remote-dwelling Aboriginal children have enabled the direct use of HI as the predictor variable in this study, instead of using its precursor or causative condition, OM, which may introduce an unknown level of misclassification. It is expected that this study will provide the first comprehensive evidence for the impact of HI on these various measures of the life-course trajectory in the study population. Furthermore, the comparatively large sample and the use of raw test scores of AEDC and NAPLAN as continuous variables will provide a robust statistical power, which will increase the likelihood of detecting significant association with the selected outcomes. In each of the component studies, we will discuss sources of potential bias. One example is that children included in the RHA database are not a random sample of remote Aboriginal children in the NT, with a risk of selection bias. A second source of potential bias is the use of complete-case analysis. We will also discuss the likely direction of potential bias and the extent to which they may affect the validity of our results.

Conclusions

The findings of this study will have significant implications for government departments and health and social service providers in policy development, service design, and resource allocation. The results can also be used as baseline measurements for monitoring interventions aimed at improving the ear and hearing health of Aboriginal children, as well as their developmental, educational, and social outcomes. The use of a linked

administrative dataset in this study will further illustrate the utility of data linkage research methods for informing comprehensive service planning and evaluation.

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Authors' Contributions

JYS, SS, and SG initiated the conception and design of the study. JYS and VH prepared the statistical analysis plan. All authors have contributed to the design of each component study, and they have participated in the writing of the paper and given approval for its publication.

Conflicts of Interest

None declared.

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Abbreviations

AEDC: Australian Early Development Census
AOM: acute otitis media
ARIA+: Accessibility and Remoteness Index of Australia

CSOM: chronic suppurative otitis media
dB HL: decibels hearing level
HeLoKids: Hearing Loss in Kids
HI: hearing impairment
NAPLAN: National Assessment Program–Literacy and Numeracy
NT: Northern Territory
OM: otitis media
OME: otitis media with effusion
RHA: Remote Hearing Assessment
SA: South Australia
SEM: structural equation modeling

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Protocol

Transperineal Laser Ablation Treatment for Lower Urinary Tract Symptoms Due to Benign Prostatic Obstruction: Protocol for a Prospective In Vivo Pilot Study

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Abstract

Background: Standard surgical treatments for lower urinary tract symptoms (LUTS) due to benign prostatic obstruction (BPO) use a transurethral approach. Drawbacks are the need for general or spinal anesthesia and complications such as hematuria, strictures, and cloth retention. Therefore, a minimal invasive technique under local anesthesia is desired to improve patient safety. Recently, SoracteLite transperineal laser ablation (TPLA) has been introduced as a novel minimal invasive treatment for BPO. The system used is unique because 4 laser sources are independently available. This 1064-nm diode laser induces coagulative necrosis. Moreover, TPLA is unique because it has a transperineal approach and can be performed under local anesthesia in an outpatient setting.

Objective: The primary objective of this study is to determine the safety and feasibility of TPLA treatment for men, who are fit for standard surgery, with LUTS due to BPO. The secondary objectives are to determine functional outcomes by flowmetry and patient-reported outcome measures (PROMs), side effects, and tissue changes observed on imaging.

Methods: This study is a prospective, single center, interventional pilot study IDEAL framework stage 2a and will include 20 patients. Eligible patients are men ≥40 years of age, with a prostate volume of 30 to 120 cc, have urodynamically proven bladder outlet obstruction, and have a peak urinary flow of 5 to 15 mL per second. All patients will undergo TPLA of their prostate under local anesthesia by using the EchoLaser system. Depending on the prostate volume, 2 to 4 laser fibers will be placed bilaterally into the prostate. Patient follow-up consists of uroflowmetry, PROMs, and imaging by using contrast-enhanced ultrasound. Total follow-up is 12 months following treatment.

Results: Presently, recruitment of patients is ongoing. Publication of first results is expected by early 2020.

Conclusions: TPLA offers the potential to be a novel minimal invasive technique for treatment of LUTS due to BPO in men fit for standard desobstruction. This study will evaluate the safety and feasibility of TPLA and report on functional outcomes and tissue changes observed on imaging following TPLA treatment.

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KEYWORDS

transperineal laser ablation; prostatic hyperplasia; lower urinary tract symptoms; laser therapy

Introduction

Background

Lower urinary tract symptoms (LUTS) in men are mainly caused by benign prostatic hyperplasia. Cross-population prevalence of LUTS in men aged above 40 years is estimated at approximately 20% [1]. The incidence of LUTS due to benign prostatic obstruction (BPO) in the Dutch male population ranges from 3 per 1000 person years at ages 40 to 45 years to 38 per 1000 person years at ages 75 to 79 years [2]. LUTS have a major impact on quality of life compared with other chronic diseases [3,4].

Transurethral surgery is the most common procedure for prostate desobstruction. Numerous techniques have been developed over the years (eg, photo-vaporization and enucleation applying various modalities). The bipolar transurethral resection of the prostate (TURP) has favorable outcomes and a better short-term safety profile compared with monopolar TURP [5]. Photo-vaporization shows equal functional outcomes with a potentially better perioperative safety profile [5]. The holmium laser is the standard for enucleation and is associated with more favorable efficacy outcomes and less complications compared with monopolar TURP [5]. However, all techniques require anesthesia and hospitalization and induce retrograde ejaculation and complications such as hematuria and possible cloth retention while urethral and bladder neck strictures still occur.

Different minimal invasive techniques (eg, interstitial laser coagulation [ILC], transurethral microwave thermotherapy, and transurethral needle ablation) were developed that aimed for equivalent functional outcomes, although with shorter hospitalization, less use of anesthesia, and less complications [6]. Studies comparing these techniques with TURP showed improved patient safety profiles [6-9]. However, long-term functional outcomes were worse when compared with TURP, and the techniques are no longer advised by the guidelines [7,8].

Recently, new techniques (eg, Rezum and Aquablation) were developed. These techniques work with water vapor and waterjet ablation, respectively [10,11]. However, these techniques also use a transurethral approach resulting in similar complications such as hematuria, for example, 3 patients out of 15 for Aquablation [11]. Moreover, Aquablation requires general anesthesia [11]. As these techniques are still being investigated, they are not advised by the guidelines yet. Thus, transurethral surgical treatments are still advised by the guidelines, and there is no percutaneous technique for prostatic desobstruction, which is currently approved [12].

SoracteLite Transperineal Laser Ablation

SoracteLite transperineal laser ablation (TPLA) of the prostate is a novel minimal invasive technique for LUTS treatment in men. Using a transperineal approach, up to 4 laser fibers can be positioned into the prostate by means of transrectal ultrasound guidance. TPLA generates light-induced thermal heating that results in coagulative necrosis around the laser fiber tip. TPLA requires only local anesthesia, and conscious sedation is optional. Hypothetically, the ablation is confined to the transition zone, respecting anatomical structures and potentially increasing the chance of preservation of antegrade ejaculation. However, as TPLA is a novel technique, only limited short-term outcomes are available. Patelli et al [13] demonstrated technical feasibility and safety of TPLA treatment and improvement of functional outcomes for patients unfit for TURP. Therefore, there is a need to study the safety and feasibility of TPLA treatment of men eligible for standard surgical treatments [13].

Aim

The aim of this study is to prove safety and feasibility of TPLA treatment for men with BPO eligible for standard surgical treatment.

Methods

Study Objectives

The primary objective is to determine safety and feasibility of TPLA treatment for men with LUTS due to BPO and if fit for standard surgical treatment.

Secondary objectives are to determine (1) functional outcomes, (2) the possibility of spontaneous voiding immediately post-TPLA, (3) observation of side effects comprising hematuria, irritative voiding complaints, erectile function, and changes in ejaculation, and (4) evaluation of tissue changes by using contrast-enhanced ultrasound (CEUS).

Outcomes

Feasibility is measured by technically successfully (without device-related adverse events) performed TPLA procedures. If 90% (18/20) of the treatments are successfully performed, we conclude that the treatment is feasible. Safety is assessed by the adverse events using the CTCAE version 5.0. TPLA is defined to be safe when ≤10% (2/20) of the patients experience adverse events of grade 3 or higher. For the secondary objectives, the functional outcomes are measured by uroflowmetry and International Prostate Symptom Score (IPSS) and erectile function by International Index of Erectile Function 15 (IIEF-15).

Study Design

This is a prospective, single center, interventional pilot study. Approval of the local medical ethical committee was obtained for the study protocol (registry number: NL66057.018.18). The study is in agreement with the IDEAL stage 2a recommendation [14].

Population and Sample Size

Patients eligible for this study are men aged ≥40 years with proven bladder outlet obstruction by urodynamic investigation and a peak urinary flow of ≥5 mL per second to ≤15 mL per second, a postvoid residual of ≤250 mL, and a prostate volume of ≥30 and ≤120 cc. The inclusion and exclusion criteria are summarized in Textboxes 1 and 2.

Textbox 1. Inclusion criteria.

- Male
- ≥40 years of age
- Peak urinary flow: ≥5 mL per second to ≤15 mL per second, minimum voided volume of >125 mL, measured with uroflowmetry
- Postvoid residual: ≤250 mL
- Prostate volume: ≥30 and ≤120 cc, measured by transrectal ultrasound
- Urodynamically proven bladder outlet obstruction

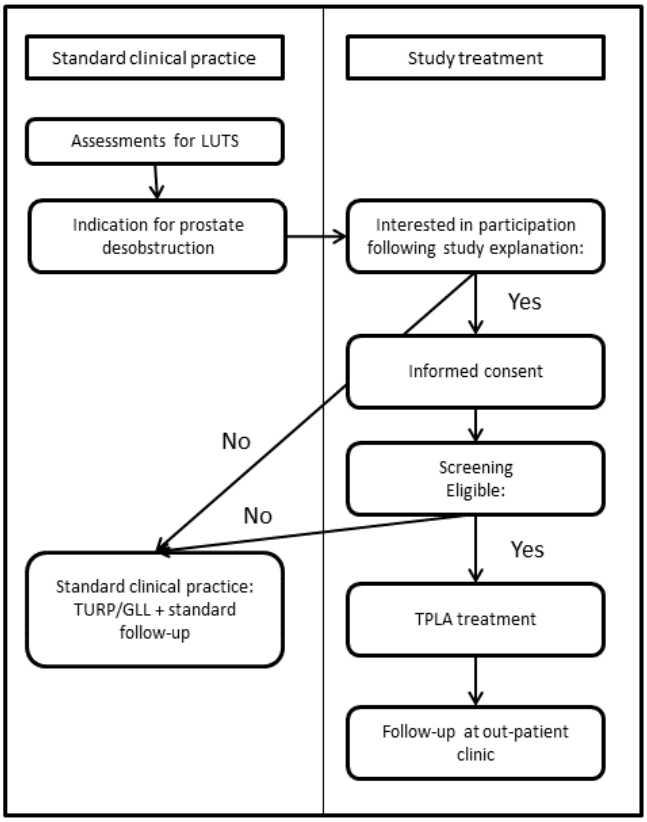
Textbox 2. Exclusion criteria.

- Previous invasive prostate intervention
- History of prostate or bladder cancer
- No spontaneous voiding (eg, indwelling Foley catheter, clean intermittent catheterization, or suprapubic catheter)
- A clinical suspicion of prostate cancer based on:
  - Abnormal digital rectal examination
  - Urologists' judgment of the PSA level, preferably supported by a nomogram (eg, Prostaatwijzer version 3 with TRUS volume [16]) outcome with an indication for prostate biopsies
- Inability of temporary discontinuation of anticoagulation or antiplatelet therapy
- Other conditions/status
  - Active urinary tract infection/prostatitis
  - Macroscopic hematuria without a known contributing factor
  - Poor detrusor muscle function or other neurological disorder that would impact bladder function (eg, multiple sclerosis, Parkinson's disease, spinal cord injuries, (diabetic) polyneuropathy)
  - Concurrent malignancy except basal skin cancer
  - History of pelvic radiation therapy or radical pelvic surgery
  - History of bladder neck contracture and/or urethral strictures within the 5 years before the informed consent date
  - Bladder stones
  - Medical contraindication for undergoing TPLA surgery (eg, infection, coagulopathy, significant cardiac, or other medical risk factors for surgery)
  - Diagnosed or suspected bleeding disorder
  - Contraindication for conscious sedation (eg, obstructive sleep apnea syndrome)

All patients will be recruited in the Amsterdam University Medical Centers, Academic Medical Center (Amsterdam, the Netherlands). Patients will be informed about this study in oral and written form. Patient approval is confirmed by signed informed consent. Patient inclusion has been summarized in a flow diagram (Figure 1).

Overall, 20 patients will be included in this study. This number is based on the IDEAL stage 2a recommendations for surgical innovations and past pilot studies [13-15].

Figure 1. Flow diagram of the study design. LUTS: lower urinary tract symptoms; TPLA: transperineal laser ablation.



Baseline Characteristics

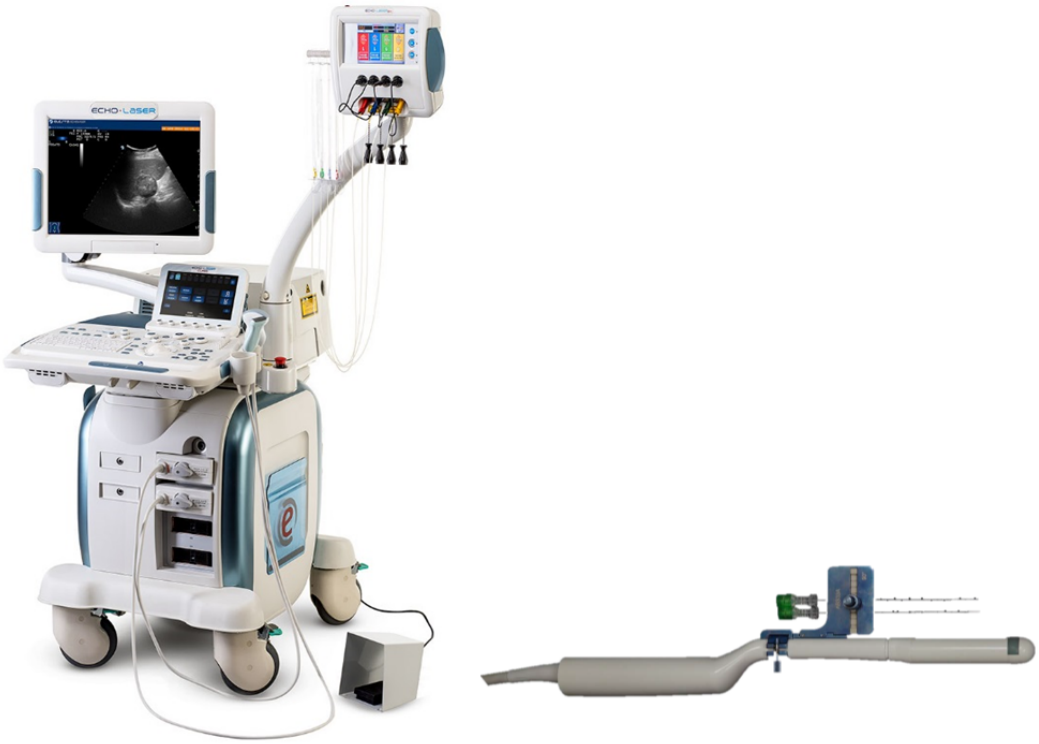
Medical history and physical examination will be evaluated. In addition, IPSS and IIEF-15 will be used to measure voiding and erectile symptoms. Pain is measured by using a visual analogue scale (VAS), ranging from 0 to 10, and hematuria by the hematuria grading scale (HGS) [17]. Voiding characteristics and bladder function will be assessed by uroflowmetry with postvoid residual measurement and urodynamic investigation. Prostate volume measurement will be performed by transrectal ultrasound.

Study Device

The TPLA treatment is performed using a diode laser system (SoracteLite, EchoLaser X4 system, Elesta; Figure 2). The system uses 4 diode laser sources, operating at 1064-nm wavelength, with a maximum energy of 7 watts continuous wave per source. The laser sources can be activated and configured individually (both separately and simultaneous), and the laser light is guided through a flexible quarts optical fiber.

The laser light induces tissue coagulation with a relatively deep penetration (up to 1 cm) because light of 1064 nm is poorly absorbed by hemoglobin and water [18]. However, fiber blood contact can lead to carbonization of the fiber tip, creating a black layer that partially absorbs the light [19]. Subsequently, the absorbed light is transformed into heat because of the black layer and other tissue constituents in the prostate. During TPLA, the prostate is continuously monitored by using transrectal ultrasound (MyLab Eight eXP, Esaote) with a biplanar probe (TRT33).

Figure 2. The EchoLaser system with 4 fibers combined with the MyLab Eight eXP ultrasound device from Esaote (left) and the TRT33 probe with needle guide system (right).



Study Procedure

The TPLA treatment will be performed by 2 urologists who followed a training to perform the TPLA procedure. TPLA treatment will be performed in an outpatient setting under local anesthesia. A single oral dose of ciprofloxacin 500 mg will be used as antibiotic prophylaxis. The patient will be placed in lithotomy position. A Foley catheter will be placed for urethral identification. The prostate will be visualized with a biplanar transrectal ultrasound probe. Pain management consists of local infiltrative anesthesia of the perineum with Lidocaine 2%, 5 to 10 mL, followed by an ultrasound-guided periprostatic block with Lidocaine 2%, 20 mL. On patients' preference, conscious IV sedation with Midazolam 1 to 3 mg is offered. Depending on the prostate volume, 1 or 2 fibers will be placed transperineally in each side of the prostate in the transition zone by using ultrasound guidance and guiding needles (Figure 3 and Table 1). The fibers will be positioned parallel to the urethra while maintaining a minimal distance of 8 to 10 mm to the urethra and the rectal wall, and a distance of at least 15 mm to the bladder neck. A needle guide system will be used to support parallel placement of the needles. Following introduction of the optical fiber through the needle, the needle will be retracted for 10 mm, allowing exposure of the fiber tip and first 10 mm of the fiber to the tissue. When 2 fibers are located within the same lobe, the distance between the needles will be 10 or 15 mm, depending on the prostate size. If a median lobe is present, it will be treated by placing a needle and fiber as well.

Ablation will be performed with 3 watts per fiber and a total energy of 1800 J will be delivered per fiber in 600 seconds. Depending on the prostate volume, a pullback can be performed, retracting the fiber 1 cm along its trajectory to deliver another 1800 J (Table 1). When the treatment is completed, the Foley catheter will be removed. Dexamethasone 8 mg is administered intravenously postoperative to reduce edema and will be continued orally with the same dosage for 7 days.

Figure 3. Transverse plane ultrasound image of the prostate. Fibres (circles) positioned in both transition zones while maintaining a safe distance from the urethra (triangle), rectum and prostatic capsule.

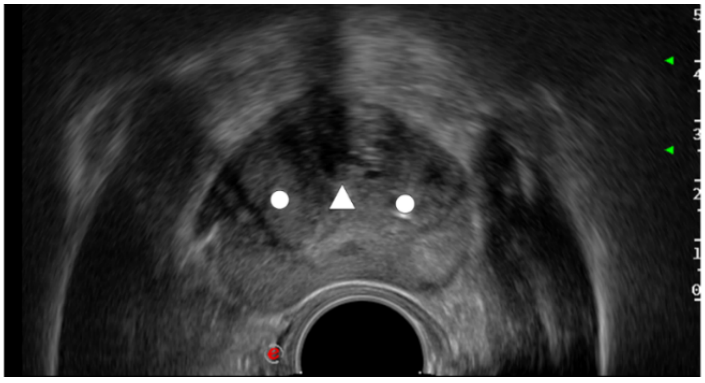


Table 1. Overview of the number of fibers used and fiber distance based on prostate volume (based on the manufacturer's instructions).

Prostate volume (cc)	Power (watts)	Energy per fiber (J)	Number of fibers per lobe	Fiber distance (mm)	Number of pullbacks	Total delivered energy (J)
30-40[a]	3	1800	1	—[b]	0	3600
	3	1800	1	—	1	7200
40-80[a]	3	1800	1	—	1	7200
	3	1800	2	10-15	0	7200
	3	1800	2	10-15	1	14,400
>80[a]	3	1800	2	10-15	1	14,400
	3	1800	2	10-15	2	21,600

[a]The operator, based on the prostate shape and length, should determine the optimal fiber setup.

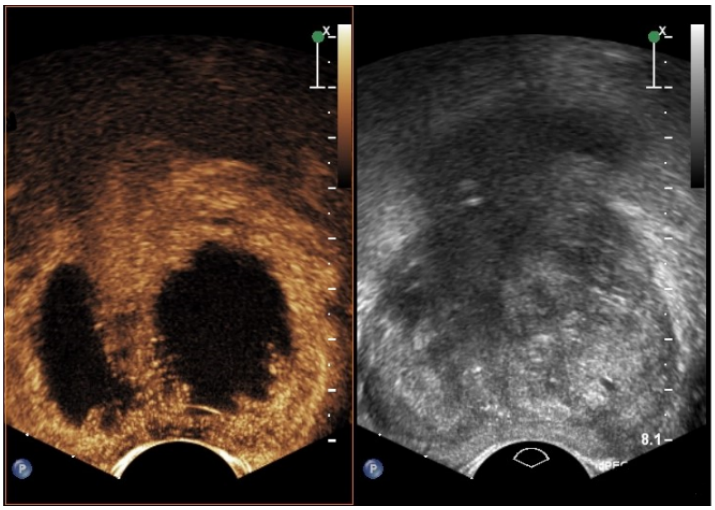
[b]Not applicable.

Following the procedure, the patient will be observed for several hours for spontaneous voiding without significant residual urine. If the patient does not have spontaneous voiding or has a residual volume of ≥500 mL, an indwelling catheter will be placed. For these cases, 10 to 14 days later, a trial without a catheter will follow.

Contrast-Enhanced Ultrasound

Multiple CEUS investigations of the prostate will be performed over the course of this study. CEUS is used because the ablation zone is not visible on gray-scale ultrasound (Figure 4) [20]. The contrast agent is a gas-filled microbubble (Sonovue, Bracco). This contrast agent enables visualization of the vascular architecture of the prostate. Thus, nonvascularized coagulated areas are visible as hypo-intense (black) regions [21]. Several studies have used CEUS for laser ablation area visualization in prostate cancer.

Figure 4. On the left the contract-enhanced ultrasound image of the prostate of the prostate 1 month following TPLA treatment, with dark areas corresponding with the treated areas. On the right the co-localized grey-scale image.



Lindner et al demonstrated that CEUS shows a clear hypo-intense zone, which corresponds with the ablated area following focal laser ablation of prostate cancer [21]. Patelli et al confirmed this result by demonstrating the applicability of CEUS for ablation zone determination following TPLA treatment [13]. CEUS is considered safe, because the lungs eliminate the contrast agent and ionizing radiation is not needed. A hypersensitivity allergic reaction to the contrast agent is a serious, but rare adverse event (<0.01%) [22].

CEUS imaging will be performed according to internal hospital protocol, with a Philips iU 22 machine interfaced with an end-firing transrectal probe (Philips Healthcare, Bothell). Prostate imaging consists of prostate volume measurement in 2 directions in B-mode (gray scale) setting. This will be followed by a transverse and sagittal sweep of the prostate in contrast mode, during peak inflow of the first bolus of 2.4 mL contrast agent. Subsequently, images will be made of the maximal diameter of both lesions in the sagittal and transverse planes. Treatment volumes will be calculated on the contrast images using an ellipsoid formula [23]. The second bolus will be used to capture contrast inflow and outflow within 1 plane over the course of 2 min.

Follow-Up

Patients will undergo a strict follow-up. The patient will be called 3 to 5 days post-TPLA treatment to inquire about health status. The patient will visit the hospital 4 times following TPLA

treatment at 4 weeks, 3 months, 6 months, and 12 months. During these visits, medical history, adverse events using the Clavien-Dindo classification, physical examination (on indication), and uroflowmetry will be performed. Patient-reported outcome measures (PROMs) (IPSS, IIEF-15, VAS, and HGS) are used to objectify functional outcomes, pain, and symptoms. Prostate imaging will comprise a CEUS +/– 2 hours following treatment, at 4 weeks and 12 months. CEUS is considered the only invasive procedure during follow-up. Follow-up is completed after 12 months.

Data Analysis

Study population characteristics (eg, age, medical history, medication, peak urinary flow rate, prostate volume, and detrusor pressure) and procedural information (eg, fibers placed, energy delivered, procedural success, adverse events, and lesion volume) will be reported descriptively. Functional outcomes by peak urinary flow and PROMs will be tested using a Wilcoxon signed-rank test. Statistical tests will be performed two-sided, and $P<.05$ is considered significant. Statistical analysis will be performed using SPSS version 25.0 (SPSS Inc).

Safety

The investigators will monitor patient safety. They can withdraw a patient from the study for medical reasons. In accordance to section 10, subsection 4, of the Wet Medisch-Wetenschappelijk Onderzoek met Mensen (medical research involving human subjects act in the Netherlands), the investigators will suspend the study if there is sufficient ground that continuation of the study will jeopardize patients' health or safety. The investigators will notify the accredited institutional review board if this is the case. In case of an adverse event or serious adverse event, the responsible authorities will be informed.

Benefits and Risks

All patients included in this study have LUTS and have an indication for prostate desobstruction. This study aims to treat patients for their LUTS by TPLA to evaluate safety and feasibility and functional outcomes. The benefits focus on the minimal invasive character of TPLA and subsequent day care setting without clinical admission. Spinal or general anesthesia is made redundant by use of local anesthesia and optional conscious sedation.

Risks for patients focus on the procedure, subsequent device-related adverse events, and unknown long-term functional outcomes of the treatment. Needles are used to introduce fibers into the prostate, possibly causing damage and perforation of surrounding structures (eg, neurovascular bundle, urethra, or rectal wall). As ultrasound guidance is being used, these events are unlikely to occur. Hemorrhage, infection, fistula formation, sepsis, and death can occur. However, risks are expected to be low because the transperineal approach is already applied for biopsies of the prostate and has proven to be safe [24]. Furthermore, Patelli et al reported no procedure-related adverse events in 18 patients [13]. Therefore, risks of adverse events are minimal as described earlier.

Nonetheless, TPLA is a relatively new technique and long-term outcomes are unknown. Patelli et al described short-term functional outcomes demonstrating that the peak urinary flow rate improved from 7.6 to 13.3 mL per second at 3 months post-TPLA. Yet, studies that applied other minimal invasive LUTS treatments showed a reduction of long-term effectiveness and increase of retreatment rates over time [8,9]. Thus, when feasibility of TPLA in patients that are candidates for surgical desobstruction can be demonstrated, future studies will be able to focus on the long-term outcomes.

Results

Presently, patient recruitment is ongoing. Initial results on safety and feasibility are expected in early 2020. Follow-up outcomes following TPLA treatment are expected in late 2020. Outcomes will be published in peer-reviewed medical journals and presented at international conferences.

Discussion

Overview

TPLA is a technique that might efficiently treat BPO under local anesthesia in an outpatient setting. This pilot study will provide initial data on the safety and feasibility of TPLA treatment in healthy men eligible for standard surgery before launching large-scale comparative studies.

Comparison With the Literature

The design of our study aims to show safety and feasibility in men fit for standard surgical treatment. The first TPLA pilot study by Patelli et al [13] showed promising results for men unfit for standard treatment. They treated 18 patients and showed technical safety and feasibility for men unfit for TURP due to comorbidities [13]. Functional outcomes showed peak urinary flow improvement from 7.6 (SD 2.7) to 13.3 (SD 76.2) mL per second at 3 months. IPSS improved from 21.9 (SD 6.2) to 10.7 (SD 4.7) at 3 months. Interestingly, a relatively long postoperative catheterization time of 17.3 (SD 10.0) days was observed. However, half of the study population already needed an indwelling catheter before TPLA treatment. Our study aims to study the safety and feasibility of TPLA treatment for men fit for standard treatment. Our study also aims to confirm the outcomes of previous studies, in a population with proven bladder outlet obstruction. Additionally, our study aims to preserve spontaneous voiding posttreatment by including men with spontaneous voiding before treatment. Nevertheless, risk for obstruction following treatment due to edema remains. Therefore, outcomes regarding spontaneous voiding post-treatment are evaluated after 10 patients have been treated. If more than 50% of treated patients do not spontaneously void, the subsequent 10 patients will receive a Foley catheter for 10 to 14 days.

Transperineal Laser Ablation Versus Interstitial Laser Coagulation

Interestingly, TPLA is based on the technique of inducing coagulative tissue necrosis, which is similar to the tissue response found in transurethral ILC. However, the long-term outcomes of ILC appeared to be inferior to TURP [7]. As ILC and TPLA are based on a similar concept, it could cause

criticism studying this approach. However, the currently available TPLA treatment has benefits when compared with the previous ILC treatment.

First, TPLA uses a transperineal approach in contrast to ILC which uses a transurethral fiber introduction. The transperineal approach of TPLA treatment aims to leave the urethra undamaged, hereby reducing post-treatment irritative voiding complaints when compared with the transurethral approach, which causes urothelial damage and subsequent irritative voiding complaints.

Second, the multifiber setup of TPLA treatment enables simultaneous treatment of both prostate lobes with 1 or 2 fibers each depending on prostate volume. If a median lobe is present, this can be treated as well. Additionally, each fiber can be configured individually, which enables shaping of the ablation zone. Hereby, a desired ablation volume is obtained faster when compared with serial treatment with 1 fiber used with ILC. Thus, the unique multifiber approach is expected to increase ablation volume faster and subsequently improved outcomes, especially in larger prostates.

Finally, TPLA is performed under continuous ultrasound imaging guidance, which provides visualization of the complete gland. This leads to improved treatment planning and ablation zone shaping, and subsequently theoretically improved outcomes.

Study Limitations

Nonetheless, this pilot study has several limitations. First, inclusion is set at 20 patients and is considered sufficient for determining safety and feasibility. However, this is not sufficient for measuring functional outcomes, as the study is not powered for this. Thus, successive studies are necessary once this study shows initial beneficial results. In addition to this, we have initiated an international registry to collect data from other centers that apply TPLA for BPO (ClinicalTrial.gov registration: NCT03776006). Second, a learning curve might be expected in the number of fibers placed and their location. Therefore, only a limited number of physicians will perform the TPLA procedures for this pilot.

Conclusion

In conclusion, TPLA treatment offers a unique multifiber and transperineal approach for the treatment of LUTS due to BPO under local anesthesia resulting in ablation zone shaping and creation of an ablation zone volume in a short period of time. We hypothesize that this study will confirm safety and feasibility of TPLA treatment of men with LUTS due to BPO and fit for standard surgery. The results of this study will broaden the knowledge on TPLA treatment in men with LUTS and are expected to be an essential basis for future BPO treatment using this approach.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

BPO: benign prostatic obstruction
CEUS: contrast-enhanced ultrasound
HGS: Hematuria Grading Scale
IIEF: International Index of Erectile Function
ILC: interstitial laser coagulation
IPSS: International Prostate Symptom Score
LUTS: lower urinary tract symptoms
PROM: patient-reported outcome measure
TPLA: soracteLite transperineal laser ablation
TURP: transurethral resection of the prostate
VAS: visual analogue scale

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Protocol

Awareness and Opinions of Research Professionals on India's New Drug and Clinical Trials Regulations: Protocol for a Cross-Sectional Web-Based Survey Study

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Abstract

Background: Although several studies have been conducted and several articles have been published on India's new clinical trial regulations, very few have examined the views of investigators and ethics board members regarding modifications to the previous regulations. Overall, they have neglected to find out the opinions of other relevant professionals, such as research assistants, coordinators, associates, and managers. To our knowledge, no study has yet investigated the awareness and opinions of Indian research professionals on the new 2019 regulations.

Objective: This study aims to describe the awareness and opinions of Indian research professionals on the new drug and clinical trial regulations.

Methods: In this cross-sectional, Web-based study, we will conduct an open survey for various Indian research professionals. These professionals will be selected randomly using multiple sources. The survey questionnaires, which have already been validated, were developed using the form function in Google docs. A Web link was generated for participants to take the survey. Descriptive statistics will be shown as means and standard deviations for constant variables, whereas certain variables will instead be shown as numbers and percentages.

Results: The survey was opened in July 2019. Enrollment has already started and will be completed in three months. The results calculations are expected to begin in October 2019.

Conclusions: The results of the survey are expected to represent the views of research professionals on the new regulations that will support the development of clinical research and the pharmaceutical industry in India. These regulations are expected to help advance clinical trials, help with the approval of new drugs, and enhance ethical norms in the country.

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KEYWORDS

online survey; professionals; clinical trial; rules

Introduction

Background

In India, the clinical trials industry has exemplified rapid growth in the last few years, driven by economic globalization, and is thus one of the most promising economic sectors in the country [1]. This rapid growth of clinical trials may be attributed to the outsourcing of clinical trials to India by various multinational pharmaceutical organizations [2]. Furthermore, the availability of infrastructure, such as comprehensive treatment, a broad

spectrum of prevalent disorders, ethnic variation, English-speaking health care specialists, and medical and information technology, provides proper conditions for conducting clinical trials in the country [2]. However, reports of irregularities in the administration of clinical trials has overshadowed the flourishing of the industry [2,3]. These ethical violations in the industry have exposed loopholes in the regulatory system, which has led to it struggling to oversee clinical trials effectively [4,5].

Due to this, the loopholes of the regulatory system were amended in 2016 by Indian authorities to strengthen the regulatory mechanisms for reviewing clinical trials. These amendments were issued based on a high level of scrutiny, significant media attention [6], the involvement of non-governmental organizations [3], hearings in the Supreme Court, and the recommendations of an expert committee [7]. Details of these three back-to-back amendments and their associated challenges have been summarized elsewhere [8-11]. Furthermore, two pilot studies have detailed the knowledge of investigators and members of ethics boards regarding the impact of these regulations [12,13].

Recently, new regulations were issued in 2019 [14], which involved amending the 2016 regulations [8] to bring further changes in the clinical research sector. These rules have focused on clarifying the terms of clinical trials of new drugs and phase IV trials, and of clarifying post-trial access to new drugs, clinical trial approval validity, equality, compensation, and monitoring, which have all been described elsewhere [15]. To our knowledge, no study has thus far described research professionals' awareness and opinions regarding these new rules and regulations.

Objectives

The purpose of this survey is to describe the awareness and opinions of research professionals on the new drug and clinical trials regulations.

Hypothesis

We hypothesize that most Indian research professionals will be aware of, will welcome new changes to, and will agree that these new changes will speed up clinical trials, new drug approval, and improve ethical standards for clinical trials in the country. Also, they will aid with the expansion of clinical research and the pharmaceutical industry in India.

Methods

Overview

The methodology used in this survey is based on previous studies [16-18], and on the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [19].

Ethics

The Institutional ethics committee was notified about the intended survey and excused from the review. This study does not require the informed consent of participants because this is an observational survey involving no risk or minimal risk to participants [20].

Design

A cross-sectional, online survey design will be adopted to collect the data. No data which directly identifies any of the participants will be collected, but data that indirectly identifies participants, such as demographic information (eg, age, gender), will be collected. Mean, or range will be used to represent age, and counts/percentages will be used to show gender. We will select participants from different sources, including databases (eg, Clinical Trial Registry India, Indian Society Clinical Research, and the Central Drugs Standard Control Organization), personal networks, hospitals, institutions, and LinkedIn.

Participant Eligibility Criteria

Those who are eligible to take part in this survey include research professionals. For this study, a research professional is defined as research investigators, members of ethics committees, assistants, coordinators, associates, and managers who have engaged in clinical trials in India. The number of target participants for this survey will be 80-100. Participants will be chosen randomly to avoid any selection bias.

Data Collection

Validated questionnaires were selected from previous studies [12,13] and obtained from the respective authors or journals with their approval for use in the present project. Each questionnaire was developed using the form function in Google docs, which is a widely used and free survey tool [21]. A link was generated to enable participants to take the survey online [22]. The Google form feature of a limit of one respondent per email (respondents will be required to sign into Google) was enabled to prevent multiple entries from the same people. The "required to answer" feature was also enabled for each question, except for the following question: "If you are a member of the ethics committee, what is your role?"

The survey was announced on LinkedIn [23]. An email or message with a website link was sent to participants on LinkedIn to request that they complete the online, self-administered questionnaire. Participants' participation in this survey is entirely voluntary and anonymous. Therefore, it does not require participants to provide a name or any other identifying information, except for age and gender. Email reminders will be sent to all the participants to ensure the maximum possible number of responses. Respondents will be able to review and change their answers before clicking on the submit button at the end of the form. All the responses will be accessible by only the study investigator.

Outcome

The outcome of this will be an enhanced understanding of research professionals' awareness and opinions of the new clinical trials rules that came into effect in 2019.

Statistical Analysis

Descriptive statistics will be estimated for continuous variables, whereas counts and percentages will be shown for categorical parameters. These data will be utilized to describe the awareness and opinions of the participants. *Post hoc* tests, such as the independent one-tailed *t* test and chi-square test, will be employed to test the significance of continuous and

dichotomized parameters, respectively. Missing data will be explored in future studies, as appropriate. Results will be presented through graphs or tables. An analysis will be carried out utilizing SAS version 9.2 for Windows (SAS Corporation Inc, North Carolina, USA).

Results

The enrollment of Indian research professionals will begin from multiple sources in July 2019 and is expected to end in November 2019. The results evaluations are expected to start in October 2019. The survey questionnaires being used in this project were previously validated by other studies [12,24], and approval was obtained for their reuse. The demographic characters of the respondents, such as age, gender, and region in India, will be presented in a table. The awareness and opinions of the respondents will be summarized in tables and illustrated as a pie chart.

Discussion

Primary Findings

This study, using a Web-based, online, open survey, aims to investigate the awareness and opinions of Indian research professionals who have engaged in clinical trials regarding the new rules put into place in 2019. It is crucial to understand the awareness and opinions of Indian research professionals, as they act as communicators and are a bridge between sponsors and patients. Therefore, understanding the awareness levels and opinions of these research professionals is crucial to determine whether clinical trials are being conducted per the new rules. Furthermore, considering the new directives, these professionals play a crucial role in addressing and reporting unethical clinical trials on vulnerable populations in India.

This open survey will be conducted online, so it will not be necessary to meet participants at any point physically. The survey will need about 10 minutes to complete. Participants will be able to take the survey on their mobile devices or their computers. Participation in this survey will be voluntary and anonymous, which is expected to boost the response rate.

The findings will expand the current knowledge base regarding the awareness and opinions of various Indian research professionals on the new clinical trial regulations, and allow for comparison to the findings of previous studies. Some professionals may have a higher level of awareness of the regulation now or may even have changed their perspectives regarding the recent amendments to Schedule Y of the Drug and Cosmetic Act.

Limitations

Nonetheless, this survey has some limitations. First, the survey will be taken by only a specific sample within the population. Therefore, the results cannot be generalizable to the whole population of India. Second, self-administered questionnaires may introduce some level of social desirability bias. Finally, the surveys are limited by their cross-sectional design, which allows us to determine the association but not causality.

Conclusion

At present, there is a significant lack of clarity on the awareness levels and opinions of various clinical research professionals in India regarding the new rules. Findings from this study will fill a glaring gap in the literature by providing a knowledge base regarding views of the new rules. The findings may improve the ethical and quality standards of clinical trials, which will further benefit the expansion of the clinical research and pharmaceutical industry in India by speeding up clinical trials, the approval of new drugs, and protecting patients, especially vulnerable ones.

Conflicts of Interest

None declared.

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys

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Protocol

Evaluation of Patterns of Presentation, Practice, and Outcomes of Upper Tract Urothelial Cancer: Protocol for an Observational, International, Multicenter, Cohort Study by the Clinical Research Office of the Endourology Society

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Abstract

Background: Available guidelines on the management of upper tract urothelial carcinoma (UTUC) are restricted due to the lack of strong evidence–based recommendations. Adequate, well-powered randomized trials are missing due to the rarity of the disease. To overcome this problem, we need alternative study designs to provide generalizable data.

Objective: The primary aim of this registry is to provide a real-world overview on patterns of presentation and management of UTUC. Secondary objectives include comparison of outcomes of different treatments and tumor stages and evaluation of compliance with the current European Association of Urology recommendations for UTUC.

Methods: For this observational, international, multicenter, cohort study, clinical data of consecutive patients suspected of having UTUC, irrespective of type of management, will be prospectively collected up to 5 years after inclusion. Data on the patterns of presentation, diagnostics, and treatment as well as short-, mid-, and long-term oncological and functional outcomes will be analyzed. Possible associations between variables, basal characteristics, and outcomes will be tested by multivariable analyses. The methodology will address potential sources of bias and confounders.

Results: The registry was initiated in November 2014 after obtaining institutional review board approval. Data collection started in December 2014. At the time of submission of this manuscript, 2451 patients from 125 centers from 37 countries were included. Inclusion of patients will be closed 5 years after initiation of the registry. Quality checks will be performed centrally with continuous communication and feedback with the centers to ensure accuracy. The first results are expected in the first trimester of 2020.

Conclusions: This large observational prospective cohort will generate landmark “real-world” data and hypotheses for further studies. We expect these data to optimize the management of UTUC, provide insights on harms and benefits of treatment, and serve as quality control.

Trial Registration: ClinicalTrials.gov NCT02281188; https://clinicaltrials.gov/ct2/show/NCT02281188.

International Registered Report Identifier (IRRID): DERR1-10.2196/15363

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KEYWORDS

upper urinary tract; urothelial cancer; incidence; management; outcomes; registry

Introduction

Background

Upper tract urothelial carcinomas (UTUCs) have a low prevalence, with an estimated annual incidence of 2 per 100,000 inhabitants in Western countries [1]. Most of them are urothelial cell carcinomas arising from the lining endoluminal urothelium, and they represent 5%-10% of all urothelial carcinomas [1]. At diagnosis, nearly 60% of UTUCs are found to be invasive, a much higher percentage than the 15%-20% reported for its sibling tumor in the bladder [1,2]. Although the general genotype of UTUC is similar to its bladder counterpart, it is different in its genetic expression and frequency by stage [3-5]. UTUC may present in a primary isolated form in the upper urinary tract or secondary form after a primary diagnosis of bladder urothelial carcinoma. Synchronous upper and lower urinary tract urothelial carcinoma has been reported in up to 17% of cases [6].

Irrespective of whether it is because of advanced diagnostic methods utilization, decreased competing death causes, or real increasing incidence, the rate of invasive UTUC tumors (>pT1) at diagnosis has been increasing in recent years [1,6]. Metastases are found in 7% of all patients with UTUCs. The 5-year survival does not reach 50% for patients with pT2/pT3 UTUCs and is lower than 10% for pT4 tumors [7,8].

The European Association of Urology (EAU) guidelines recommend risk stratification of UTUC in low- and high-risk disease, based on clinical and pathological factors. These include focality and size of the tumor, presence of high-grade urinary cytology or high-grade histology on biopsy, imaging characteristics, and presence of previous radical cystectomy for bladder cancer or variant histology [1,7]. This risk classification is intended to drive treatment, and some of these risk factors, either isolated or integrated, have prognostic implications [7-9].

The gold standard of UTUC remains radical nephroureterectomy (RNU) with complete bladder cuff excision [10,11]. However, there is a growing interest in minimally invasive, kidney-sparing approaches by ureterorenoscopy (URS). This shift in treatment management is fueled by the development and evolution of flexible instruments. Indications for kidney-sparing management are discussed in detail in the current guidelines and should be considered in patients with low-risk disease [1,7,12]. A particular challenge during endoscopic management is appropriate grading and staging of tumors, both necessary for accurate risk assessment, which is essential for successful therapeutic management [1,13].

Rates of recurrence, either distant or local, are correlated with various factors, the most important of which are pathological stage and grade. A common site of recurrence after treatment of UTUC is the bladder. Intravesical recurrence following RNU is a common problem, with an incidence of nearly 20%-50% [1]. In a meta-analysis (4057 participants) assessing the impact of diagnostic URS prior to RNU, a strong correlation was found between previous URS and development of intravesical recurrence during follow-up after RNU (hazard ratio=1.53, P<.001) [10]. Tumor location also plays a role in the choice of therapy based on anatomic location [1,6,14].

Rationale for a Clinical Registry

Available clinical information on the management of UTUC relies mainly on historical cohorts. Monocentric data from merging international databases or population-based studies have provided the highest level of evidence so far and are challenging the standard management algorithms [15-17]. Although valuable, this type of information is prone to bias. Patient selection criteria, attrition bias, and verification bias are among the most frequent confounders in spite of efforts to adjust for them. Even in large cohorts, confounding variables cannot be completely corrected for. Although associations may be observed, they rarely confirm causality and may have unknown effects [18,19].

In an intent to increase the quality of evidence, systematic reviews and meta-analysis have explored specific UTUC outcomes of distinct treatment modalities as well as predictive and prognostic factors [19-27]. Obviously, they provide insights in the natural history of UTUC, but they are still the product of a low-evidence report. Therefore, they do not result in strong recommendations due to the flaws in accuracy and generalizability [28].

Although randomized trials (RCTs) would provide sound answers, the rarity of the condition prevents studies from obtaining an adequately powered sample size for correct comparison in a reasonable study time. The late onset and comorbidity of the affected population will limit inclusion and likely preclude generalizability of RCT results. In this scenario, it is rational to rely on alternative study designs that allow rapid data collection with inclusion of a large population with a broader geographic and ethnic spectrum [29,30].

Clinical registries are defined as “a system that collects a defined minimum data set from patients undergoing a particular procedure, diagnosed with a disease or using the health care resource” [29]. They are observational databases focusing on a specific clinical condition, therapy, or population without specific mandate approaches and are intended to reflect “real world” practice in a large population. When properly designed and executed, they serve to improve the quality of health care and as hypothesis generators [29].

Very little is known about the prevalence of registries worldwide. Overall, the interest has increased rapidly in the last decade in countries such as the United States, Sweden, and the United Kingdom, with more than 100 registries per country. Whether named registries, quality registries, clinical databases, clinical audits, or quality improvement programs, the medical societies unanimously recognized their value in the clinical research context [31,32].

We hereby present the design of the Clinical Research Office of the Endourology Society (CROES)-UTUC registry.

Objectives

Overall, the registry aims to provide a contemporary real-world overview and generalizable comparative outcomes on the incidence and management of UTUC across the globe. The CROES-UTUC registry focusses primarily on incidence, indications, treatment, and patient outcomes. When possible, comparative clinical effectiveness of different interventions and assessment of safety of these interventions will be performed.

The primary objective is to describe contemporary patterns of presentation, practice, and treatment of UTUC according to geographic characteristics.

The secondary objectives identified by the steering committee during the design of the registry include several short- and long-term comparative outcomes listed below:

- To assess the compliance with the current EAU guidelines on UTUC recommendations
- To assess the validity of risk stratification, as recommended by the current EAU guidelines on UTUC
- To assess the intra- and postoperative complications stratified by type of treatment
- To determine the rates and type of recurrences (upper tract and bladder/local or distant) as well as risk factors for patients presenting with primary UTUC stratified by type of treatment (kidney-sparing treatment vs radical nephroureterectomy vs segmental ureterectomy), stage at presentation, select clinicopathologic characteristics, and gender
- To determine comparative overall survival stratified by type of treatment and stage at presentation.

Methods

Study Design

This is an observational, international, multicenter, cohort study, prospectively collecting clinical data on consecutive patients with UTUC. The registry is set up by the CROES, and its design follows the recommendations of the Agency for Healthcare Research and Quality (US) of 2014 for design and use of patient registries for scientific, clinical, and health policy purposes [29].

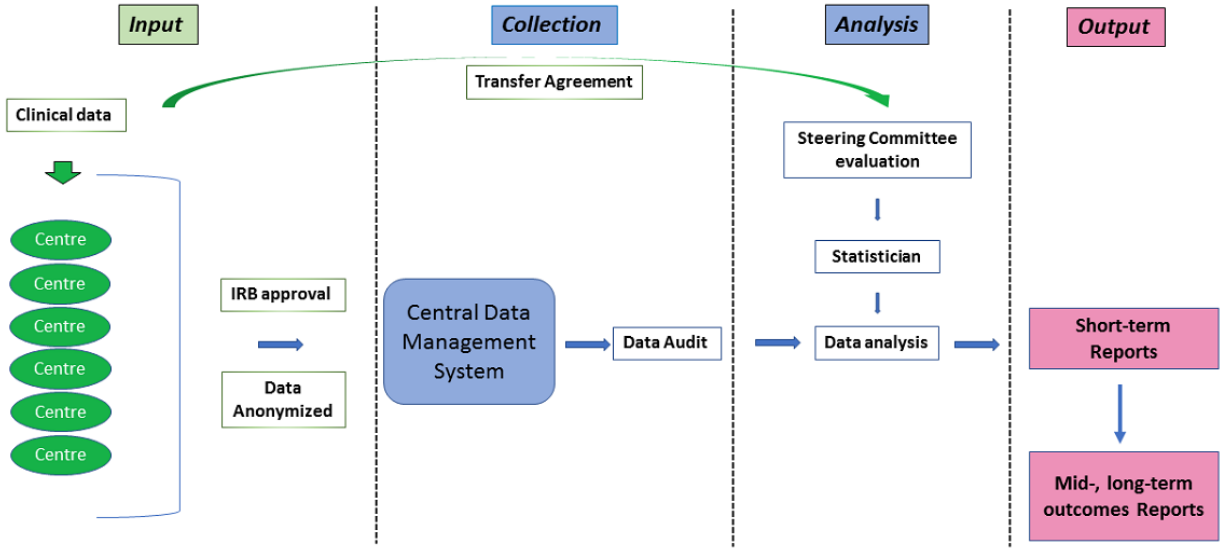
This registry collects clinical data on patients with UTUC, irrespective of onset, location, or type of treatment. It enrolls patients at the moment of their health care visits and includes baseline information on demography, symptoms, risk factors, and laboratory variables. Diagnostic procedures are captured as well as management, treatment, and follow-up details (up to 5 years after inclusion). In summary, it captures patterns of presentation, diagnostics, and treatment as well as short-, mid-, and long-term oncological and functional outcomes. The operational flow diagram design of the registry is provided in Figure 1. Patients were not involved in the design of the registry.

Version 2 of the protocol was registered in September 2014 in Clinical trials.gov (trial registration: NCT02281188). The data and material for this study are available from CROES upon request.

A steering committee composed of six international experts in the field oversaw the design process and checked the structure of the registry. Primary and secondary objectives were defined before design and initiation of the registry. The different centers have the opportunity to identify “ad hoc” secondary objectives and propose studies across the duration of the study. The steering committee will review the different study proposals; modify the proposal, if necessary; and consequently approve or deny them. Proposals will be handled according to chronological submission.

Due to the amount of data and the opportunity for the centers to propose studies, not all secondary objectives were predefined prior to initiation of the registry. They will be identified “ad hoc” by the participating centers or the steering committee according to the data available at the time of study proposal. We foresee that the large sample size will allow for comparative studies on benefit of interventions, evaluation and definition of risk factors for recurrence, as well as associations and quasi-randomized outcomes comparisons.

Figure 1. Operational flow diagram of the CROES-UTUC (Clinical Research Office of the Endourology Society for urothelial carcinomas of the upper tract) registry. Colors indicate the different levels of data input, management, and output as well as the interaction directions among them. Green color indicates external sources of information (participating centres); blue colour indicates central registry office tasks; pink/blue color indicates a combination of centres and central office registry output. IRB: institutional review board.



Participant Characteristics

Adult patients (age≥18 years) suspected of having UTUC either as primary onset or after previous bladder urothelial cancer (during follow-up) and scheduled to undergo any type of diagnostic instrumentation of the upper urinary tract or any surgical treatment (ie, RNU, kidney sparing surgery by URS or percutaneous treatment or segmental ureter or pelvic resection with or without any other neoadjuvant, perioperative, or adjuvant interventions) will be included in the registry. In line with the design and objectives of a registry, the inclusion criteria are broad, while the exclusion criteria are minimized.

No direct benefits or risk for patients are derived from the participation in the registry. The registry data do not imply any change in management policy or practice apart from the standard practice in the respective centers at any moment of the diagnostic and therapeutic follow-up processes.

Data Collection and Analysis

Data from all participating centers will be collected through electronic case report forms by using an online data management system (DMS). The DMS is a Web-based system, which makes it convenient for participants worldwide to use, and multiple users of the same institution can be connected to the same data. The DMS is located and maintained at the CROES Office. A more detailed overview of the CROES DMS is provided in Multimedia Appendix 1 [33,34].

Local sites will fill out the electronic case report forms in the DMS prospectively and continuously over time and at the appropriate time. The correspondent local principal investigator is responsible for the reliability of the data and for controlling the accuracy of data. Patient data entered in the DMS was coded, and according to the European General Data Protection Regulation that went "into force" in May 2018, that data is pseudonymized. This means that only the controller (principal investigator responsible for the respective center) can link the code to the patient for audit purposes and follow-up data provision. The identity of the patients is not accessible through the CROES-DMS.

The DMS provides detailed overview reports of included data and runs queries to check for data inconsistencies and outlying values in order to ensure a reliable high-quality dataset. To minimize missing data, the CROES Office sends updates of the database to the principal investigator and is responsible for sending reminders to encourage provision of missing or follow-up data. The managers of the CROES office are in charge of monitoring the registry. Reports are regularly made to the steering committee. Data inconsistencies will be addressed by the local principal investigator, and decisions will be made by the steering committee on a case-by-case scenario.

Essential data elements aim to capture the multiple dimensions of the condition, from diagnosis to survival outcomes; baseline characteristics; risk factors; imaging and clinical assessment; management; complications up to 30 days after intervention; and survival data at 1, 3, and 5 years.

Data variables included in the electronic case report forms are categorized into six domains: general data, pretreatment assessment, treatment, pathology results, postoperative course, and follow-up. Each domain includes multiple variables.

All variables are defined, and they can be categorical (including descriptive, eg, type of complication for rare complications) or continuous. The variables collected include demographic and clinical patient characteristics, risk factors and symptoms, imaging and laboratory tests, treatment type, and pathological and survival outcomes. The key variables are described in Textbox 1.

Textbox 1. Domains, key variables, and total number of variables in the UTUC-CROES registry.

- General data (number of variables=71)
  - Patient demographics
  - Medical and family history
  - Risk factors
  - Symptoms
  - Medication (anticoagulants)
- Pretreatment assessment (number of variables=80)
  - Imaging (local, regional, and distant)
  - Cystoscopy
  - Cytology
  - Clinical tumor, node, and metastasis stage
- Treatment data (number of variables=141)
  - Use of antibiotic prophylaxis
  - Treatment type
  - Intraoperative details
  - Instrumentation details
  - Neoadjuvant treatment
- Pathological data (number of variables=44)
  - Grade and Stage (2016 World Health Organization International Society of Urologic Pathologists)
  - Pathological Stage
- Perioperative data (number of variables=29)
  - Use of antibiotics
  - Complications up to 30 days (number and type)
  - Clavien-Dindo classification complications
  - Use of intravesical instillation
  - Indication for adjuvant therapy
- Follow-up (number of variables=76; 76 variables per follow-up domain (maximum 5-year follow-up). Maximum of 21 follow-up visits possible in the data management system per patient.
  - Survival status
  - Presence of recurrence
  - Location of recurrence
  - Diagnostics performed
  - Results of the diagnostics
- Total variables (number of variables=441)

As described in the operational flow diagram of the registry, the CROES statisticians will perform statistical analysis after data audit and data cleaning. The analysis will be performed after identification of specific objectives and attaining study approval from the steering committee.

Descriptive statistics will be used to summarize the data. Results will be presented in tables reporting at least the number of subjects, mean, SD, and minimum and maximum for continuous data and the number of subjects and percentages for categorical data. For testing, a significance level of 5% will be maintained, and all tests will be two-sided.

All analyses will be carried out on available data, and proportions of missing data will be reported. All analyses will be performed using SPSS version 25 (IBM Corporation,

Armonk, New York) or R studio (RStudio Team, Boston, Massachusetts).

Multivariable analyses will be performed to assess possible associations with geographical or ethnic differences and risk factors for complications after surgery. The methodology will address potential sources of bias. When necessary, sensitivity analysis will be conducted. We will not use external data sources for comparison unless they are considered to be of outmost importance for specific objectives.

After closure of the primary inclusion process, an audit will be planned. The audit will focus on data source verification of the values of the identified critical variables and on internal consistency by cross checking among exclusive variables.

Availability of Data

Individual centers have signed a data transfer agreement. The centers are responsible for providing data and can use their own data for individual publications upon request and authorization of the steering committee of the registry.

The steering committee will revise and give final approval to any paper derived from the data collected in the course of the study and will determine authorship based on contribution on any paper derived from this registry. Findings and reports derived from this registry will be presented at international urology and oncology conferences and published in peer-reviewed journals. CROES will summarize the findings on the Web by regular information letters [35].

Results

The registry was initiated in November 2014 and aims to recruit up to 3000 patients in a 5-year period. The study has been registered at the competent authority for observational studies. Institutional review board approval was requested and judged not necessary according to the Medical Research Involving Human Subjects Act (date of resolution: October 15, 2014; ref W14-273#14.17.329).

The study recruitment was initiated in November 2014. Data collection started in December 2014 and as of submission of this manuscript, 2451 patients from 125 centers from 37 countries have been included. Inclusion of patients will be closed 5 years after initiation of the registry. Quality checks are performed centrally with continuous communication and feedback with the centers to ensure accuracy. First results in terms of descriptive outcomes, patterns of practice, and compliance with the current guidelines are expected soon after patient inclusion is closed. Mid- and long-term outcomes are expected in the first trimester of 2020.

Discussion

Because prospective data are scarce, many unanswered questions remain about the management and comparative outcomes of UTUC. Conversely, the grade of recommendations is supported by low evidence, although this fact does not always preclude a strong recommendation in a disease with a low prevalence. Besides the rapidly evolving technological field that impacts diagnosis and treatment, several obstacles hinder the implementation of a RCT on the subject [30]. The advanced age of patients, limited availability of armamentarium, high rate of comorbidities of the affected population, and undesired outcomes of standard treatment are some of these obstacles. A recent study showed that comorbidity is inversely associated with being offered participation in clinical oncologic trials even after adjusting for the effects of demographic and socioeconomic factors [36]. Furthermore, it is unlikely that several RCTs may provide recommendations that will fit the whole spectrum of patients and various aspects of the disease. It is under these conditions that outcomes derived from observational cohorts or pragmatic clinical trials will be filling the gaps [37-39]. The biggest clinical challenge in UTUC is the high rate of overtreatment in patients who could be safely offered a kidney-sparing approach as well as the high rate of undertreatment in patients with invasive disease who need more than RNU (ie, [neo]adjuvant systemic therapy to treat occult metastasis).

In line with the definition of a clinical registry, the inclusion criteria of our registry are broad, to capture real-world data on presentation, diagnosis, treatment indication, and outcomes of UTUC. In case of a disease with a low prevalence, registries have a great potential in supporting clinical research and as a source of future trials [29,37]. Registries face practical and operational challenges [29,38,40]. Matters that may compromise the functionality of the CROES-UTUC registry were taken into account at the design phase.

Regarding the logistic organization, the data are centrally collected in a standardized way; they are clinically oriented and adequately frame the affected population. Furthermore, rapid and regular communication and feedback between the central management core of the registry and the participating centers are provided. Regarding quality control, patient data are anonymized and the CROES office monitors the data and sends reminders to encourage the respective principal investigators to ensure completeness and accuracy of essential data elements, especially when missing data are detected. The audit process of the data is independent from the steering committee and participating centers. Secondary data quality checks, cleaning, and analysis will be performed by professional statisticians.

Once these operational questions are addressed with satisfaction, there are still challenges that may hinder the internal validity of a registry as well as the attainment of reliable data [29,37]. Erroneous capture of patients' information remains a potential source of bias that is difficult to solve in any type of study, especially in studies with retrospective designs. It is our experience that proactive continuous auditing and checking contradictory or exclusive variables minimizes this error, although it is unknown to what extent. Confounding will be considered for any of the planned and proposed studies under clinical and statistical supervision, and information regarding data transfer to the registry (manually or from electronic health records) will be taken into account as possible sources of bias.

Differences exist in local practices and protocols as well as regional variations in standard of care or access to care [37]. Although inherent to any multicentric registry and precisely one of the outcomes to be captured, interpretation may be

difficult. Therefore, efforts will be made to adjust for these differences, with a thorough critical analysis. As any center can participate independent of case volume or experience, differences in volume outcomes may surface. These differences may become important and potentially have a positive impact in the quality of care and value-based health care parameters, as highlighted in a recent systematic review [40].

In fact, clinical registries such as pragmatic clinical trials are a valuable complement to RCTs [39] and continue to evolve as a possible niche for RCTs, and incorporation of patient participation becomes a point of reference for evidence-based medicine [40-42]. Despite recognizing the subordinate level of evidence of registry-generated data with respect to RCTs [39], we strongly believe that this internationally prospective collected data will be helpful in understanding the current scenario in management of UTUC and will generate hypotheses to nurture focused RCTs.

With all this in mind, we are aware that the large amount of data collected may be a burden for the centers and that the research output may be limited by missing data. As centers are allowed and encouraged to propose different hypothesis-driven studies, the steering committee together with the statisticians will thoroughly examine the different proposals. The possibility remains that some of the preliminary defined secondary objectives may not be reached, while some others may turn out to be feasible.

In conclusion, the CROES-UTUC registry is a powerful source of information by compiling international clinical data on real-world presentation and treatment of UTUC. The design and logistics of the registry provide adequate operational flow, functionality, and quality control and ensure transparency. An effort is being made to minimize bias in data collection and analysis by means of regular reminders and feedback. The central management and the steering committee guarantee the statistical and clinical support. Lastly, the implication of the centers in proposing secondary objectives and authoring different studies represents, in our view, an additional scientific incentive.

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Authors' Contributions

JB was involved in drafting of the manuscript, acquisition of data, and critical revision of the manuscript for important intellectual content. MC was involved in acquisition of data and drafting of the manuscript. JD was involved in study conception and design and critical revision of the manuscript for important intellectual content. AA was involved in acquisition of data and critical revision of the manuscript for important intellectual content. SS was involved in acquisition of data and critical revision of the manuscript for important intellectual content. LC was involved in acquisition of data and critical revision of the manuscript for important intellectual content. VC was involved in acquisition of data and critical revision of the manuscript for important intellectual content. PL was involved in study conception and design, drafting of the manuscript, acquisition of data, and critical revision of the manuscript for important intellectual content.

Conflicts of Interest

SS: Honoraria: Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Richard Wolf, Roche, Sanochemia, Sanofi, Takeda, Urogen. Consulting or advisory role: Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Richard Wolf, Roche, Sanochemia, Sanofi, Takeda, Urogen, Movember Foundation. Patents: Method to determine prognosis after therapy for prostate cancer (granted 2002/09/06), method to determine prognosis after therapy for bladder cancer (granted 2003/06/19), prognostic methods for patients with prostatic disease (granted 2004/08/05), and soluble Fas urinary marker for the detection of bladder transitional cell carcinoma (granted 2010/07/20). All other authors declare no conflicts of interest.

Multimedia Appendix 1
Data management system.
[DOCX File , 302 KB - resprot_v9i1e15363_app1.docx]

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Abbreviations

CROES: Clinical Research Office of the Endourology Society
DMS: data management system

EAU: European Association of Urology
RCT: randomized controlled trial
RNU: radical nephroureterectomy
URS: ureterorenoscopy
UTUC: upper tract urothelial carcinomas
WHO-ISUP: World Health Organization International Society of Urologic Pathologists

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Protocol

Prospective Evaluation of HIV Testing Technologies in a Clinical Setting: Protocol for Project DETECT

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Abstract

Background: HIV testing guidelines provided by the Centers for Disease Control and Prevention (CDC) are continually changing to reflect advancements in new testing technology. Evaluation of existing and new point-of-care (POC) HIV tests is crucial to inform testing guidelines and provide information to clinicians and other HIV test providers. Characterizing the performance of POC HIV tests using unprocessed specimens can provide estimates for the window period of detection, or the time from HIV acquisition to test positivity, which allows clinicians and other HIV providers to select the appropriate POC HIV tests for persons who may be recently infected with HIV.

Objective: This paper describes the protocols and procedures used to evaluate the performance of the newest POC tests and determine their sensitivity during early HIV infection.

Methods: Project DETECT is a CDC-funded study that is evaluating POC HIV test performance. Part 1 is a cross-sectional, retrospective study comparing behavioral characteristics and HIV prevalence of the overall population of the Public Health–Seattle & King County (PHSKC) Sexually Transmitted Disease (STD) Clinic to Project DETECT participants enrolled in part 2. Part 2 is a cross-sectional, prospective study evaluating POC HIV tests in real time using unprocessed whole blood and oral fluid specimens. A POC nucleic acid test (NAT) was added to the panel of HIV tests in June 2018. Part 3 is a longitudinal, prospective study evaluating seroconversion sensitivity of POC HIV tests through serial follow-up testing. For comparison, HIV-1 RNA and HIV-1/HIV-2 antigen/antibody tests are also performed for participants enrolled in part 2 or 3. A behavioral survey that collects information about demographics, history of HIV testing, STD history, symptoms of acute HIV infection, substance use, sexual behaviors in the aggregate and with recent partners, and use of pre-exposure prophylaxis and antiretroviral therapy is completed at each part 2 or 3 visit.

Results: Between September 2015 and March 2019, there were 14,990 Project DETECT–eligible visits (part 1) to the PHSKC STD Clinic resulting in 1819 part 2 Project DETECT study visits. The longitudinal study within Project DETECT (part 3) enrolled 27 participants with discordant POC test results from their part 2 visit, and 10 (37%) were followed until they had fully seroconverted with concordant positive POC test results. Behavioral survey data and HIV test results, sensitivity, and specificity will be presented elsewhere.

Conclusions: Studies such as Project DETECT are critical for evaluating POC HIV test devices as well as describing characteristics of persons at risk for HIV acquisition in the United States. HIV tests in development, including POC NATs, will provide new opportunities for HIV testing programs.

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KEYWORDS

HIV testing; point-of-care tests; acute HIV infection; nucleic acid tests

Introduction

The Centers for Disease Control and Prevention (CDC) provides guidelines for HIV testing in the United States and must continually update its guidance to reflect advancements in testing technology, availability of new tests, and test performance across various specimen types and during both early and established HIV infection [1]. Acute HIV infection, the period between first detection of viral markers of HIV infection and the development of a mature antibody response, is a period characterized by a high viral load and potential for false-negative HIV antibody tests, leaving individuals unaware of their HIV infection. These conditions lead to an elevated risk of HIV transmission to others during this earliest period of infection [2]. Due to the higher transmission risk during early infection, the CDC and Association of Public Health Laboratories published a new algorithm in 2014 for laboratory testing to help identify persons recently infected with HIV that incorporated the use of an HIV antigen/antibody (Ag/Ab) test, which can detect HIV sooner than tests that detect only antibodies [3-8].

Data released by the CDC in 2017 [7] showed that, for laboratory-based Ag/Ab testing, the median time from the estimated dates of HIV acquisition to test positivity (the window period) was 18 days (interquartile range [IQR] 13-24 days), and it was 44 days before all specimens tested positive. CDC, therefore, recommends that persons tested less than 45 days after being exposed to HIV who receive a negative result on a laboratory-based HIV Ag/Ab test should have a follow-up test at 45 days postexposure [9]. Similar estimates for window periods of point-of-care (POC) tests have been difficult to calculate because POC tests are intended for use with specimens that are difficult to store or not commercially available, including unprocessed blood and oral fluid. Thus, to date the CDC has not been able to update recommendations for when to retest after possible HIV exposure when using POC HIV tests.

In 2014, CDC and University of Washington (UW) began the Diagnostic Evaluation To Expand Critical Testing Technologies (Project DETECT). The goals of this project are to evaluate the (1) performance of the newest POC HIV tests with unprocessed whole blood and oral fluid specimens and (2) sensitivity of various POC HIV tests during early infection. Results from Project DETECT will be used to inform HIV testing guidelines and technical guidance and provide information to clinicians and other HIV test providers on the appropriate use of different POC HIV tests and retesting procedures. In this manuscript, we describe the protocol and study populations on which these test evaluations are based and the types of behavioral and laboratory data and specimens collected by the study.

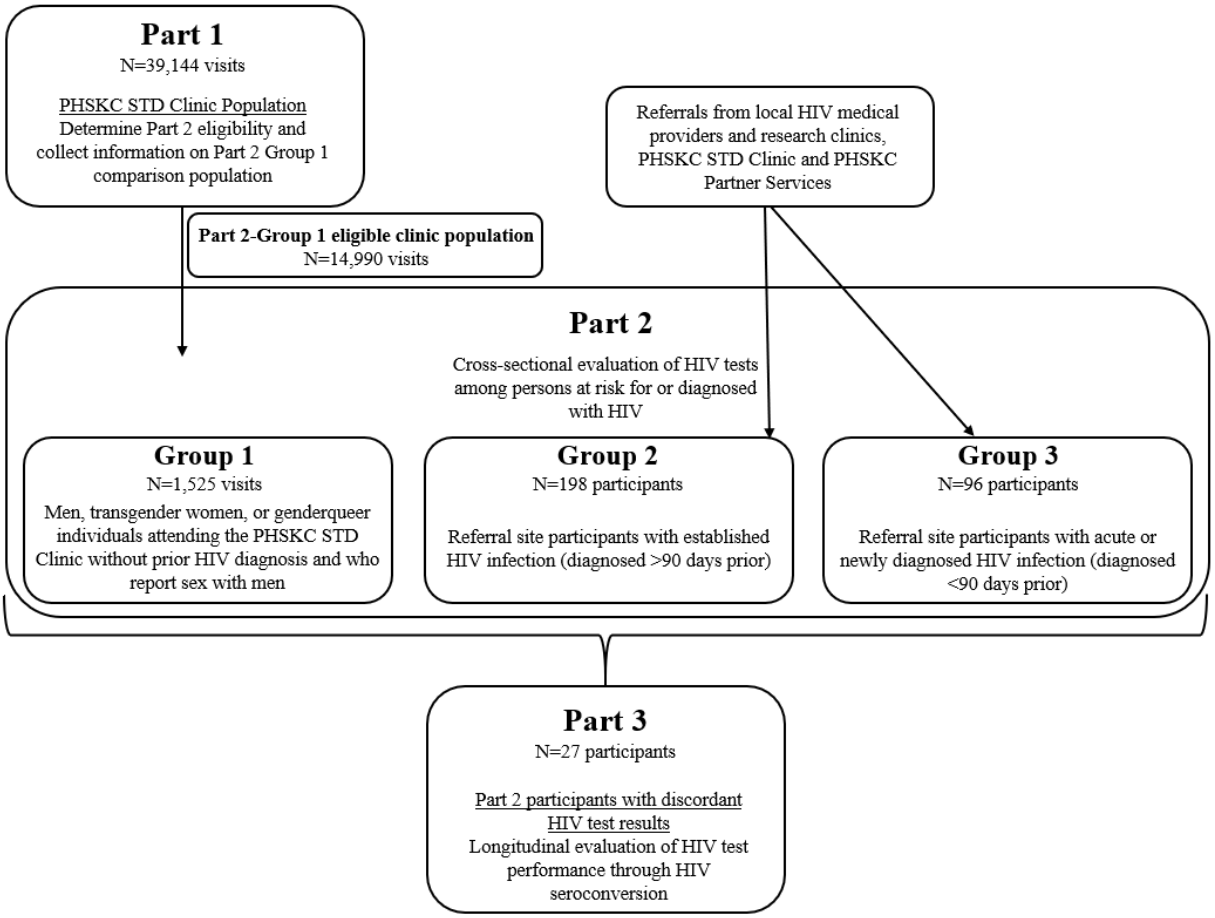
Methods

Description of the Protocol for Project DETECT

Study Populations

Project DETECT comprises three parts as depicted in Figure 1. It includes evaluations of POC HIV test performance in a cross section of participants with and without prior HIV diagnosis (part 2) and over the course of seroconversion (part 3) as well as a comparison of study participants to the overall clinic population from which study participants were drawn (part 1). The study received ethical approval from the UW Human Subjects Division (STUDY#00001637).

Figure 1. Project DETECT study design.



Project DETECT: Part 1

Project DETECT part 1 is a cross-sectional, retrospective study designed to use behavioral and testing data collected for clinical purposes to describe the population of the Public Health–Seattle & King County (PHSKC) Sexually Transmitted Diseases (STD) Clinic and compare behavioral characteristics and HIV prevalence of the overall clinic population with participants enrolled in part 2, described below. Persons are eligible for inclusion in part 1 if they are aged 14 years or older and presenting for a visit at the PHSKC STD Clinic. The majority of clinic clients are not eligible for part 2 based on criteria described in the next section. These participants receive standard care for sexual health services. A waiver of informed consent was granted by the UW Human Subjects Division for part 1 procedures.

Project DETECT: Part 2

Project DETECT part 2 is a cross-sectional, prospective study designed to evaluate the performance of new POC HIV tests in real time with unprocessed whole blood and oral fluid specimens. Part 2 participants are aged 18 years and older and are assigned to one of three groups:

- Part 2–group 1 consists of English-speaking cisgender men, transgender men, transgender women, and genderqueer individuals who have sex with men who come to the PHSKC STD Clinic seeking sexual health services and report being HIV negative or of unknown HIV status. Part 2–group 1 participants can reenroll as a part 2–group 1 participant every 90 days if they have concordant negative HIV POC and lab-based test results at their previous study visit and remain HIV negative or of unknown status.
- Part 2–group 2 consists of English-speaking HIV-positive persons whose first positive HIV test was more than 90 days prior to referral. Participants could be antiretroviral (ARV)-naïve, currently receiving antiretroviral therapy (ART), or persons who have discontinued ART.
- Part 2–group 3 consists of English- and Spanish-speaking persons with possible or diagnosed acute or early HIV infection. This group was included to enrich the sample of persons likely to have discordant HIV test results for part 3, as was done in a prior project [10]. All persons whose first positive HIV test was within 90 days preceding their part 2 visit, regardless of whether they were ARV-naïve or were newly taking ART, were enrolled into part 2–group 3.

The primary study site for part 2–group 1 recruitment and study-related activities is the PHSKC STD Clinic, drawing from a patient population of approximately 6500 patients and more than 10,000 visits per year.. Other referral and performance sites for part 2–groups 2 and 3 include the UW AIDS Clinical Trial Unit (ACTU), which has co-enrolled a subset of Project DETECT participants in an acute HIV infection treatment study, and other clinical providers or medical facilities in Western

Washington. Project DETECT staff also screen daily patient intake lists for the HIV clinic that is co-located with the UW ACTU and approach patients for participation in part 2–group 2 or 3, as appropriate. All subjects provide verbal (part 2–groups 1 and 2) or written (part 2–group 3) informed consent for general study procedures as well as an additional consent specifically for specimen storage in a CDC repository. Participants are compensated $40 for their time; since October 2017, part 2–group 3 participants have received an additional $10 for fingerstick procedures.

Project DETECT: Part 3

Project DETECT part 3 is a prospective, longitudinal study designed to evaluate the seroconversion sensitivity of new POC HIV tests through serial follow-up and gather information on characteristics of persons undergoing seroconversion. Data from part 3 will be used to describe differences in the window periods of HIV tests by test and by specimen type.

Part 3 consists of English- or Spanish-speaking part 2 participants with discordant HIV test results (ie, at least one positive result and one or more negative results) who consent to longitudinal follow-up. Initially, any part 2 participant with discordant results was offered enrollment in part 3. Since April 2016, we have no longer offered part 3 enrollment to part 2–group 2 participants with negative POC test results, as discordant results in these participants likely indicates seroreversion.

Part 3 participants provide written informed consent for general study procedures and separate informed consent specifically for specimen storage in the CDC repository. Visits are targeted to be scheduled 3, 7, 10, 14, 21, 28, 42, 56, and 70 days after the part 2 visit and then monthly (Multimedia Appendix 1). Follow-up continues on schedule until participants test concordant positive on all POC HIV tests, concordant negative on all tests at two consecutive visits (indicating false-positive part 2 test results), or they complete one year of follow-up. Part 3 participants receive $50 at each study visit.

Study Procedures

HIV Testing Procedures

HIV testing procedures for parts 2 and 3 are shown in Table 1 and Figure 2, respectively. When part 2 recruitment began in September 2015, the standard of care HIV testing protocol for the PHSKC STD Clinic was the Genetic Systems HIV-1/2/O IgM-sensitive HIV antibody test (3rd generation; Bio-Rad Laboratories, Inc) followed by pooled HIV nucleic acid testing (NAT) for HIV antibody-negative men who have sex with men (MSM) [11]. On October 12, 2015, the PHSKC laboratory changed to use the HIV-1/HIV-2 Ag/Ab Combo assay (Bio-Rad Laboratories, Inc) for all PHSKC clinic patients, and routine pooling of specimens with negative screening test results was discontinued due to cost concerns. POC testing using the INSTI HIV-1/HIV-2 antibody test (bioLytical Laboratories, Inc) [12] on fingerstick whole blood is offered as part of clinic standard of care selectively to MSM and all persons testing as part of HIV partner services.

Project DETECT study procedures require all participants to undergo POC HIV testing using oral fluid and venipuncture whole blood with results compared to the PHSKC clinic standard of care (Table 1). In addition, all part 3 participants provide fingerstick specimens for POC tests at all visits (Figure 2), and fingerstick specimen testing was added for part 2–group 3 participants after October 19, 2017, following our identification of possible differences between the estimated window periods for fingerstick and venipuncture whole blood specimens that could not be well characterized without a fingerstick specimen collected at the first (part 2) study visit [13]. The devices included in the project remained consistent since the study began in September 2015 except that the Simple Amplification Based Assay (SAMBA, Diagnostics for the Real World), a POC NAT [14,15], was added in June 2018. Specimen collection and testing are performed in accordance with package inserts for each device. For a video demonstrating specimen collection and testing during a mock part 3 visit (including fingersticks) see Multimedia Appendix 2. Part 2 participants with a reactive result on any POC HIV test receive an HIV-1/HIV-2 supplemental test and the clinic standard Ag/Ab laboratory assay and, for part 2–group 1 participants (ie, those with no prior HIV diagnosis), additional blood drawn for a CD4+ T-cell count, HIV-1 RNA level, and connection to PHSKC staff for linkage to HIV care. Laboratory Ag/Ab assays using serum were ordered for all part 2–groups 2 and 3 participants and part 3 participants who were attending their first part 3 visit, had a negative Geenius HIV 1/2 (Bio-Rad Laboratories, Inc) result using either venipuncture or fingerstick whole blood, had no laboratory-based Ag/Ab assay ordered at a previous part 3 visit, or had a previous laboratory-based Ag/Ab result that was nonreactive. Serum specimens are submitted for the Ag/Ab assay under a coded research ID to avoid triggering a public health investigation into persons who are known to be HIV positive.

Since October 12, 2015, when the PHSKC HIV/STD Program discontinued pooled NAT, part 2–group 1 participants who test negative on all POC tests are pooled [11] into a single 10-member pool and then tested using the RealTi*m*e HIV-1 viral load assay (Abbott Laboratories). Plasma is sent for quantitative HIV-1 RNA level for any part 2 participant with any reactive HIV test to confirm HIV infection. Initially, part 3 participants had only one additional HIV-1 RNA test that was performed at the final visit. After the introduction of SAMBA in June 2018, an HIV-1 RNA level has been sent at every part 3 visit. Project DETECT staff provide part 2 participants with all POC test results and, for part 2–group 1 participants, enter these results into the PHSKC electronic medical record.

Table 1. Project DETECT part 2 procedures.

Study procedure	Group 1: HIV negative or unknown	Group 2: established HIV infection (>90 days since diagnosis)	Group 3: newly diagnosed HIV positive (≤90 days since diagnosis)
Obtain verbal consent	X	X	
Obtain written consent			X
Release of information to obtain previous HIV results[a]			X
Oral fluid tests[b]	X	X	X
Venipuncture whole blood tests[c]	X	X	X
Fingerstick whole blood tests[d]			X
Geenius HIV 1/2 confirmatory test[e]	X[f]	X	X
Collection of DBS[g] and samples for storage[h]	X[i]	X	X
Laboratory Ag/Ab[j] test performed through STD[k] clinic[l]	X[m]		
Laboratory Ag/Ab test performed through research[l]		X	X
Pooled NAT[n,o]	X[p]		
Individual NAT[q]	X[r]	X	X
Complete part 2 of behavioral survey	X	X	X
Offer and consent, if applicable, part 3 enrollment if POC[s] tests are discordant	X		X

[a]Release of information is sent to the provider who performed first positive HIV test and/or last negative HIV test if within 365 days.

[b]Oral fluid tests include Dual Path Platform (DPP) HIV 1/2 Assay (Chembio Diagnostics System, Inc) and OraQuick ADVANCE Rapid HIV 1/2 Antibody test (Orasure Technologies, Inc).

[c]Venipuncture whole blood tests include DPP HIV 1/2 Assay, OraQuick ADVANCE Rapid HIV 1/2 Antibody test, INSTI HIV-1/HIV-2 Rapid Antibody Test (bioLytical Laboratories, Inc), Determine HIV 1/2 Ag/Ab Combo (Abbott Laboratories), and SAMBA II HIV-1 Qual test (Diagnostics for the Real World). SAMBA II HIV-1 Qual test was added to the Project DETECT study protocol in June 2018.

[d]Fingerstick whole blood tests include DPP HIV 1/2 Assay, OraQuick ADVANCE Rapid HIV 1/2 Antibody test, INSTI HIV-1/HIV-2 Rapid Antibody Test, Determine HIV 1/2 Ag/Ab Combo, and SAMBA II HIV-1 Qual test. SAMBA II HIV-1 Qual test was added to the Project DETECT study protocol in June 2018.

[e]Geenius HIV 1/2 Supplemental Assay (Bio-Rad Laboratories, Inc).

[f]Geenius HIV 1/2 Supplemental Assay performed as point-of-care test on venipuncture whole blood if at least one point-of-care test is positive.

[g]DBS: dried blood spot.

[h]Includes DPP HIV 1/2 oral fluid swabs, HIV-1 Oral Specimen Collection Device (Orasure Technologies, Inc), and a Whatman 903 Protein Saver Card (dried blood spot; GE Healthcare).

[i]If point-of-care results are discordant, the point-of-care oral fluid and venipuncture whole blood DPP HIV 1/2 Assays are saved and stored.

[j]Ab/Ag: antibody/antigen.

[k]STD: sexually transmitted disease.

[l]GS HIV-1/HIV-2 Combo EIA (Bio-Rad Laboratories, Inc).

[m]If the STD clinic does not order an Ab/Ag test for clinical purposes, the Project DETECT research team will order the test to be performed by PHSKC Public Health Laboratory.

[n]NAT: nucleic acid testing.

[o]10-member pools using RealTi*m*e HIV-1 (Abbott Laboratories).

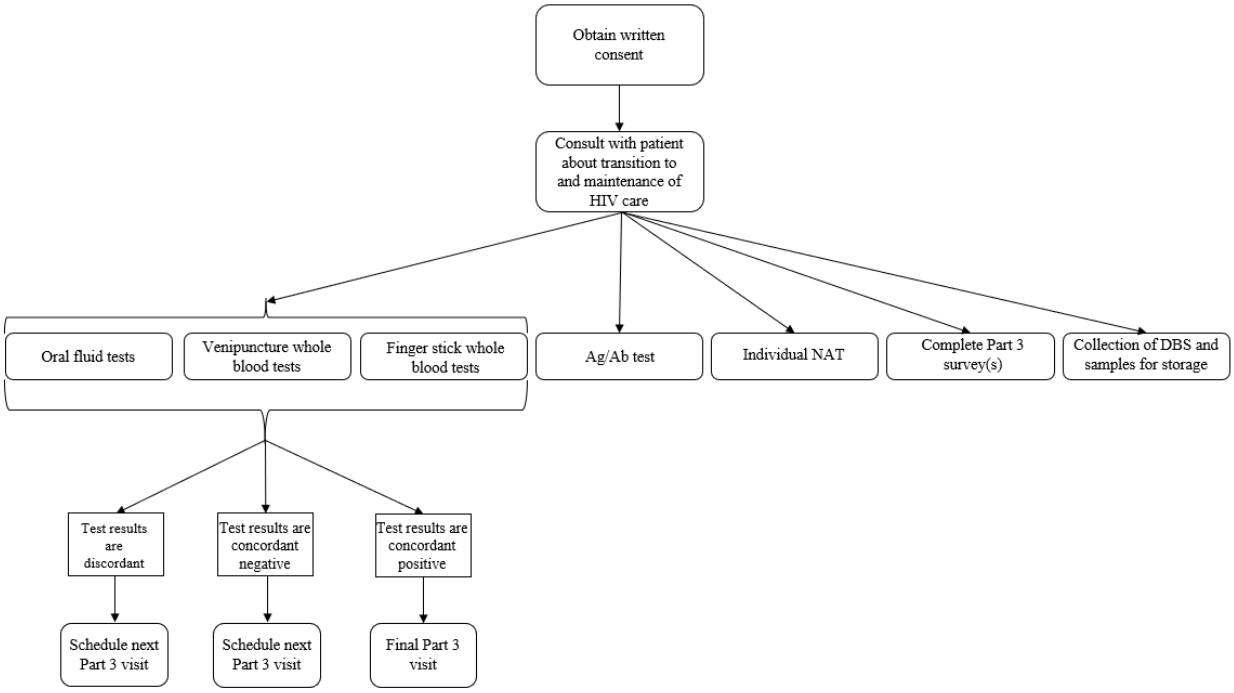
[p]Pooled NAT is performed only if participant is concordant negative on all point-of-care tests.

[q]RealTi*m*e HIV-1.

[r]Individual NAT is performed if participant has discordant point-of-care test results. Individual NAT has been validated for diagnostic and monitoring purposes.

[s]POC: point-of-care.

Figure 2. Project DETECT part 3 procedures. Ag/Ab: antigen/antibody; NAT: nucleic acid test; DBS: dries blood spot.



Specimen Storage and Shipping

At every visit, specimens are collected for processing, storage, and eventual shipping to CDC for creation of a specimen repository to retain samples to evaluate new and yet-to-be-developed HIV tests seeking US Food and Drug Administration (FDA) approval. These specimens include one Dual Path Platform (DPP) oral fluid swab, one OraSure oral fluid collection device, up to ten 1 mL plasma aliquots, and one dried blood spot (DBS) card. In addition, for all part 2 participants with discordant results on POC tests and all part 3 participants, study staff also store the DPP oral fluid swab and DPP whole blood specimens that were used for POC testing.

The repository includes the above specimens from the first 1000 part 2 participants with negative results on all HIV tests and all specimens from participants with at least one reactive HIV test result. These deidentified specimens will be associated with detailed behavioral data (described below) and available for public use in the future.

Behavioral Surveys

The PHSKC STD Clinic routinely collects medical and sexual history data from clients seeking clinical services using a computer-assisted self-interview completed at a kiosk in the clinic waiting area. Clients who do not complete the kiosk interview complete a supplemental form during their visit with their clinical provider. As part of the consent process, part 2–group 1 participants agree to have study staff create a link between their clinic and Project DETECT visits to reduce the number of survey questions asked during the study visit and link to HIV test results performed as standard of care at the clinic to the study record.

The three surveys specific to Project DETECT are programmed in Questionnaire Design Studio (Nova Research Company) in which participants are identified only by their study research ID number. Participants complete the part 2 survey, providing electronic affirmation of consent for study participation and specimen storage within the survey as well as demographics; history of HIV testing and recent STDs; symptoms of acute retroviral syndrome [16]; substance use; sexual behaviors, including group sex events [17]; and use of pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), and ART.

At every part 3 study visit, research staff complete the part 3 Symptom and Care Survey to characterize presence and duration of symptoms associated with acute retroviral syndrome over time as well as the timing of ART initiation; at the initial part 3 visit, the participant completes an affirmation of consent for research participation and specific consent for specimen storage for all specimens to be collected during follow-up. In addition to the Symptom and Care Survey, a part 3 behavioral survey is completed at either the participant's last study visit, if it occurred prior to visit 9 (approximately 70 days of follow-up), or at visit 9 and at the last study visit when follow-up extends beyond 70 days (Figure 2). At the beginning of the part 3 behavioral survey, research staff complete administrative questions that detail the reason for the final visit and then enter the nicknames of up to three recent male anal sex partners who were reported at the participant's part 2 visit to collect longitudinal data on partner-specific sexual behaviors. The participant then completes the remainder of the survey. This survey asks similar questions to the part 2 survey and is intended to evaluate changes in behavior following HIV diagnosis.

Data Collection and Statistical Analysis

Data sources for Project DETECT are shown in Multimedia Appendix 3. For part 1 analyses, Project DETECT staff receive a deidentified dataset from PHSKC staff that includes key sociodemographic variables for all PHSKC STD Clinic patients. The Project DETECT team uses these data to determine the number of clinical patients potentially eligible for Project

DETECT, report the participation rate, and describe the characteristics of the overall clinic population.

We present behavioral and demographic data for Project DETECT parts 1 and 2 as descriptive statistics (Table 2). When there is discrepancy, self-reported research data are prioritized over data collected as part of clinical care. When data were not available from the part 2 survey, clinic kiosk data completed by the participants at the clinic visit were used. If neither part 2 data nor clinic kiosk data were available, we used demographics as recorded in the clinic medical record to populate the variable. To define current gender identity, we applied a two-step method involving questions regarding sex assigned at birth and gender identity [18,19]. Participation rates for part 2–group 1 are reported as a proportion of the total STD Clinic population eligible for Project DETECT, although not all enrolled clients may be reflected in the eligible population due to errors or missing data in the clinical database.

Table 2.

Characteristic	Project DETECT[a] part 2–group 1 participant visits n=1525 n (%)	Project DETECT part 2–group 1–eligible PHSKC[b] STD[c] clinic visits[d] n=14,990 n (%)	Participation percentage
Age group in years			
18-24	299 (19.6)	2367 (15.8)	12.6
25-34	667 (43.7)	6588 (44.0)	10.1
35-44	306 (20.1)	2988 (19.9)	10.2
45-54	165 (10.8)	2050 (13.7)	8.0
≥55	88 (5.8)	997 (6.7)	8.8
Race/ethnicity			
Asian	112 (7.3)	1425 (9.5)	7.9
Black/African American	116 (7.6)	1107 (7.4)	10.5
Hispanic/Latinx[e]	239 (15.7)	2545 (17.0)	9.4
Multiracial	56 (3.7)	337 (2.2)	16.6
Native American	15 (1.0)	107 (0.7)	14.0
Pacific Islander	11 (0.7)	129 (0.9)	8.5
White	934 (61.3)	8814 (58.8)	10.6
Missing/no response	42 (2.8)	526 (3.5)	8.0
Current gender identity[f]			
Cisgender man	1468 (96.3)	14,566 (97.2)	10.1
Transgender woman	24 (1.6)	130 (0.9)	18.5
Transgender man	6 (0.4)	56 (0.4)	10.7
Nonbinary/genderqueer	24 (1.6)	217 (1.4)	11.1
Other	3 (0.2)	21 (0.1)	14.3
Sexual orientation			
Bisexual	190 (12.5)	1540 (10.3)	12.3
Gay	1109 (72.7)	11,188 (74.6)	9.9
Queer	60 (3.9)	585 (3.9)	10.3
Straight/heterosexual	33 (2.2)	265 (1.8)	12.5
Other	21 (1.4)	215 (1.4)	9.8
Missing/no response	112 (7.3)	1197 (8.0)	9.4
Reason for STD clinic visit (check all that apply)			
HIV follow-up visit[g]	59 (3.9)	537 (3.6)	11.0
Symptoms	361 (23.7)	3907 (26.1)	9.2
Want to be tested for STD	1005 (65.9)	8445 (56.3)	11.9
Referred from another clinic or doctor	30 (2.0)	493 (3.3)	6.1
Treatment or follow-up testing for STD	83 (5.4)	1349 (9.0)	6.2
Research visit	177 (11.6)	755 (5.0)	23.4
Contacted by the health department	59 (3.9)	804 (5.4)	7.3
Want to be tested for HIV	930 (61.0)	6257 (41.7)	14.9
Other	185 (12.1)	2465 (16.4)	7.5
Missing/no response	171 (11.2)	1143 (7.6)	15.0
STD diagnoses during the past year (check all that apply)			

Characteristic	Project DETECT[a] part 2–group 1 participant visits n=1525 n (%)	Project DETECT part 2–group 1–eligible PHSKC[b] STD[c] clinic visits[d] n=14,990 n (%)	Participation percentage
Chlamydia	281 (18.4)	3747 (25.0)	7.5
Gonorrhea	281 (18.4)	3997 (26.7)	7.0
Syphilis	98 (6.4)	1841 (12.3)	5.3
Missing/no response	171 (11.2)	1143 (7.6)	15.0
Substance use during the past year (check all that apply)			
Injection			
Heroin	55 (3.6)	193 (1.3)	28.5
Methamphetamine	106 (7.0)	610 (4.1)	17.4
Other drugs	37 (2.4)	172 (1.1)	21.5
Noninjection			
Methamphetamine	180 (11.8)	1199 (8.0)	15.0
Missing/no response	171 (11.2)	1143 (7.6)	15.0
Ever tested for HIV?			
Yes	1450 (95.1)	13,360 (89.1)	10.9
No	51 (3.3)	429 (2.9)	11.9
Missing/no response	24 (1.6)	1201 (8.0)	2.0
Ever taken PrEP[h]			
Yes	441 (28.9)	5323 (35.5)	8.3
No	1055 (69.2)	6613 (44.1)	16.0
Missing/no response	29 (1.9)	3054 (20.4)	0.9

[a]DETECT: Diagnostic Evaluation To Expand Critical Testing Technologies.

[b]PHSKC: Public Health–Seattle & King County.

[c]STD: sexually transmitted disease.

[d]There are 27 Project DETECT part 2–group 1 participant visits that were recruited for Project DETECT based on anecdotal evidence of reported sex with men. There is no data evidence of reported sex with men but were included in the Project DETECT part 2–group 1–eligible PHSKC STD Clinic population because they enrolled in Project DETECT.

[e]Persons who identified as Hispanic or Latinx ethnicity were classified as Hispanic/Latinx regardless of race.

[f]Transgender women and transgender men have higher rates of misclassification due to inconsistent reports of sex at birth and current gender identity between the PHSKC STD Clinic kiosk and medical record.

[g]"HIV follow-up visit" was removed as a response option in December 2018.

[h]PrEP: pre-exposure prophylaxis.

Results

From September 2015 to March 2019, 1331 unique people completed 1819 Project DETECT part 2 research visits. During this period, there were 34,820 visits to the PHSKC STD Clinic by clients not known to be HIV positive, of whom 14,990 (43.05%) were considered to have been eligible for part 2–group 1 enrollment (Table 2). Of the part 2–group 1 eligible visits, 1037 unique people were enrolled and had a total of 1525 part 2–group 1 visits (Table 2). Of the 1037 unique people, 777 participants were seen for a single Project DETECT visit, 151 participants had two visits, and 109 participants had three or more visits. Overall, eligible STD Clinic clients were estimated to participate in approximately 10.17% (1525/14,990) of visits. Participation rates varied by client characteristics: higher rates were seen among younger persons; clients who reported attending the STD Clinic for a research visit (possibly including Project DETECT) or because they wanted to be tested for HIV; clients with no history of PrEP use; and those who reported substance use, specifically injection of heroin, during the past year. Lower rates of participation were seen among persons who had been diagnosed with at least one bacterial STD in the last year, were referred from another provider, were seeking treatment or follow-up testing for an STD, or had been contacted by the health department and asked to come into the STD Clinic.

During the same time period, 198 and 96 participants enrolled in part 2–groups 2 and 3, respectively (Table 3). The majority (241/294, 82.0%) of these participants were recruited from the ACTU or the Madison Clinic, a Ryan White–funded HIV clinic. Characteristics of Project DETECT participants were similar to those of current King County residents living with diagnosed

HIV infection [20]. Self-reported STD diagnoses in the previous 3 months ranged between 2.7% (8/294) and 7.8% (23/294) for part 2–groups 2 and 3 participants, with gonorrhea reported most often. More than half (168/294, 57.1%) of the participants reported current ART use; 35.4% (104/294) were ART-naïve at their study visit, the majority of whom were newly diagnosed with HIV (data not shown); 3.7% (11/294) had been ARV-exposed but were not currently on treatment at the time of their study visit; the remaining 3.7% (11/294) had no information on current treatment status.

Twenty-seven persons had discordant HIV test results in part 2 and enrolled in part 3 (Table 4). Participants were followed for a median of 33 days (IQR 10-209 days). Of the 22 participants who were truly HIV positive, 16 (73%) were on treatment at their first part 3 visit and 6 (27%) were ART-naïve. By their last visit, 4 (67%) of the 6 ART-naïve participants had started treatment while 2 (33%) remained ART-naive. Of 27 enrolled participants, 23 (85%) completed the full follow-up period per protocol, including 5 participants with false-positive test results. There were 10 of 27 (37%) participants who tested concordant positive at their final part 3 visit and were considered to be fully seroconverted. There were 8 participants who were discordant through follow-up: one had persistent discordance and 7 had persistent discordance with partial seroreversion, meaning at least one of the POC tests was positive and then became negative at a subsequent visit.

Specimens from Project DETECT are currently maintained in a repository at the CDC and are described by confirmed HIV status after the study visit, HIV test results at the study visit, and self-reported ARV status (Multimedia Appendix 4).

Preliminary data describing HIV test results and partial results from behavioral surveys are presented elsewhere [13,17,21-23]. A description and discussion of one Project DETECT participant with false-positive test results while receiving PrEP has been recently published [24].

Table 3. Characteristics of Project DETECT part 2–group 2 and group 3 participants (September 2015 to March 2019) compared with current King County residents living with diagnosed HIV infection as of December 31, 2017.

Characteristics	Project DETECT[a] group 2 and 3 participants n=294 n (%)	Current King County residents living with diagnosed HIV infection, Dec 2017[b] n=6907 n (%)
Project DETECT part 2 participants		
Group 2: patients with established HIV infection	198 (67.3)	—
Group 3: patients with acute or newly diagnosed HIV infection	96 (32.7)	—
Referral site/process		
AIDS Clinical Trial Unit/Madison Clinic	241 (82.0)	—
PHSKC[c] STD[d] clinic	38 (12.9)	—
Other site	1 (0.3)	—
Missing	14 (4.8)	—
Age group in years		
18-24	26 (8.8)	122[e] (1.8)
25-34	52 (17.7)	948 (13.7)
35-44	47 (16.0)	1445 (20.9)
45-54	74 (25.2)	2209 (32.0)
≥55	59 (20.1)	2169 (31.4)
Missing[f]	36 (12.2)	0 (0)
Race/ethnicity		
Asian	4 (1.4)	303 (4.4)
Black/African American	84 (28.6)	1340 (19.4)
Hispanic/Latinx[g]	39 (13.3)	924 (13.4)
Multiracial	15 (5.1)	387 (5.6)
Native American	10 (3.4)	50 (0.7)
Pacific Islander	2 (0.7)	27 (0.4)
White	94 (32.0)	3876 (56.1)
Missing	46 (15.6)	0 (0)
Current gender identity		
Cisgender man	232 (78.9)	6004[h] (86.9)
Cisgender woman	43 (14.6)	839[h] (12.1)
Transgender woman	4 (1.4)	59 (0.9)
Transgender man	0 (0)	5 (0.1)
Nonbinary/genderqueer[i]	4 (1.4)	—
Missing	11 (3.7)	0 (0)
Gender of sex partners in last year		
Cisgender male participants		
Men only	139 (47.3)	—
Women only	37 (12.6)	—
Men and women	18 (6.1)	—
Men and other partners	2 (0.7)	—
Men and transgender men	2 (0.7)	—
Men, women, and transgender women	2 (0.7)	—

Characteristics	Project DETECT[a] group 2 and 3 participants n=294 n (%)	Current King County residents living with diagnosed HIV infection, Dec 2017[b] n=6907 n (%)
Men, women, and transgender men	1 (0.3)	—
Women and transgender men	1 (0.3)	—
Women and transgender women	1 (0.3)	—
Men, women, transgender men, and transgender women	1 (0.3)	—
Cisgender female participants		
Men only	29 (9.9)	—
Women only	1 (0.3)	—
Men and women	1 (0.3)	—
Men and other partners	2 (0.7)	—
Transgender female participants		
Men only	3 (1.0)	—
Men and nonbinary/genderqueer partners	1 (0.3)	—
Nonbinary/genderqueer participants		
Men only	1 (0.3)	—
Men and women	1 (0.3)	—
Men and nonbinary/genderqueer partners	1 (0.3)	—
Men, women, transgender men, and other partners	1 (0.3)	—
No sex partners	36 (12.2)	—
Missing	13 (4.4)	—
Sexual orientation		
Bisexual	34 (11.6)	—
Gay	128 (43.5)	—
Queer	4 (1.4)	—
Straight/heterosexual	91 (31.0)	—
Other	1 (0.3)	—
Missing	36 (12.2)	—
Self-reported ART[j] status		
ART-naïve	104 (35.4)	—
ART-experienced but not currently on ART	11 (3.7)	—
Currently on ART	168 (57.1)	—
Missing	11 (3.7)	—
HIV RNA level at study visit		
Undetectable or <40 copies/mL	144 (49.0)	—
40-200 copies/mL	14 (4.8)	—
201-1000 copies/mL	10 (3.4)	—
>1000 copies/mL	119 (40.5)	—
Specimen not available[k]	7 (2.4)	—
Self-reported STD diagnosis in previous 3 months		
Chlamydia	18 (6.1)	—
Gonorrhea	23 (7.8)	—
Syphilis	22 (7.5)	—

Characteristics	Project DETECT[a] group 2 and 3 participants n=294 n (%)	Current King County residents living with diagnosed HIV infection, Dec 2017[b] n=6907 n (%)
Other STD	8 (2.7)	—
Missing	15 (5.1)	—
Substance use in previous 3 months		
Injection		
Heroin	38 (12.9)	—
Methamphetamine	69 (23.5)	—
Other drugs	6 (2.0)	—
Noninjection		
Methamphetamine	80 (27.2)	—
Missing	15 (5.1)	—

[a]DETECT: Diagnostic Evaluation To Expand Critical Testing Technologies.

[b]Data are from the HIV/AIDS Epidemiology Unit, Public Health–Seattle & King County and the Infectious Disease Assessment Unit, Washington State Department of Health. HIV/AIDS Epidemiology Report 2018, Volume 87.

[c]PHSKC: Public Health–Seattle & King County.

[d]STD: sexually transmitted disease.

[e]Includes unspecified number of persons ages 13 to 17 years.

[f]Age of participants is confirmed by medical record in the absence of a part 2 behavioral survey.

[g]Persons who identified as Hispanic or Latinx ethnicity were classified as Hispanic/Latinx regardless of race.

[h]Data do not specify cisgender.

[i]Category not used in PHSKC HIV/AIDS Epidemiology Report 2018.

[j]ART: antiretroviral therapy.

[k]No venipuncture whole blood was drawn at the study visit.

Table 4. Project DETECT part 3 enrollment and follow-up (September 2015 to March 2019).

Part 3 follow-up	Project DETECT[a] part 3 participants n=27 n (%)
Enrolled	27 (100)
Completed follow-up	23 (85.2)
False positive[b]	5 (18.5)
Concordant positive results with full seroconversion	10 (37.0)
Discordant through follow-up	8 (29.6)
Persistent discordance without seroreversion	1 (3.7)
Persistent discordance with partial seroreversion[b]	7 (25.9)
Lost to follow-up	4 (14.8)

[a]DETECT: Diagnostic Evaluation To Expand Critical Testing Technologies.

[b]A false positive is confirmed by a negative viral load result (target not detected) by the RealTi*m*e HIV-1 viral load assay (Abbott Laboratories).

[c]Seroreversion is defined as having at least one point-of-care test result that is positive or reactive followed by a negative or nonreactive test result at a subsequent visit.

Discussion

Principal Findings

Project DETECT is a study designed to evaluate the performance of POC HIV tests with oral fluids and venipuncture and fingerstick whole blood specimens and establish a specimen and data repository. This manuscript describes the current protocol and initial populations of persons recruited for study participation.

In the first 2 years of study enrollment, Project DETECT enrolled 1525 visits with persons who were HIV negative or unknown status. While these individuals represent a small proportion (10%) of the 14,990 eligible visits to the PHSKC STD Clinic, willingness to participate was high among people who were approached by study staff (data not shown). Clients

seeking HIV testing may have been more motivated to participate, and some clients may have been aware of the study from prior participation or word of mouth and attended the clinic specifically to participate in the study. Although a recent bacterial STD is a strong predictor of HIV acquisition, clients diagnosed with at least one bacterial STD were underrepresented in the study population [25]. There also may have been time, structural, or other barriers to enrolling clients in a research project when they needed to prioritize seeing a clinician for STD care.

During this same time, Project DETECT enrolled 294 persons into part 2–groups 2 and 3 who had established or newly diagnosed HIV infection. A panel of specimens is available from this group, who include HIV-positive persons who are ARV-naïve, ARV-experienced but not currently receiving ART, and ARV-treated. The number of HIV-infected participants and available specimens will increase as enrollment continues.

Participants also continue to enroll into longitudinal follow-up in part 3 when they have discordant HIV results in part 2, providing critical data on the window periods of different HIV tests and specimen types when performed in real time. Although we and others have evaluated POC tests in the past, either in cross-sectional studies [10,26] or on frozen plasma specimens [27-30], to our knowledge this is the first project to evaluate these tests longitudinally and in real time using the unprocessed specimens typical of POC testing. These data are necessary for CDC to provide guidance on the use of POC HIV tests and recommendations on the period for retesting persons at risk for HIV infection based on the test and specimen type.

Project DETECT is also the first research study in the United States to evaluate SAMBA, a POC NAT [14,15], for use in screening high-risk persons for acute HIV infection (including persons on PrEP) as well as its ability to monitor HIV-positive persons on ART for virologic failure. As new HIV test technologies and diagnostic approaches performed on unprocessed whole blood or oral fluid continue to reach the US market, the protocol described here can serve as a model for evaluating their performance.

Limitations

Project DETECT does have limitations that could impact the reproducibility or generalizability of some of our future findings. The majority of the HIV-negative study population consists primarily of cisgender MSM because of the epidemiology of HIV infection in Seattle, Washington [20], although there is no evidence that HIV test sensitivity varies by gender. Similarly, most HIV-positive participants are presumed to have been infected with subtype B virus, when it is possible they have another subtype. Finally, the high level of PrEP uptake among HIV-negative participants and ART among people with HIV in Seattle [31-33] may impact our estimates of the sensitivity, specificity, and window periods of the different HIV tests. However, these results provide critical information on test performance in the context of PrEP as communities across the United States and elsewhere continue to bring PrEP to scale. In particular, the use of SAMBA in Project DETECT will provide much needed information on the utility of screening for cell-associated DNA in addition to plasma RNA in populations receiving PrEP.

Next Steps

Additional analyses based on the Project DETECT protocol described here are in progress. Future reports will include descriptions of HIV test sensitivity, specificity, and window periods; an in-depth evaluation of SAMBA; and analyses of behavioral data to evaluate risks associated with participation in group sex events. Furthermore, the specimen repository and paired behavioral data will be used and disseminated by CDC to evaluate new HIV tests as they become available. The Project DETECT specimen repository now includes oral fluids, plasma, whole blood, and DBS from the first 1000 part 2 study visits in which participants tested HIV negative on all tests, from 390 part 2 visits in which participants had at least one HIV-positive test result, and from all 206 part 3 visits.

In July 2018, the FDA's Blood Products Advisory Committee met to discuss the potential reclassification of HIV POC and laboratory-based serological and NAT diagnostic devices from Class III (high-risk devices) to Class II (moderate-risk devices) [34]. If enacted, this reclassification will reduce regulatory burden and facilitate timelier access to HIV testing devices for clinicians and patients. CDC will continue to use data from Project DETECT or similar protocols to evaluate and report on the performance of POC HIV tests, including those that become available in the US market following reclassification.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Project DETECT part 3 visit schedule.

[DOCX File , 13 KB - resprot_v9i1e16332_app1.docx]

Multimedia Appendix 2
Project DETECT specimen collection and HIV testing.
[MP4 File (MP4 Video), 49678 KB - resprot_v9i1e16332_app2.mp4]

Multimedia Appendix 3
Characteristics of Project DETECT part 2 data.
[DOCX File , 12 KB - resprot_v9i1e16332_app3.docx]

Multimedia Appendix 4
Laboratory specimens from Project DETECT participants stored in the US Centers for Disease Control and Prevention specimen repository (September 2015 to September 2019).
[DOCX File , 14 KB - resprot_v9i1e16332_app4.docx]

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Abbreviations

ACTU: AIDS Clinical Trials Unit
Ag/Ab: antigen/antibody
ART: antiretroviral therapy

ARV: antiretroviral
CDC: US Centers for Disease Control and Prevention
DBS: dried blood spot
DDP: dual path platform
FDA: US Food and Drug Administration
IQR: interquartile range
MSM: men who have sex with men
NAT: nucleic acid test
PEP: postexposure prophylaxis
PHSKC: Public Health–Seattle & King County
POC: point-of-care
PrEP: pre-exposure prophylaxis
Project DETECT: Diagnostic Evaluation To Expand Critical Testing Technologies
SAMBA: Simple Amplification Based Assay
STD: sexually transmitted disease
UW: University of Washington

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Protocol

Development of a Core Set of Patient-Reported Outcomes for Population-Based Cancer Survivorship Research: Protocol for an Australian Consensus Study

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Abstract

Background: Core outcome sets seek to improve the consistency and quality of research by providing agreed-upon recommendations regarding what outcomes should be measured as a minimum for a population and setting. The problems arising from a lack of outcome standardization in population-based cancer survivorship research indicate the need for agreement on a core set of patient-reported outcomes (PROs) to enhance data quality, consistency, and comparability.

Objective: This study aims to identify a core set of PROs, representing the most important issues impacting on cancer survivors' long-term health, functioning and quality of life, to inform population-based research on cancer survivorship.

Methods: In Phase I, a list of all potentially important outcomes will be generated through focus group discussions with cancer survivors and a review of measures for assessing quality of life in cancer survivorship. The consolidated list will be advanced to Phase II, where a stakeholder consensus process will be conducted with national experts in cancer survivorship to refine and prioritize the outcomes into a core outcome set. The process will consist of a two-round Delphi survey and a consensus meeting. Cancer survivors, oncology health care professionals, and potential end users of the core outcome set with expertise in cancer survivorship research or policy will be invited to participate. In Phase III, recommended measures for assessment of the core outcome set will be selected with advice from experts on the assessment, analysis, and interpretation of PROs.

Results: As of April 2019, data collection for Phase I is complete and data analysis is underway. These data will inform the list of outcomes to be advanced into Phase II. Recruitment for Phase II will commence in June 2019, and it is anticipated that it will take 6 months to complete the three-step consensus process and identify a provisional core outcome set. The study results are expected to be published in early 2020.

Conclusions: Expert consensus-driven recommendations on outcome measurement will facilitate the inclusion of survivorship outcomes considered important by cancer survivors and health professionals in future research. Adoption of the core outcome set will enable comparison and synthesis of evidence across studies and enhance the quality of PRO data collected in cancer survivorship research, particularly when applied to address macro-level questions.

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KEYWORDS

cancer survivorship; quality of life; patient-reported outcomes; core outcome set; Delphi study; consensus

Introduction

Due to the increasing incidence of cancer and advancements in its detection and treatment, the number of people living with cancer as a chronic condition is increasing [1,2]. With improved survival comes new challenges, as secondary health problems and symptoms related to cancer and treatment can persist for years following diagnosis [3]. Adverse effects including functional and cognitive impairments, physical symptoms, risk of secondary cancers, comorbidities, and poor psychosocial outcomes can have debilitating and lifelong consequences for cancer survivors and their families [3]. Accordingly, the definition of treatment efficacy has moved beyond survival alone, and there is a greater emphasis on establishing the impact of treatments on quality of life [4]. Increasing efforts to quantify the subjective experience of illness, treatment, and side effects using patient-reported outcomes (PROs) have led to a proliferation in the number of patient-reported outcome measures (PROMs) available to assess aspects of health, functioning, and quality of life from the patient's perspective [4].

The potential uses of PRO data can be understood using the Lipscomb framework for cancer outcomes research, which proposes three arenas for the application of PROs: micro, meso, and macro [5]. At the micro or individual level, PRO data are used to support and enhance patient-centered care, patient-clinician interactions, and decision making in clinical settings [4]. At the meso or service level, PRO data are used to understand the variables that influence health outcomes. PRO data collected at a macro level can be used to monitor and understand trends in health outcomes across a population [5]. Although there are few established systems internationally for the routine collection of macro-level PRO data (known as PRO surveillance), there is increasing recognition that expanding and optimizing the role of cancer registries to include PRO surveillance would improve our understanding of the long-term trajectory of survivorship outcomes on a national scale [6].

A challenge in PRO research is the lack of standardization and comparability of scores from different PROMs. For any given outcome, there may be multiple measures developed for different purposes, populations, and disciplines. Core outcome sets have been proposed as a way of addressing these problems. A core outcome set is a recommended, standardized, and minimum set of outcomes to be measured and reported in research on a specific health condition and which should be agreed upon by relevant stakeholders [7,8]. By standardizing the outcomes that are examined across studies, use of core outcome sets can help minimize bias in outcome selection and reporting and facilitate data comparison and synthesis [9]. Core outcome sets have been developed for various diseases including cancer, but not for the assessment of long-term cancer survivorship concerns at a population level. Predominantly tumor-specific core outcome sets with a typically acute focus have been developed to facilitate standardized assessment of treatment-related symptoms and toxicities in clinical trials.

This study aims to develop a core outcome set, recommending what PROs should be collected as a minimum for surveillance of cancer survivorship concerns in Australia and how these outcomes should be measured. The need for a set of outcomes applicable to all cancers is underscored by research identifying issues common across cancer sites in the long-term [10] including psychosocial outcomes, fatigue, functional impairment, fear of recurrence, and limitations in health care and insurance access [11]. The core outcome set will be developed using recommended methods, including a Delphi consensus process. The Delphi technique is a well-recognized method for obtaining expert consensus on a defined problem [12] and is used frequently in health research and core outcome set development.

Methods

Study Design

The core outcome set will be developed using a comprehensive, stepwise approach based on recommendations for core outcome set development [7] and previous studies [13,14]. This approach draws on the lived experiences of cancer survivors, published literature, and expert opinion. The study design was informed by the Core Outcomes Measurement in Effectiveness Trials (COMET) initiative and the Outcome Measures in Rheumatology (OMERACT) initiative, which provide methodological guidance to support evidence-based core outcome set development [15,16]. The OMERACT framework was developed in rheumatology and proposes a recommended process for core outcome set development that can be applied to different health conditions [16,17]. Both initiatives agree that the development of a core outcome set requires consensus to be reached first on “what” to measure (ie, the core outcomes) and then on “how” to measure the outcomes (ie, the measures) [7]. Therefore, a list of recommended outcomes to be measured will be one deliverable independent of the recommended PROM(s) for assessing the outcomes. Given that PROMs are continually researched and improved, this will allow for periodical revision of the recommended measures, given new advances. The Core Outcome Set-Standards for Reporting (COS-STAR) statement will be used to demonstrate transparency and complete reporting. The statement comprises an 18-item checklist covering the minimum reporting requirements for the sections of a paper describing the development of a core outcome set [18].

The research will involve three phases:

- Phase I: Identifying all possible outcomes relevant to cancer survivorship via focus groups with cancer survivors and a review of available PROMs.
- Phase II: Reaching expert consensus on the most important outcomes for inclusion in the core outcome set.
- Phase III: Determining how to best measure the core outcomes.

This study has been approved by the University of South Australia Human Research Ethics Committee (application number: 200370)

Phase I: Generating a List of Possible Outcomes

In Phase I, a list of possible outcomes will be generated via two processes: (1) focus groups with cancer survivors and (2) a review of cancer survivorship PROMs.

Focus Groups with Cancer Survivors

Aims and Scope

Focus groups will be conducted with adult cancer survivors to explore their experiences of living with cancer and its impacts on physical, functional, social, and psychological health and wellbeing. Five focus groups of 8-10 participants will be held with cancer survivors in Adelaide and Sydney.

Participants

Adult cancer survivors who are over 18 years of age, English speaking, have been diagnosed with any type of cancer, and are not currently undergoing primary treatment will be eligible to participate. A diverse sample of participants in terms of age, geographical location and cancer type will be sought to ensure that a range of views are considered. Participants will be recruited via the networks of the University of South Australia and state and national cancer organizations. The study will be advertised on social media, the University of South Australia Cancer Research Institute volunteers website, and flyers posted at the University of South Australia

Format

The focus group discussions will be guided by open-ended questions about the long-term impacts of cancer and treatment on everyday life.

Data Analysis

A list of outcomes derived from the transcribed focus group discussions will be generated and organized into a conceptual PRO framework. The outcomes will be periodically reviewed and modified, where necessary, to ensure fit with the data.

Review of Cancer Survivorship Patient-Reported Outcome Measures

Aims and Scope

To determine the outcomes considered relevant in cancer survivorship research, an updated review of PROMs developed to assess quality of life in long-term cancer survivors will be conducted. In concordance with previous studies, long-term cancer survivors will refer to people who have been diagnosed with cancer, are not currently receiving primary treatment, and are likely facing challenges and symptoms unique to those experienced by cancer patients under treatment and the general population [19].

Inclusion Criteria

English-language papers describing the characteristics of PROMs developed to assess quality of life in long-term adult cancer survivors will be included. PROMs developed specifically for pediatric cancer survivors will be excluded.

Data Sources

Searches for peer-reviewed articles will be performed in Medline, EMBASE, CINAHL, Scopus, the Joanna Briggs Institute Database of Systematic Reviews, and the Cochrane Library. Indexing terms and subject headings for each database will be added.

Data Extraction

Identified articles will be classified based on the PROMs they refer to. For each measure, the intended population, number of items, included dimensions or constructs, study sample, scoring information, and tested validity and reliability will be extracted. A list of outcome domains will be extracted from the identified instruments and examined for overlap in content and terminology, consistent with the approach taken by Macefield et al [9] for esophageal cancer.

List Consolidation

The list of outcome domains will be used in Round 1 of the consensus process. To consolidate the list, the outcome domains derived from the focus groups and review will be combined and examined by the research team to ensure that there is no duplication and that definitions are clear. The following three criteria adapted from Reeve et al [10] will be required for inclusion of an outcome domain: (1) present across diverse cancer types, (2) attributable to cancer or treatment, and (3) amenable to patient self-report. Additionally, it is proposed that outcomes must be appropriate for the intended end use of PRO surveillance.

Phase II: Consensus Process

Delphi Method

The consensus process will incorporate a three-step modified Delphi method. The Delphi method involves administering sequential surveys anonymously to a group of selected experts. The process traditionally begins with open-ended questions that are subsequently refined through a series of rounds, interspersed with controlled feedback based on the group views, until consensus is reached [7,12,20]. This study will use a modified Delphi method, limited to two survey rounds and a final consensus meeting. The modifications to the Delphi method are beginning the process with purposely selected (rather than open-ended) questions and including a final face-to-face meeting. Key advantages of preselecting items are that it provides a solid grounding in existing evidence and can improve response rates [20]. Benefits of including a face-to-face meeting are that it allows panel members to interact and discuss, clarify, and justify their voting [21]. This approach has been favored over other consensus methods by participants and is perceived as highly cooperative and effective [22]. Both modifications are consistent with recommended methods for evidence-based core outcome set development [23].

Aims and Scope

To refine the list of outcomes identified in Phase I into a cancer survivorship core outcome set, key stakeholders will be invited to participate in an online Delphi survey. The list of outcome domains will be formatted into questionnaire items and participants will be asked to rate the importance of each item

for inclusion in the core outcome set, with higher scores indicating higher importance.

Participants

Recent methodological work has demonstrated the importance of receiving feedback from different groups of stakeholders in order to reach consensus on a core outcome set [8]. Therefore, three expert panels of approximately 25 participants will be recruited for the study: (1) adult cancer survivors, (2) clinicians (ie, physicians, nurse practitioners, and clinical nurse specialists with expertise caring for and treating people with cancer), and (3) other health care professionals (ie, allied health workers, psycho-oncologists, nurses) and potential end users of the core outcome set that have cancer survivorship expertise (ie, researchers, policy advisors).

Recruitment

As it is common practice to purposefully select experts to participate in a Delphi process, health and research professionals with cancer survivorship expertise will be identified via professional networks. Focus group participants will be invited to participate and, if necessary, additional cancer survivors will be identified via the same recruitment channels as the focus group participants. All identified stakeholders will receive an email outlining the aims and significance of the research, with a link to register their interest in participating. Online registration will be open for 4 weeks, and two reminder emails will be sent. Written consent will be obtained from the study participants.

Round 1

All registered stakeholders will receive an email detailing the study purpose, a participant information sheet, and a link to the online survey for Round 1. The participant information sheet will explain the study background and objectives, intended end use of the core outcome set, key definitions, and ethical considerations in lay terms. The survey will contain questions about participants' demographics and expertise in cancer survivorship and the list of outcome domains formatted into items. Participants will be asked to rate the importance of each item for inclusion in a core outcome set for surveillance of the long-term impacts of cancer on quality of life using the 9-point Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale for the quality of evidence of outcomes. The GRADE scale has been previously used in the development of core outcome sets involving the Delphi technique [14,24]. Scores of 7-9 indicate critical importance, scores of 4-6 indicate importance, and scores of 1-3 indicate limited importance. A blank text response option will be provided for participants to add nonlisted outcomes and explain their rankings if they wish to. Nonresponders will receive up to three reminders to participate.

Feedback and Round 2

Score allocations from Round 1, for each panel and overall, will be presented to participants along with the link to the Round 2 survey. A recent trial found that the type of feedback given to participants (ie, whether they received a summary of the voting for their own group, all groups, or all participants regardless of group) did not influence voting [25]. After receiving feedback, participants will be invited to rescore the outcomes from Round 1 as well as any additional outcomes suggested.

Consensus Definition

Items with a median score ≥7 and an interquartile range no larger than two units, that receive rankings of 7-9 by ≥70% of participants and 1-3 by ≤15% of participants after Round 2 will be eligible for inclusion in a provisional core outcome set and progressed to the consensus meeting. There are no universally agreed-upon consensus criteria in Delphi studies; these thresholds follow published recommendations and previous core outcome set development studies in cancer [23,26]. To ensure that outcomes considered important to individual stakeholder groups are not rejected without the opportunity for reflection, items for which consensus is ambiguous will also be discussed in the consensus meeting. Consensus will be deemed ambiguous if an outcome with a median score ≥7 has an interquartile range no larger than three units and ≥65% majority agreement for at least one panel.

Analysis of Voting

Descriptive statistics will be used to summarize the results for each round, including the median score for each item and percentage of ratings between 1-3, 4-6, and 7-9. The results will be presented for each panel and overall. A measure of the distribution of scores will be presented for each outcome domain considered in Round 2. This is recommended because major disagreement can be masked by cut-off scores, which do not capture the strength of minority opinion [27].

Consensus Meeting

After Round 2, 10-15 Delphi participants will meet to review, discuss, and agree on a final set of core outcome domains. The participants will be purposively sampled from those who completed both survey rounds to ensure a range of perspectives are represented.

Phase III: Instrument Appraisal and Selection

After reaching consensus on the core outcome domains, the final step will be to identify and select measures for their assessment. The PROMs identified in the review will be evaluated by applying the OMERACT Filter 2.0, a tool for selecting measures that summarizes three key measurement properties: truth, discrimination, and feasibility [17]. Truth refers to face, content, and construct validity; discrimination captures reliability and sensitivity to change; and feasibility refers to whether a measure can be applied in the intended setting, given the constraints of time, money, and interpretability [17]. The final selection of PROMs will be undertaken through consultation with the Quality of Life Office, which is a national resource funded by Cancer Australia that provides expert advice related to the design, assessment, analysis, and interpretation of PROs. Feedback on the final core outcome measurement set will be sought from the Delphi participants via an informal process.

Results

As of April 2019, data collection for Phase I is complete and data analysis is underway. These data will inform the list of

outcomes to be progressed into Phase II. Recruitment for Phase II will commence in June 2019, and it is anticipated that it will take 6 months to complete the three-step consensus process and identify a provisional core outcome set. The study results are expected to be published in early 2020.

Discussion

Problems arising from the heterogeneity of PROMs have been documented in cancer survivorship research [28] and other areas of health research [15]. A review of registries that systematically collect PRO for population-level surveillance of cancer survivorship outcomes recommended that consensus be obtained on a core set of outcome domains and measures to improve the consistency and comparability of data collected [28]. Adoption of the proposed core outcome set by researchers could enhance the quality of future research by helping ensure the inclusion of relevant survivorship outcomes that are important to consumers and the use of validated tools that are sensitive to survivorship. In addition to macro-level application, the proposed core outcome set could also guide researchers seeking to use survivorship PROMs in clinical trials or extended follow-up beyond acute settings. To maintain relevance, the core outcome set may need to be periodically checked and updated to reflect consequences of new treatment modalities.

This is not the first core set of outcomes to be developed for all cancers, although it is unique in its scope and intended end use. In 2011, the National Cancer Institute's Symptom Management and Health-Related Quality of Life Steering Committee led an international effort to identify a core set of patient-reported symptoms to be measured in all adult cancer treatment trials [10] as well as disease-specific core symptom sets for head and neck, prostate, and ovarian cancers [29-31] to be used in conjunction with the generic cancer set. Since self-reported symptoms offer important insight into intervention efficacy and toxicities, increased consistency of symptom assessment across trials using the patient-reported core symptom sets may help improve care quality for clinical trial participants [10]. Our study aims to promote consistent assessment across the growing number of systems collecting PRO data from cancer survivors at a population level. Therefore, agreement on a core set of PROs similar to the set developed by the National Cancer Institute but (1) representing the health, functioning, and quality of life issues that are important in long-term cancer survivorship (ie, not exclusive to disease and treatment-related symptoms) and (2) suitable for the purpose of macro-level surveillance (ie, not specific to clinical trials) is warranted [10,28]. Despite a shared aim of facilitating consistent assessment of PROs in research with cancer populations [10], the core outcome set developed by the National Cancer Institute will inform assessment of disease- and treatment-related symptoms in clinical trials, while the proposed core outcome set for cancer survivorship will play a complementary role in informing population-based surveillance of quality of life among cancer survivors beyond clinical settings.

In the Netherlands, Geerse et al [32] developed a core set of International Classification of Functioning, Disability, and Health (ICF) categories for health-related problems in adult cancer survivors. In addition to being based on the ICF, their Cancer Survivor Core Set differs from the proposed core outcome set in intended purpose and development methods. Three panels of 25 survivorship experts for colorectal, breast, and lung cancers participated in a two-round Delphi study where 265 ICF categories were used for item selection [32]. The resulting core outcome set included 19 items, 11 of which were linked to corresponding item(s) on at least one of three selected cancer survivorship PROMs. The intended application of the core outcome set developed by Geerse et al [32] is not specified, although the authors state that it could be used as a screening tool. In contrast, the proposed core outcome set is intended to reflect the most important and relevant survivorship issues beyond acute symptoms that should be collected in routine PRO surveillance in Australia. Item selection will be informed by existing PROMs and oncological PRO frameworks rather than the ICF. Adults of different ages with a diverse range of cancers will be represented in the development process. It will be beneficial to understand the similarities and differences in outcomes prioritized by the current Australian-led research and the core outcome set developed in the Netherlands.

We based the study methods on recommendations for evidence-based core outcome set development [23], guidelines for using the Delphi technique to obtain consensus on core outcomes [27], standards for core outcome set study design [33], and previous core outcome set studies with cancer populations that employed Delphi methods [26,34]. However, there is no agreed-upon methodology for developing a core outcome set. It is therefore unclear to what extent the results from this study would be concordant with those obtained in different settings, using alternate consensus methods, or applying different criteria. Despite these limitations, the study design is considered suitable for the scope and setting of this core outcome set and will allow a large and geographically diverse sample of stakeholders to participate.

Although there is little scientific evidence regarding the optimal number of Delphi rounds, two or three rounds have been frequently recommended [35] and commonly used in core outcome set development studies [23]. Given that we will undertake a rigorous process to identify, select, and refine the initial outcome list to be progressed into the Delphi and include a face-to-face meeting to agree on the final core outcomes, two survey rounds were considered sufficient. An advantage of restricting the number of rounds is that this can limit potential bias due to attrition, which is likely to increase with each round. A limitation of restricting the study to two survey rounds is that it may not be possible to confirm stability of voting, although this is generally thought to be a measure of internal reliability and not consensus. Instead, we will be measuring the extent to which participants agree with the statements under consideration (agreement) and the extent to which participants agree with each other (consensus) [36]. It is not possible to determine the validity of any specific definition of consensus in Delphi studies, but the proportion of ratings within a range is one of the most commonly employed consensus definitions and the median is considered the most robust measure of central tendency [36].

Another potential limitation is that we are conducting a review of cancer survivorship PROMs rather than of all outcomes that

have been examined in cancer survivorship research, and therefore, we may not identify all possible relevant outcomes. This risk will be mitigated by additionally identifying outcomes in Phase I from focus groups with cancer survivors and providing Delphi participants with the opportunity to suggest additional outcomes in Phase II.

This protocol describes the development methods for a core set of PROs to inform our understanding of the long-term impacts of cancer on survivors' quality of life at a population level. Since the proposed set represents the minimum outcomes that should be collected and reported on, it can be supplemented with other outcomes or measures relevant to a given study setting or population. By providing consensus-driven recommendations from stakeholders with expertise in cancer survivorship research, practice, policy, and lived experience, the study findings will facilitate the inclusion of meaningful survivorship outcomes and enhance the quality and comparability of PRO data collected in survivorship research, particularly when applied to address macro-level questions.

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Authors' Contributions

All authors contributed to the study conception and design. IR drafted the manuscript and ADH, ME, NC, and JM provided feedback on the draft. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

COMET: Core Outcome Measures in Effectiveness Trials
COS-STAR: Core Outcome Set-Standards for Reporting
GRADE: Grading of Recommendations Assessment, Development and Evaluation
ICF: International Classification of Functioning, Disability and Health
OMERACT: Outcome Measures in Rheumatology
PRO: patient-reported outcome
PROM: patient-reported outcome measure

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Corrigenda and Addenda

Correction: Examining the Effects of Mindful Eating Training on Adherence to a Carbohydrate-Restricted Diet in Patients With Type 2 Diabetes (the DELISH Study): Protocol for a Randomized Controlled Trial

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The authors of "Examining the Effects of Mindful Eating Training on Adherence to a Carbohydrate-Restricted Diet in Patients With Type 2 Diabetes (the DELISH Study): Protocol for a Randomized Controlled Trial" (JMIR Res Protoc 2019;8(2):e11002), noticed two errors in the author information of their publication.

Priyanka K Wali, MD, was inadvertently omitted from the author list of the manuscript. Dr Wali's name has now been included as the fifth author of the paper, between authors Sarah Kim and Hiba Abousleiman. Dr Wali's affiliation is:

> *UCSF Osher Center for Integrative Medicine, Department of Medicine, University of California San Francisco, San Francisco, CA, United States*

Furthermore, the affiliation for author Laura Saslow was incorrectly listed in the original published manuscript as:

> *UCSF Osher Center for Integrative Medicine, Department of Medicine, University of California San Francisco, San Francisco, CA, United States*

Laura Saslow's correct affiliation is:

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These changes do not impact the Acknowledgments or Conflicts of Interest statement, nor do they impact the equal contribution footnote.

The corrections will appear in the online version of the paper on the JMIR website on January 13, 2020, 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

A Crowdsourcing Open Contest to Design Pre-Exposure Prophylaxis Promotion Messages: Protocol for an Exploratory Mixed Methods Study

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Abstract

Background: In the United States, black men who have sex with men (BMSM) are disproportionately affected by HIV. Pre-exposure prophylaxis (PrEP) can reduce HIV incidence. However, real-world implementation of PrEP outside of clinical trials has identified racial disparities in PrEP awareness, uptake, and adherence. In the context of a long history of medical mistrust and power imbalances between scientists and community members, strategies to increase uptake of PrEP among BMSM should consider ways to ensure messages address the needs and priorities of the community. Crowdsourcing contests shift traditional individual tasks to a large group and may enhance community engagement.

Objective: This paper describes the research protocol of a contest approach to soliciting PrEP promotion messages among BMSM in Baltimore.

Methods: Open-contest implementation and evaluation will proceed as follows: (1) organize a community steering group; (2) develop platforms to solicit crowd input; (3) engage the community to contribute ideas through a Web-based forum and in-person events; (4) evaluate contest entries using both community panel judge assessment and crowd voting; (5) utilize mixed methods to evaluate feasibility, acceptability, and community engagement; and (6) disseminate contest results.

Results: This study was funded by the National Institutes of Health (National Institute of Mental Health: R34MH116725) in May 2018 and was approved by the institutional review board in April 2018. The open contest started in February 2019, and data analyses for the mixed method evaluation are expected to complete in December 2019.

Conclusions: The contest will potentially bring new ideas in developing more impactful and locally defined PrEP promotion campaigns. We will determine whether an open-contest approach is acceptable among BMSM in Baltimore. If successful, this study can inform future projects using a similar approach on how to identify and implement programs and policies that are more responsive to community needs and that build up community assets.

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KEYWORDS

crowdsourcing; HIV; pre-exposure prophylaxis (PrEP); sexual and gender minorities

Introduction

Despite the development of efficacious biomedical HIV prevention and treatment methods, the history of HIV/AIDS includes many examples in which most vulnerable populations have not equally benefited from proven biomedical interventions [1,2]. Significant racial and ethnic disparities in new HIV infections persist in the United States [3]. Black men who have sex with men (BMSM) have the highest rate of HIV infection in the United States, accounting for over half of all new HIV infections each year [4]. The US Federal Initiative to End the HIV Epidemic recommends enhancing pre-exposure prophylaxis (PrEP) uptake among those most at risk for HIV transmission in the United States [5]. However, emerging studies of populations at risk of HIV in the United States have identified racial disparities in PrEP awareness, uptake, and adherence [6-8]. Major social and structural barriers for PrEP uptake, such as stigma and mistrust of the health system [9], are often unaddressed, especially among racial minority men who have sex with men (MSM) [10]. Power dynamics between researchers and community members infrequently provide meaningful community engagement, ownership, and authorship in the process of research and program development, which create barriers to acquiring information that could drive better decision making for HIV program development and implementation. Research indicates stigma and mistrust of the health system as possible barriers to taking PrEP [9], especially among minority MSM [10]. This is problematic because minority MSM would benefit most from HIV-preventative treatment. Strategies to increase uptake of PrEP among BMSM should utilize a bottom-up approach, such as a community-engagement approach, and allow community members to play prominent roles in developing, vetting, and implementing PrEP campaigns and ensure messages can better address the needs and priorities of the community.

Crowdsourcing is "an approach to problem solving which involves an organization having a large group attempt to solve a problem or part of a problem, then sharing solutions [2]." Open contests [11], a form of crowdsourcing, allow members of a community to provide solutions to the problem in the form of a contest, and the crowdsourcing organization processes and consolidates these solutions into a unified product [12]. The solutions are expected to be highly relevant to the community because open contests explicitly incorporate local knowledge, culture, and style by directly involving a large number of community members in developing, vetting, and implementing ideas [13]. Open contests have collected new ideas or directions that address public health problems, such as identifying food deserts [14], improving sanitation [15], and sharing public health policy [13]. Multiple randomized controlled trials have provided evidence of the effectiveness of utilizing crowdsourcing approaches to improve sexual health [16-18]. This approach has yet to be fully realized as a method for improving the health and well-being of historically marginalized populations such as MSM. A recent scoping review stated that additional studies evaluating crowdsourcing to improve PrEP uptake are needed [19].

To tap into the community's attitudes and values, we will implement a crowdsourcing open contest to solicit PrEP promotion messages for MSM in Baltimore and will evaluate the persuasiveness of the crowdsourced messages. This paper describes the research protocol and explores the feasibility and acceptability of a crowdsourcing open-contest approach to soliciting PrEP promotion messages.

Methods

Overview

This open contest will be implemented in Baltimore City, Maryland. National HIV Behavioral Surveillance data in 2017 indicated that the HIV prevalence among BMSM was 44% in Baltimore [20]. Less than two-thirds (63%) of HIV-negative BMSM were aware of PrEP as compared with 87% of white MSM. Only 14% of BMSM reported taking PrEP in the past year as compared with 21% of white MSM.

Open-contest implementation and evaluation will proceed as follows: (1) organize a community steering group; (2) develop platforms to solicit crowd input; (3) engage the community to contribute ideas through a Web-based forum and in-person events; (4) evaluate contest entries using both community panel judge assessment and crowd voting; (5) use mixed methods to evaluate feasibility, acceptability, and community engagement; and (6) disseminate contest results.

Organize a Community Steering Group

A community steering group will be formed to represent various community-based organizations (CBOs), advocacy groups, and individuals who represent diverse segments of MSM communities. Members of the community steering group will be involved in every stage of the proposed study. The community steering group will meet bimonthly to provide guidance on how to promote the open contest to the communities and to assist with crowd recruitment strategies. The community steering group will also give suggestions for the study website design, contest prize structure, contest entry evaluation, and plans to disseminate findings.

Develop Platforms to Solicit Crowd Input Through Both a Web-Based Forum and In-Person Events

We will work with our crowdsourcing technical partner, Community Expert Solutions, to organize a customized website where the crowd can submit their ideas. Before launching the Web-based forum, an evaluation of the acceptability of the specific features of the website and effective strategies to recruit participants online will be conducted and assessed among members of the community steering group.

On the basis of our previous experience [21] and feedback from community members, complementing Web-based activities with strong in-person activities is an essential component of organizing more effective and inclusive contests [22]. In-person activities are intended to reach marginalized groups with limited internet access and are key to building a rapport and trust with local partners and contributors. Collaborating with local CBOs, we will participate in various community events to promote and explain the rules of the contest. Individuals can submit their

ideas during in-person events. Information about the open contest, including the call for challenges, criteria for judging, and contest prize structure, will be posted on the project website and distributed during in-person events.

Complex tasks, such as designing PrEP promotion campaigns, need to be broken down into small and discrete components to increase the probability that individuals will be able to contribute to the campaign. In this study, we will focus on generating novel content that can increase awareness and uptake of PrEP among BMSM in Baltimore. Content of interest in the current contest will be (1) hashtag (#) of the PrEP campaign and (2) a 1- or 2-sentence *call for action*. The criteria for judging will be shared with the crowd, but no examples will be provided to avoid cognitive fixation, which has been found to be a pervasive impediment to developing innovative ideas [23-25]. A contest prize structure will be developed based on the standard principles of the inducement prize contest theory [26] and with input from the community steering group. We will include both monetary and nonmonetary prizes and avoid focusing exclusively on the *winners*. The top 3 finalists will work with a team of experts to develop a final product of PrEP promotion posters.

Engage the Community to Contribute Ideas

We will design the open contest to be as inclusive as possible. The eligibility to participate in the contest will be limited to those who are aged 18 years or older because of human subject restrictions on involving minors in research. Individuals will be able to submit more than one entry. All individuals who submit contest entries will provide a Web-based informed consent and fill out a brief survey that includes questions on sociodemographics, sexual identity, and PrEP awareness and use. To elicit contest entries that are most likely to be relevant to local BMSM, we will implement a target recruitment of BMSM. Potential participants for the open contest will be recruited from a venue-based outreach (within CBOs and at community events), social media (project's Facebook, Instagram, and Twitter accounts), and word-of-mouth referral. Our recruitment team has developed a presence and strong partnerships with local communities and service agencies. There are no preestablished set points for knowing when a sufficient crowd threshold has been reached to yield crowd wisdom [27]. We will keep the contest submission open for 3 months and closely monitor the number of submissions. On the basis of our previous experiences with similar contests [19,21], we anticipate receiving 100 entries in 12 weeks.

Evaluate Contest Entries and Announce Finalists

We will implement a 2-step approach to select the top finalists. A community panel of judges will first evaluate deidentified submissions to select the top-10 finalist submissions. The judging panel will include community steering committee members, health communication experts, public health officials, and CBO staff. We will create a mechanism for the judges to remove themselves based on conflict of interest (ie, any financial, organizational, or other interest that could be perceived). We will then host an open call for the public to vote on the top-10 finalist submissions. We will create a poll hosted on the contest website to enable users to vote for their favorite submission. The top-3 finalists will be selected based on the evaluation from the panel of judges and the popular votes.

After consulting with the community steering committee, we will host a public announcement of the 3 finalists, potentially in concurrence with other community-driven events, such as gay pride events in Baltimore. No identifiable information will be released without individual consent. Wider participation from individuals and CBOs will also be recognized to increase awareness of pressing issues among key populations with hard-to-reach groups. This acknowledgment of contribution is critical because most individual submissions will not be awarded prizes. We will ask participants about continued engagement for future open contests so that the end of the first contest also serves as the beginning of a process of sustained community engagement [26].

Evaluate Feasibility, Acceptability, and Community Engagement

To explore the feasibility, acceptability, and community engagement of the open contest, we will conduct semistructured interviews with a purposive sample of 25 participants who (1) have participated in the open contest, (2) voted in the open contest, or (3) helped to organize the contest (eg, the in-person event). A preliminary interview guide will include major topics regarding expectations of participating in the contest, facilitators and barriers to contest participation, engagement in contest activities, and participants' experience throughout the entire process of the contest. The preliminary interview guide will be pilot tested with 3 to 4 participants from the community. Feedback will be subsequently incorporated into the interview guide after discussion with the steering group and principal investigator. The interview questions will be open ended to allow participants to share their own ideas and expand on issues that are important to them. The interviews will be conducted by 2 trained qualitative researchers. All interviews will be audio-recorded, transcribed verbatim, reviewed for accuracy, and uploaded to Atlas.ti 7.1 (ATLAS.ti Scientific Software Development GmbH) for coding. The coding scheme will be developed using an iterative and collaborative process. Furthermore, 2 research team members will first review each transcript, and an initial coding framework will be formed based on predetermined questions that are used to design the in-depth interview guide and identified emergent themes. Coded quotes will be then chosen by group consensus to illustrate the variation and most common responses within each theme. After discussion among investigators, the coding scheme will be revised to ensure the coding process incorporates a range of perspectives [28]. The final coding scheme will then be applied to the remaining interviews. One of the goals of this analysis is to expand the literature by examining the process of organizing an open contest, differentiating stages of contest engagement, and examining how contest engagement may influence behaviors.

We will also evaluate the open contest by collecting online engagement statistics. Online engagement measures will be extracted using Facebook, Instagram, and Twitter analytics for the project's social media sites and Google Analytics for the contest website. The measures of active online engagement include contest submissions, page follows (unique users who

subscribed to page update alerts), page visits (unique users who visited a page), and demographic (age range and sex) and geographic (city and country) information about unique users who visit the social media pages or contest website. Finally, the reach will be measured by the number of unique users who passively viewed any posted content from the contest's Twitter, Facebook, or Instagram pages. We will also examine the number of votes for each submission, page visits, and geographic information. These metrics have been used to examine the scope of community engagement for previous crowdsourcing contests [21].

Dissemination

At the end of the study, the findings related to the open contest will be disseminated to the community steering committee, CBOs, and local health departments. These materials will include information needed to implement a crowdsourcing open contest, common barriers and issues experienced by participants, a protocol for needs assessments, and training materials. We will also present the study findings to HIV-prevention scientists through publications and conference presentations. We will also deposit the messages and materials in an open access database.

Results

This study is funded by National Institutes of Health (National Institute of Mental Health: R34MH116725) in May 2018 and was approved by institutional review board in April 2018. The open contest started in February 2019, and data analyses for the mixed method evaluation are expected to complete in December 2019.

Discussion

The study will make important contributions to the literature on crowdsourcing and health promotion among BMSM. This project will result in the creation of BMSM community-engaged PrEP promotion campaign messages that will be fielded and evaluated in an urban setting. We will determine whether a crowdsourcing open-contest approach is acceptable among BMSM in Baltimore. PrEP promotion messages selected as the top finalists can serve as a template for future contests that will focus on visual images (eg, color photographs, black-and-white photographs, and videos of less than 1 min) and distribution networks (eg, social media networks, in-person businesses, and in-person social networks relevant to BMSM). The sequential organization allows us to utilize different types of crowd talent while linearly building on the overall theme. The open-contest processes are applicable to organizations or programs regardless of the size of the organization or program or resources available, thus allowing scalability. Evaluation data from this study will inform similar future studies among BMSM that will be conducted in the United States. The findings of this proposed study will potentially bring new ideas to Baltimore City for the development of more impactful PrEP campaigns. By partnering closely with local CBOs, this project will give members of the BMSM community the tools and capacity to perform similar activities and further strengthen the relationship between CBOs and the local government. Finally, this approach could be used to identify and implement programs and policies that are more responsive to community needs and build up existing community assets, which is critical for strengthening health systems [29].

Conflicts of Interest

AM owns Community Expert Solutions, the company contracted to build the contest website, design recruitment materials, and manage the social media pages for the contest. AM does not have any financial interest in the findings from the study. All authors declare no conflict of interest.

Multimedia Appendix 1
Resume and summary of discussion of NIH peer review.
[PDF File (Adobe PDF File), 62 KB - resprot_v9i1e15590_app1.pdf]

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Abbreviations

BMSM: black men who have sex with men
CBO: community-based organization
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis

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Protocol

Testing the Effectiveness and Cost-Effectiveness of a Combination HIV Prevention Intervention Among Young Cisgender Men Who Have Sex With Men and Transgender Women Who Sell or Exchange Sex in Thailand: Protocol for the Combination Prevention Effectiveness Study

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Abstract

Background: Pre-exposure prophylaxis (PrEP) is highly effective in the prevention of HIV acquisition, particularly for men who have sex with men (MSM). Questions remain on the benefits of PrEP and implementation strategies for those at occupational risk of HIV acquisition in sex work, as well as on methods to support adherence among young people who initiate PrEP.

Objective: The Combination Prevention Effectiveness study for young cisgender MSM and transgender women (TGW) aims to assess the effectiveness and cost-effectiveness of a combination intervention among HIV-uninfected young MSM and TGW engaged in sex work in Thailand.

Methods: This open-label, nonrandomized assessment compares the relative effectiveness of a combination prevention intervention with and without daily oral emtricitabine and tenofovir disoproxil fumarate (Truvada) PrEP with SMS-based adherence support. HIV-uninfected young MSM and TGW aged 18 to 26 years in Bangkok and Pattaya who self-report selling/exchanging sex at least once in the previous 12 months are recruited by convenience sampling and peer referral and are eligible regardless of their intent to initiate PrEP. At baseline, participants complete a standard assessment for PrEP eligibility and may initiate PrEP then or at any time during study participation. All participants complete a survey and HIV testing at baseline and every 3 months. Participants who initiate PrEP complete monthly pill pickups and may opt-in to SMS reminders. All participants are sent brief weekly SMS surveys to assess behavior with additional adherence questions for those who initiated PrEP. Adherence is defined as use of 4 or more pills within the last 7 days. The analytic plan uses a person-time approach to assess HIV incidence, comparing participant time on oral PrEP to participant time off oral PrEP for 12 to 24 months of follow-up, using a propensity score to control for confounders. Enrollment is based on the goal of observing 620 person-years (PY) on PrEP and 620 PY off PrEP.

Results: As of February 2019, 445 participants (417 MSM and 28 TGW) have contributed approximately 168 PY with 95% (73/77) retention at 12 months. 74.2% (330/445) of enrolled participants initiated PrEP at baseline, contributing to 134 PY of PrEP adherence, 1 PY nonadherence, and 33 PY PrEP nonuse/noninitiation. Some social harms, predominantly related to unintentional participant disclosure of PrEP use and peer stigmatization of PrEP and HIV, have been identified.

Conclusions: The majority of cisgender MSM and TGW who exchange sex and participate in this study are interested in PrEP, report taking sufficient PrEP, and stay on PrEP, though additional efforts are needed to address community misinformation and stigma. This novel multilevel, open-label study design and person-time approach will allow evaluation of the effectiveness and cost-effectiveness of combination prevention intervention in the contexts of both organized sex work and exchanged sex.

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KEYWORDS

HIV; prevention; pre-exposure prophylaxis; men who have sex with men; transgender persons; sex work; Thailand; cost-effectiveness

Introduction

Background

Although there have been remarkable scientific advances in HIV prevention and control, many HIV epidemics globally remain concentrated among key populations [1-4]. In particular, men who have sex with men (MSM) and transgender women (TGW) continue to experience high HIV incidence [1,4]. Expanding HIV epidemics among MSM and TGW are occurring in high- and low-income countries, in North and South America and in South and Southeast Asia [1,5]. Though contextually different settings, the United States and Thailand have observed similar epidemiologic trends in HIV infections, with the highest rates of new HIV infections reported in the youngest age strata, among young MSM aged 15 to 24 years (in the United States) and among MSM aged 18 to 21 years in Thailand [1,6]. In a recent report from the United Nations Children's Fund Thailand, 55% of young MSM in Bangkok reported being sexually active at or below age 15 years, and young MSM accounted for 41% of all new HIV infections in the country in 2013 [7]. A 2005 venue-based study of TGW in 3 urban settings in Thailand found that 8.4% of TGW aged 15 to 22 years were already living with HIV and being aged 13 years or younger at the time of anal sexual debut was associated with a 2.5-fold increased odds of HIV infection [8]. Young MSM and TGW who sell sex are consistently among the highest risk subgroups for HIV infection within key populations [9-11].

Pre-exposure prophylaxis (PrEP) is a powerful prevention tool with demonstrated efficacy and effectiveness among MSM and some promise of effectiveness among TGW [12] and has been met with high levels of anticipated acceptability among both populations [13]. Yet, observational studies, demonstration projects, and program data indicate that uptake, retention, and adherence to PrEP is insufficient in many settings [14]. The subset of young MSM and TGW who sell and exchange sex with men are at exceptionally high risk for acquisition and transmission but have been studied less than other MSM and TGW, making development and assessment of HIV prevention packages particularly urgent for these populations [1]. As significant numbers of young MSM and TGW may occasionally sell sex and may not identify or be organized as sex workers, outreach, engagement and prevention tools, and approaches must be tailored for these individuals to fit their dynamic risks [9].

Thailand has a history of long-standing community partnerships with organizations that advocate on behalf of populations that sell or exchange sex. This, coupled with the regional HIV epidemiology and cultural openness to the discussion of sex work and other forms of exchanged sex, makes Thailand an important setting for implementation science research of combination HIV prevention approaches with antiretroviral (ARV) drug–based components among young MSM and TGW who exchange sex. A large observational cohort of MSM and TGW in Bangkok has demonstrated high and sustained HIV incidence (11.1/100 person-years [PY]) among 511 young (aged 18-21 years) MSM and TGW who sold or exchanged sex. Incidence was elevated despite regular HIV testing and counseling, condom and lubricant provision, care for sexually transmitted infections (STIs), and a national program of universal and free ARV access [15]. This has direct relevance to HIV epidemics underway among young and minority MSM

and TGW in multiple settings. Understanding how to reduce HIV transmission rates in these contexts is a shared scientific challenge with common features at biological, behavioral, and network levels [16,17].

Study Objectives

The Combination Prevention Effectiveness (COPE) study for young (aged 18-26 years) cisgender MSM and TGW described here uses a combination prevention approach that was developed based on a modified Social Ecological Model (SEM). The SEM posits that individual-, couple-, network-, community-, and policy-level factors all impact an individual's risk for HIV and also likely affect uptake, adherence to, and cessation of combination HIV prevention modalities among young MSM and TGW [18]. To address the multilevel factors, the combination package of individual-level condom and lubricant distribution, HIV testing, and PrEP provision was developed and coupled with a structural community empowerment intervention. The package was made available in Thailand in 2014, when the Thai government was reviewing methods/mechanisms to provide daily PrEP for use among key populations as part of the National HIV programming for MSM and TGW [19]. The COPE study aims to assess the effectiveness and cost-effectiveness of this prevention intervention among HIV-uninfected young MSM and TGW who are engaged in sex work or who exchange sex in urban Thailand.

Methods

Summary

This study uses a mixed methods exploratory sequential design to develop and test the effectiveness of a combination HIV prevention intervention, with or without daily oral PrEP, in preventing HIV acquisition among young cisgender MSM and TGW who sell or exchange sex. The intervention and research methods are underpinned by ongoing community mobilization and informed by formative research, which is followed by an open-label implementation science study of intervention effectiveness and costing analysis.

The specific aims of this study are as follows: Aim 1 conducts formative research to assess the acceptability, feasibility, and optimal design of a combination HIV preventive intervention with and without daily oral Truvada PrEP for HIV-uninfected MSM and TGW in Bangkok and Pattaya, with a focus on MSM and TGW who currently sell sex to other men or who have sold sex in the previous 12 months. Aim 2 assesses the effectiveness of an open-label combination HIV preventive intervention with and without daily oral Truvada PrEP with mobile phone–based SMS support, among young MSM and TGW. Sub-aim 2.1 analyzes and describes the associations of sex work with sexual risk taking among young MSM and TGW, including numbers and types of partners and condom use, and assesses the impact of sex work, including transitions in and out of sex work, on PrEP uptake, adherence, and cessation among young MSM and TGW. Aim 3 assesses the incremental costs associated with combined HIV prevention with PrEP use, the number of infections averted through PrEP use, the discounted treatment costs saved, and the discounted disability-adjusted life years (DALYs) averted to assess whether the use of PrEP relative to the standard intervention is cost-saving, highly cost-effective, cost-effective, or not cost-effective.

Community mobilization principles guide the study design and implementation to optimize implementation, the value of results obtained, and translation of study findings to practical use. At the foundation of the community engagement is ongoing input and coordination with local community-based organizations (CBO) who work with MSM and TGW communities in Bangkok and Pattaya.

Setting and Context

In Thailand, sex work is not legal, but there are open and clear channels for community engagement. There is an openness and accessibility to those practicing sex work, and a substantial sex tourism industry, estimated to be US $6.4 billion a year as of 2015 [20,21]. The COPE study is centrally focused on PrEP implementation and effectiveness for young MSM and TGW who are engaged in sex work or otherwise exchanging sex for money, substances, or other items of value (here forward broadly referred to as *exchange*) in Bangkok and Pattaya, and who are at highest risk for HIV acquisition. As the early period of exchanging sex is a very high-risk period for HIV acquisition, this study aims to address risk for young MSM and TGW who are newly entering sex work or exchanging sex.

The study was initially proposed for MSM engaged in the sex work/exchange but was expanded to include TGW in response to community requests. Sexual and gender identities are not distinct in Thailand as they are in Western cultures, and although we use terms MSM and TGW that are accepted in the scientific literature, these broadly include approximately 15 unique identities that encompass both sexual and gender identities and expression [20,22]. MSM and TGW who exchange sex have overlapping communities and venues and are often served by the same organizations; thus, it was determined to be appropriate and equitable to extend this intervention to both groups.

This research effort is highly integrated with Thailand national policy development around the integration of PrEP into national HIV programming for MSM and TGW. The government provides free PrEP to key populations through community-based programs but has called for the development of appropriate implementation models for PrEP and cost-effectiveness analyses to support policy decisions on government-supported PrEP distribution for key populations. As a result, several community-based clinics have been established and trained to provide PrEP, including clinics operated by the Rainbow Sky Association of Thailand (RSAT) and Service Workers In Group (SWING) Foundation.

The COPE study is supported by a joint collaboration between the Thai Ministry of Public Health (MOPH) and the United States Centers for Disease Control and Prevention (US CDC; known as the Thai-US Collaboration [TUC]) and in partnership with Mahidol University, Emory University, Johns Hopkins University School of Public Health, CBOs, SWING, RSAT, and the Asia Pacific Coalition on Male Sexual Health (APCOM). Primary implementation is at Silom Community Clinic (SCC) Clinical Research Site, operated by TUC. All recruitment and study implementation activities are done through

SCC, SWING, and RSAT sites in Bangkok and SWING in Pattaya. Each study site has a site coordinator who provides oversight on study activities and communicates regularly to the multisite coordinator and study coordinator. Research teams also provide a physician-in-charge who is responsible for all clinical activities and care provided at each study site.

Community Mobilization

Community engagement principles and mobilization activities are intended to create an enabling HIV prevention environment for young MSM and TGW. For this study, our partners SWING and RSAT serve as the initial conduit for community engagement. These partners have extensive experience in providing HIV prevention programs to gay, bisexual, transgender, and other MSM, including those who exchange sex.

The chief community mobilization activity is an ongoing series of forums targeting various venue types, age groups, and geographic subzones that are led by CBO staff in conjunction with young MSM and TGW. Point persons at participating venues who introduce the study also aid in raising awareness about and invite participants to community engagement activities. Forums can range in size from 5 to 50 community participants, depending on the venue and focus. In some cases, activities may be combined with larger community events, such as PRIDE and Songkran events, facilitating more space and engagement of more participants. Community engagement activities are ongoing through the life of the study, although participants in the community engagement activities can determine the frequency in which they participate in the events. Community mobilization facilitates scientific literacy specific to PrEP and acceptability and engagement with this HIV prevention strategy, building on gaps and concerns identified by young MSM and TGW in an earlier qualitative phase of this study. We anticipate that the community mobilization process will create an enabling, supportive environment to collectively identify and address broader issues of concern to the young MSM and TGW communities.

Through these forums and supportive activities, young MSM and TGW may (1) reflect on PrEP implementation, including any perceived implementation barriers and concerns about acceptability and uptake across the SEM, and (2) identify, prioritize, and address broader problems facing the community. We anticipate that issues will be raised across the SEM, for example, risk perception, culturally competent care, stigma related to HIV and/or PrEP, and structural risk sources such as owner/manager issues. In turn, the forums provide a mechanism for mounting a community-led response, by which we anticipate that young MSM and TGW will take on increasing leadership roles, and the group will iteratively identify problems and develop shared goals and activities deemed to be meaningful, safe, and feasible. The meetings also provide ongoing feedback to identify PrEP-related questions or concerns among forum members, including the ethical considerations noted in the "Ethical Review" section of this paper. This intervention element targets the community level; thus, activities are not limited to study participants and are open to all young MSM and TGW who meet age eligibility criteria.

Formative Research

Formative, qualitative research among young MSM and TGW engaged in sex work informs the development of recruitment and advertising campaigns, study methods, combination prevention package, and community empowerment methods. Key informant interviews (KIIs) provide preliminary information about the acceptability, feasibility, and optimal ways to deliver combination of HIV preventive interventions to these communities.

Qualitative data collection focuses on 2 groups: (1) young MSM and TGW with a recent (within previous 12 months) history of having sold or exchanged sex and (2) the management and other staff in sex work venues. To participate in the qualitative research, MSM and TGW must meet the following eligibility criteria: aged 18 to 26 years, male assigned sex at birth, Thai nationality, able to speak and read Thai, report selling or trading sex to men in the last 12 months, currently living in the Bangkok metropolitan area or Pattaya, and willing to give written informed consent to participate.

SWING estimates that there are more than 65 venues with staff and management already participating in HIV outreach and education activities from which participants can be drawn. Two to three staff are invited to participate from each participating venue. Venue staff and management are eligible if they are aged greater than or equal to 20 years, Thai nationality, worked for one of the identified sex work venues for at least 12 months, and willing to give written informed consent.

Recruitment comprises a maximum of 132 participants (76 young MSM and TGW who have exchanged sex and 56 venue staff/managers) for KII. In this study, each participant can provide one KII only. Participant numbers and numbers of events will be determined when saturation of information has been achieved, insofar as additional interviews do not provide additional useful information beyond what has already been gained through prior interviews.

A short questionnaire is used to assess key sociodemographic characteristics and risk behaviors. A qualitative interview guide is used to guide conversations. Guides for use among young MSM and TGW include the following domains: knowledge and attitudes toward existing HIV prevention services; perceived accessibility of existing services; barriers to service use including stigma, knowledge, and local practices around issues concerning sex, and sex and substance use; perceived structural/contextual factors influencing sexual decision making; appropriate messaging/logos for educational materials; appropriate mechanisms for recruitment into the subsequent effectiveness evaluation; and feasibility and acceptability of community mobilization activities including perceived willingness to participate across subpopulations, and optimal timing, location, and scope of community mobilization activities. Guides utilized for KIIs with venue staff include the following research domains: knowledge of the local context of sex work and exchange; perceived ability and barriers to provide health care services to young MSM and TGW in venues or off-site; attitudes and perceptions of venue staff regarding HIV status of employees, of HIV testing, and of worker autonomy, privacy, and choice of HIV status disclosure, and acceptability and

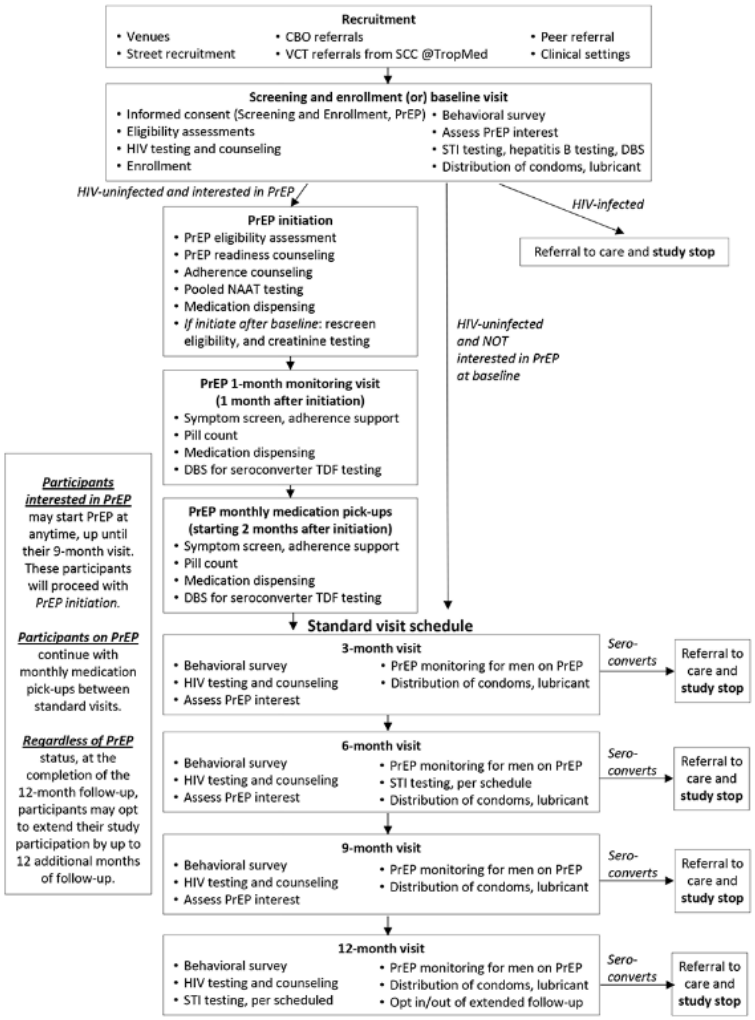
perceived barriers to community mobilization activities. All interviews are anonymous, conducted in Thai, and recorded using digital audio recorders, with participant consent. Participants are offered a modest reimbursement for travel and their time, 800 Thai Baht (THB) per session (approximately US $25).

Using the Thai transcripts and English-language translations, study staff conduct coding of text in Atlas.ti (Scientific Software Development). Study staff review transcripts to develop an initial coding scheme specific to the chief aims. An initial set of transcripts for each group (ie, young MSM and TGW and venue staff) are coded by 2 separate reviewers on the coding team; once agreement on core constructs is achieved, the coding team independently codes the remaining interviews, while staying in communication to identify and discuss emergent themes. For this formative study, field notes and preliminary results are also consulted as needed for timely use of these data.

Intervention Effectiveness Study Design

The study is an open label, nonrandomized assessment comparing the relative effectiveness of a combination preventive intervention with and without daily oral tenofovir/emtricitabine (FTC; Truvada) PrEP with adherence support. We follow those young MSM and TGW who choose to initiate PrEP as part of the combination package, and those who agree to participate but do not choose to start on PrEP, for whom all other intervention components will be offered. The outcome will be assessed using a person-time approach, assessing HIV incidence densities among young MSM and TGW on and off daily oral PrEP over 12 to 24 months of follow-up. Participants are enrolled for a standard follow-up period of 12 months; however, given the importance of remaining on PrEP for people in high-risk contexts, we offer the option to re-enroll for an additional 12 months. All participants, regardless of PrEP status complete quarterly study visits and weekly, brief behavioral SMS surveys. Participants who initiate PrEP are required to attend monthly medication pickup visits. Figure 1 displays the flow diagram of the study with a brief description of study visit activities.

Figure 1. Study flow diagram and participant study visits for the Combination Prevention Effectiveness study for young men who have sex with men (MSM) and transgender women (TGW), Thailand (2015–2020). CBO: community-based organization; DBS: dried blood spots; NAAT: nucleic acid amplification test; PrEP: pre-exposure prophylaxis; SCC: Silom Community Clinic; STI: sexually transmitted infection; VCT: voluntary counseling and testing.



Combination Prevention Intervention

All participants will receive regular (every 3 months) HIV testing with risk-reduction counseling. Participants who have negative HIV rapid test results are counseled on the benefits of using PrEP in preventing HIV infection. This counseling includes a clear message on the efficacy of PrEP, discussion of barriers to initiating PrEP, and potential solutions to address these barriers. Although participants are not required to initiate PrEP as part of the study, study staff regularly promote the benefits of PrEP uptake. Condom and condom-compatible lubricant distribution occur at every study visit, including monthly medication pickups for those using PrEP. Syphilis, rectal gonorrhea, and chlamydia screenings with treatment for all identified infections are conducted every 6 months beginning at the baseline visit.

Daily Oral Pre-Exposure Prophylaxis

Daily oral PrEP with adherence support is offered to all participants (open label). Tenofovir disoproxil fumarate (TDF) and FTC (locally known as Teno-EM) is approved for PrEP in Thailand. The PrEP drug for the COPE study is Truvada, which contains identical chemical components as Teno-EM. The tablet includes 200 mg of FTC and 300 mg of TDF. Truvada is approved for treatment in Thailand (registration number: 2C 28/2551[NC]) and is manufactured and donated by Gilead Sciences for the COPE study. Truvada is a once daily oral tablet taken with or without food.

Participants who take PrEP are counseled on the mild side effects that are expected with Truvada including nausea, headache, abdominal pain, rash, and flatulence. They are also counseled to avoid medications with potential drug interactions as outlined in the 2014 Clinical Practice Guideline, CDC [23]. These include acyclovir, valacyclovir, cidofovir, ganciclovir, valganciclovir, aminoglycosides, high-dose or multiple nonsteroidal anti-inflammatory drugs, or other drugs that reduce renal function.

Participants on PrEP have monthly medication pickups for the entire duration they are using PrEP. At each monthly medication pickup, participants return to their selected clinic for the following procedures: unused medication drop-off, tablet count adherence, dispensing of one 30-tablet bottle of Truvada; collection of dried blood spots (DBS) for storage; assessment of signs and symptoms of acute HIV infection; assessment of side effects associated with PrEP use; and adherence assessment and counseling, informed by weekly SMS survey responses.

Short Message Service–Based Adherence Support

SMS-based adherence support is provided as part of the combination package with PrEP, in addition to standard adherence counseling. Adherence has been a significant challenge to the efficacy of PrEP and may be an important challenge for PrEP effectiveness. A 2014 systematic review and meta-analysis demonstrated that text-messaging interventions effectively supported adherence to PrEP more than control groups and were also associated with improved viral load and/or CD4 counts for individuals on antiretroviral therapy (ART) [24]. Text message reminders that were sent less frequently than daily tended to have greater effects [24]. Weekly SMS adherence prompts are therefore offered to participants choosing PrEP. SMS adherence prompts are dispatched through FrontlineSMS, with additional management by the research team. For participants agreeing to weekly prompts, participants' FrontlineSMS profiles are configured for adherence messaging at the visit in which they initiate PrEP. The FrontlineSMS participant profile can be updated for any changes in PrEP use or for changes in timing of prompts, mobile device numbers, or carrier.

Study Population

Eligible young MSM and TGW participants must meet the following key criteria: assigned male sex at birth; aged 18 to 26 years; HIV-negative at baseline testing; self-report that they have sold or exchanged sex to cis-gender men for money, drugs, or other goods in the past 12 months; self-report living in greater Bangkok metropolitan area or Pattaya; are Thai citizens; and are willing and able to complete study instruments. Participants do not have to self-identify as MSM or TGW, although such terms will be used in recruitment scripts to attempt to recruit participants from these populations.

Additional eligibility criteria for PrEP includes the following: HIV-negative at the visit (if acute HIV symptoms, can start PrEP at a subsequent return visit if the nucleic acid amplification test [NAAT] is negative); estimated creatinine clearance (eCrCl)≥60 mL/min; no major known allergy to tenofovir and/or FTC or the combination of the two; and able and willing to follow the PrEP prescribing guidelines.

Recruitment and Consent

Convenience sampling methods are used, recruiting participants from a variety of venues including bars, clubs, saunas, brothels, karaoke parlors, cabarets, street-based locations, and other venues frequented by young MSM and TGW. These currently include 68 venues mapped by SWING in their 2015 census of venues in Bangkok. Outreach and recruitment are conducted by staff who have been trained in confidentiality and study procedures.

Recruitment also occurs online, using materials such as videos and fliers developed in collaboration with the community and produced by APCOM [25]. Staff are trained on how to avoid coercing individuals to participate in the study. Recruitment materials are posted on dating apps, Facebook, and other frequently used online venues. These recruitment materials also serve to raise awareness about and increase demand for PrEP. In addition, the study website, study clinic websites, and Facebook pages are used to provide community-wide access to information about services and the goals of the study [26]. All interested individuals are invited to contact the study staff for preliminary screening and to learn more about the study. Figure 2 displays an example study flier for MSM and TGW.

Study participants are invited to refer peers to the study. Participants are provided study information cards that they can distribute to potentially eligible peers who are MSM or TGW who are newly engaged in sex work or who have recently exchanged sex. Referred peers may be enrolled into the study upon meeting inclusion criteria. Participants who successfully recruit peers are compensated per similar standard practices

implemented in the LINKAGES program in Thailand to support peer referral to HIV testing and care [27]. Study participants will be reminded to maintain confidentiality before referring peers and distributing information cards.

Candidate participants are not screened in person during recruitment events or peer or community referrals. Interested individuals are provided study information cards with a phone number, email address, and link to a website with more information about the study eligibility criteria, purpose, available clinics, and clinic hours. Interested individuals may indicate whether they would prefer to call the study offices to schedule an appointment at their own convenience or to provide their phone number and be contacted by study staff. During the initial phone call with study staff, candidate participants are informed of the study purpose and eligibility criteria and determine whether or not they would like to proceed with study recruitment. Aggregate data are collected from these phone calls on the number of individuals contacted or who contacted the study, those that were scheduled, and reasons not scheduled.

Consent is obtained from recruited young MSM and TGW, and they are screened for eligibility in private at one of the study sites. Those who are eligible are enrolled in the study. The screening visit includes an assessment of demographic criteria and rapid HIV testing. Participants identified with HIV infection complete their screening visit, including facilitated referral to care but do not attend any study follow-up visits. Participants who are determined to be living with HIV at their screening visit do not count toward the target sample size. At baseline, participants are also screened for hepatitis B and may initiate the vaccine series during follow-up, if susceptible.

Participants who are identified as being HIV-uninfected by rapid HIV testing are prospectively enrolled into the study. Enrolled participants are offered a combination prevention intervention package, with the option to initiate daily PrEP. Prospectively enrolled participants have an initial follow-up period of 12 months; participants who complete their 12-month follow-up period, regardless of PrEP initiation status, are offered the option of further extending their follow-up for another 12 months if the study timeline permits.

Figure 2. Promotional flier for the Combination Prevention Effectiveness Study for young men who have sex with men and transgender women, Thailand.

Study Visits

Participants, regardless of PrEP initiation, have standard follow-up study visits every 3 months (quarterly) that include HIV testing and counseling, condom and lubricant distribution, and surveys using computer-assisted self-interview (CASI) or with audio-assisted CASI (ACASI) technology. Participants are screened for syphilis, rectal gonorrhea, and chlamydia at their baseline study visit and every 6 months (semiannually) thereafter. Table 1 describes data collection activities that take

place quarterly or semiannually, regardless of PrEP use. Through these visits and biological and survey outcomes, the study staff are able to assess the acceptability, uptake, adherence, and effectiveness of the combination intervention package for young MSM and TGW.

At any time during the study period from baseline to the 9-month visit, participants can be screened for PrEP eligibility with point of care creatinine testing. If eligible, they can initiate PrEP at that visit. Ineligible participants, or participants who do not express an interest in initiating PrEP during the initial 9-month study period may continue study participation as non-PrEP participants. Non-PrEP participants complete quarterly study visits and receive all standard procedures, including the CASI, HIV testing, hepatitis and STI testing, and DBS collection.

All participants initiating PrEP complete a PrEP monitoring visit 1 month after PrEP initiation to assess for acute HIV symptoms and provide adherence support. Participants on PrEP are then asked to complete monthly visits for medication pickup. Medication pickups can be combined with quarterly study visits during months in which they are due.

Participants can initiate, discontinue, and restart PrEP at any point during the study period. Changes to PrEP use can be communicated during any study visit, via weekly SMS surveys, or can be communicated to study staff outside of study visits. Reasons for discontinuing PrEP are recorded. Participants who restart PrEP after more than 2 weeks cessation must be rescreened. Study investigators consider someone stopped on PrEP if the participant's weekly SMS adherence measures indicate that he/she had 2 consecutive weeks with 0 to 3 doses taken, or if the participant has >16 pills remaining from the month during a medication pickup. PrEP rescreening includes HIV testing and an assessment of willingness to commit to PrEP adherence. Participants who stop PrEP may continue in the study and continue with their remaining quarterly study visits. Participants who permanently stop PrEP or who do not want to immediately restart PrEP are instructed to return all Truvada as soon as possible.

Participants who seroconvert during the study period complete a close-out survey, receive facilitated referral to care with assistance by the case manager or site coordinator at each site, are discontinued from the study and do not attend subsequent study visits.

Table 1. Description of quarterly and semiannual study visits for the Combination Prevention Effectiveness Study for cisgender men who have sex with men and transgender women, Thailand.

Study visit	Description
Quarterly study visits (every 3 months)	• Confirm participant contact and locator information • Administer CASI[a] behavioral questionnaire • Assess participant experience and impacts of study participation (including adverse events and social harms) • Screen for signs and symptoms of acute HIV infection • Provide HIV testing (including pooled NAAT[b] testing if the participant has symptoms of acute HIV infection) • Collect DBS[c] for storage • Distribute condom and lubricant
Semiannual study visits (every 6 months)	• All procedures conducted at quarterly study visits • Syphilis testing • Rectal swab collection for rectal gonorrhea and chlamydia testing • Serum creatinine measurement and estimated creatinine clearance calculation (for participants on PrEP[d])

[a]CASI: computer-assisted self-interview.

[b]NAAT: nucleic acid amplification test.

[c]DBS: dried blood spots.

[d]PrEP: pre-exposure prophylaxis.

Behavioral Survey

Sociodemographic and behavioral data are collected from all participants at baseline and at each follow-up visit using a standard survey. The survey is administered using CASI or ACASI depending on participant preference. Use of CASI on a standard personal computer or tablet occurs in a structurally secluded and quiet area at the study clinic to ensure confidentiality and to encourage candid disclosure of risk behavior. Trained staff are available to answer questions pertaining to the survey questionnaire.

Survey questionnaires span the following domains and are administered over the course of the study: sociodemographic; knowledge, awareness, and use history of PrEP, postexposure prophylaxis, or ART; health care utilization; engagement in the lesbian, gay, bisexual, and transgender (LGBT) communities; postrecruitment questions; sexual risk behavior; stigma; substance abuse; and mental health. Additional information on the focus of each domain is provided in Table 2.

Table 2. Sociobehavioral survey domains, descriptions, and measures for the Combination Prevention Effectiveness study for young cisgender men who have sex with men and transgender women, Thailand.

Domain	Description
Sociodemographic	Information collected in this domain includes, but is not limited to, age, education, income, mobility, and insurance status.
PEP[a]/PrEP[b]	Information collected in this domain focuses on initial knowledge, awareness, acceptability of and attitudes about PEP/PrEP, and history of use (including recreational use and source of PEP/PrEP).
Sexual risk behavior	Information collected within this domain includes information on number and types of partners (sex work client, nonpaying casual, and stable relationship), frequency and types of sexual acts, condom use during intercourse, and location of the sexual experiences. This includes details on sex work (initiating and stopping), average number of clients per night and week, average number of nights worked per week, and regular/non-commercial sexual partners.
Health care utilization	Information collected in this domain includes information on health care utilization and services to assess engagement at baseline. Information in this domain is also collected at the final visit to assess any supplemental services that have been accessed outside the study.
Engagement in the MSM[c], TGW[d], and sex work communities	Information collected in this domain includes information on knowledge of and engagement within community forums, PrEP-related contact with outreach workers, social support, connection and collective efficacy within the LGBT[e] community and in the sex worker community, and perceived support for PrEP and related topics within these communities. Receipt of condoms and contact with outreach workers will also be assessed. This domain allows the team to evaluate the effectiveness of the community mobilization intervention component.
Stigma	Information collected in this domain is focused on self-stigma (internalized homonegativity). This survey domain is adapted from Herek et al [28].
Substance abuse	Information collected in this section includes information on any substances used (amphetamine type substances, alcohol, etc) particularly around sexual experiences and frequency of substance use.
Mental health	The information collected in this section focuses on brief depression, posttraumatic stress disorder, and anxiety screeners using the Substance Abuse/Mental Illness Symptoms Screener [29,30].

[a]PEP: postexposure prophylaxis.

[b]PrEP: pre-exposure prophylaxis.

[c]MSM: men who have sex with men.

[d]TGW: transgender women.

[e]LGBT: lesbian, gay, bisexual, and transgender.

Weekly Short Message Service Surveys

An open-source software, FrontlineSMS, is used to survey participants via text messages (SMS). FrontlineSMS is able to send and receive messages, respond to messages, and trigger other events. FrontlineSMS is programmed with the cell phone number of the study participant after study enrollment, informed consent, and selected preventive option. Through FrontlineSMS, weekly, brief behavioral surveys are sent to participants to obtain information on exchange sex and condom use in the last week. For participants currently using PrEP, additional measures are used to collect information on when they last took PrEP and the number of doses of PrEP taken within the last 7 days. For those reporting less than 4 doses, additional questions inquire about intention to continue taking PrEP, and, if applicable, reason for discontinuing PrEP use. To ensure participant privacy, SMS surveys are only unlocked by a unique code assigned to each participant upon registration. Participants who are unable to immediately complete an SMS survey because of privacy concerns may opt to postpone their response within an allowable timeframe. Participants will receive cash compensation (30 THB, equivalent to approximately US $1) for responding to reminders and to reimburse cellular data costs.

Monthly Medication Pickups

Additional study data are collected during monthly medication pickups. These include count of unused tablets and DBS collection for storage and testing for tenofovir diphosphate if the participant becomes HIV-infected. Participants are requested to bring PrEP bottles with them to their monthly medication pickup, which also permits appropriate destruction of unused medication. Participants can receive new PrEP refills if they do not have their unused tablets with them, and the study team submits a memo-to-file. We collect both tablet-count adherence data (measured as number of unused tablets at the end of the month) and self-reported SMS adherence for the purposes of having the most complete and comprehensive measures of adherence.

Biologic Measures

One standard blood draw is done for all participants, as it is done before knowing HIV status. Blood collected is used for rapid HIV testing as outlined below. If HIV rapid test(s) is positive, blood is then tested for CD4 count and syphilis only. If rapid tests are negative, the following tests are conducted: syphilis, hepatitis B, and DBS for storage. Table 3 summarizes all laboratory tests conducted for COPE participants at each study visit.

DBS samples are used to measure study drug levels for those initiating PrEP and subsequently become HIV infected. If participant initiates PrEP at the visit or displays symptoms of acute HIV infection, a pooled NAAT test is also conducted. Study staff store blood specimens collected from quarterly study visits at least through the end of the study. Additional DBS collected from participants on PrEP at each study visit and medication pickup after PrEP initiation are stored in a −20°C freezer after drying. DBS specimens for participants prescribed PrEP who seroconvert will be shipped in bulk in dry ice to the University of Cape Town laboratory quarterly for testing. DBS from these participants will be assayed to measure levels of intracellular tenofovir diphosphate.

Table 3. Biologic measures taken per participant, by Combination Prevention Effectiveness Study visit.

Study visit	Biologic measure
Baseline visit	• HIV rapid testing • Pooled NAAT[a] • Syphilis • Hepatitis B • DBS[b] • CD4 (if HIV-infected) • Creatinine
Follow-up visit with STI[c] screening only	• HIV rapid testing • Pooled NAAT • Syphilis • DBS • CD4 (if HIV-infected)
Follow-up visit with STI and creatinine screening (for participants initiating PrEP[d] outside of baseline only)	• HIV rapid testing • Pooled NAAT • Syphilis • DBS • CD4 (if HIV-infected) • Creatinine
Monthly PrEP pickup (for PrEP participants only)	• DBS

[a]NAAT: nucleic acid amplification test.

[b]DBS: dried blood spots.

[c]STI: sexually transmitted infection.

[d]PrEP pre-exposure prophylaxis.

HIV Testing

HIV testing is completed at each regular study visit at 3-month intervals. For participants initiating/restarting PrEP or for those who display signs or symptoms of acute HIV infection at a study visit, HIV testing consists of a rapid antibody test supplemented by reflex pooled NAAT testing for antibody-negative specimens. Those with symptoms of acute HIV infection are restricted from starting on PrEP until their NAAT test results return negative. Those without symptoms of acute HIV infection can initiate PrEP if interested and eligible; if the NAAT result is positive these participants are contacted, instructed to stop taking PrEP, and asked to return to the clinic as soon as possible to reduce usage of PrEP during acute infection. All HIV-positive results will be confirmed by additional rapid and/or NAATs, in accordance with the recommended HIV testing algorithm for Thailand.

To reduce the risk of drug dosing post-HIV infection, participants on PrEP are advised to return for HIV testing and clinical evaluation, even if outside of scheduled visits, if they experience possible symptoms of acute HIV infection including fever, myalgia, fatigue, oral ulcer, skin rash, sore throat, or headache. All participants who become HIV infected while on PrEP are offered TDF and FTC resistance (K65R, M184V) testing and are referred to HIV care and treatment. Participants not on PrEP are advised to return for HIV testing if they display any of the acute HIV symptoms mentioned above.

All participants found to be HIV-infected either during the screening process or during the course of the study are able to access HIV treatment and care services through the national health scheme in Thailand, which guarantees universal access to ARVs for Thai citizens. The case manager or site coordinator at each site will complete a facilitated referral for all participants who test positive for HIV, which includes CD4 count, referral letter, and case management as needed according to standard, site-specific practices.

Sexually Transmitted Infection Testing

Participants are screened for syphilis and rectal gonorrhea and chlamydia at their baseline study visit and every 6 months thereafter. Rectal gonorrhea and chlamydia are assessed using either provider-collected or a self-administered rectal swab depending on participant preference. Self-administered swabs have been used in prior studies with good acceptability [31]. Participants with positive results are provided treatment either at the clinic per MOPH guidelines or are supported to get STI

treatment at a local health care facility. Participants reporting signs or symptoms of other STIs are evaluated and either treated on site or referred to care.

Hepatitis B Screening

Given the current use of Truvada in current treatment regimens for hepatitis B, all prospective participants are screened for hepatitis B infection at their baseline visit. If susceptible, they can initiate the hepatitis B vaccination series at their next visit or medication pickup. Participants initiating the hepatitis B vaccine series are referred to SCC @TropMed, or a local hospital.

Assessment of Renal Function

A serum creatinine test is completed for all participants before PrEP initiation. eCrCl is calculated using the Cockcroft-Gault formula below.

> eCrCl=[[(140 age in years)actual body weight in kg](serum creatinine in mg/dL72)]

Any participant with an eCrCl of <60 mL/min is not eligible for PrEP. PrEP users complete creatinine testing every 6 months while on PrEP.

Cost Analysis Data Collection

Broad intervention categories include community outreach and recruitment, HIV testing, condom and condom-compatible lubricant promotion, STI testing, and PrEP distribution. Community engagement and technology are also provided to support and encourage PrEP use. Costs associated with PrEP and technology use capture a majority of the costs associated with PrEP use and are a primary component of the incremental cost-effectiveness analysis.

Study participation primarily consists of visits with procedures related to the intervention, related to research questions, or a combination of the two. However, all research-related costs are excluded in cost-effectiveness analysis. In addition, participant involvement may vary across procedures, as some may be conditional (eg, given positive test result) and some may be repeated to varying degrees (eg, adherence assessment). For each program procedure, we establish the types of resources used, the value of each unit of resource, the quantity of resources used each time the procedure occurs, including the *best estimate* of the mean and the distribution or range, and the frequency with which the procedure occurs.

The majority of procedure-based costs are expected to be variable costs, as they are consumed each time the procedure occurs. These are complemented by procedure-specific fixed costs, such as the costs associated with the development of an SMS system. In addition to procedure-specific costs, there are general costs. Fixed general costs may include facility-related costs (eg, rent and utilities), electronic equipment, software, maintenance, administrative staff, and administrative overhead. General variable costs may include personnel time not directed to specific participant procedures, including staff meetings, trainings, and supervision.

A microcosting approach [32-34] is used to directly enumerate the cost of every input used in the intervention, such as staff time spent on each intervention-related activity, facility space, equipment, materials [32,34-36], and all in-kind contributions.

Procedure-specific resources are identified from walk-throughs of procedures, surveys and interviews with program staff, and review of program records. A walk-through consists of a member of the costing team performing a real-time observation of study procedures during a participant visit, beginning with initial referrals of potential participants to the study. Visits (and procedures) include the following: recruitment; eligibility screening; enrollment; PrEP education, offer, and eligibility screening; PrEP initiation; PrEP monitoring; monthly PrEP medication pickup; and quarterly study visits. Walk-throughs of visits or procedures also evaluate contingencies that may depend on test results, eligibility, or participant preferences. Through this process, the costing team identifies activities conducted and materials consumed through each procedure. Walk-throughs from the perspective of program staff are also conducted to help identify ancillary activities such as procedure-related administrative tasks. Resources needed for the prospective component of the study are assessed through observation of practices and not through human subjects activities.

Fixed and variable general costs are identified through surveys completed by program managers. Interviews with program staff and management are used to confirm the use of identified resources and to identify any additional resources that may have been missed through this process. Budgetary and other administrative records are also reviewed to identify any additional resources.

The number of units consumed during procedures is established through a combination of the abovementioned walk-throughs of procedures, direct observation of procedures, periodic surveys with study staff, and routine data collection. Data on the number of units consumed per procedure are complemented by data collection on the number of times different iterations of a procedure occurs, the number of participants receiving procedures, and the PY on PrEP per participant. Collection of these data is integrated into data collection for program evaluation (ie, study records) and data collection for the provision of clinical services (ie, participant clinical records).

From the costing data, we estimate for each procedure the mean procedure-specific cost per occurrence of the procedure. The frequency of procedures informs our estimations of the mean general costs per participant, the total costs across all participants, and the incremental cost per person-year on PrEP. The granularity of the costing data also allows estimates of alternative protocols, such as PrEP with and without adherence support, and PrEP with a reduced biological testing protocol. Data collection instruments and methods were pilot-tested and refined during the formative phase and reviewed and validated by the study partners.

Quality Assurance/Quality Control Measures

Study coordinators regularly inspect study facilities and documentation (eg, informed consent forms, clinic and laboratory records, other source documents, and case report forms), as well as observe the performance of study procedures.

Investigators also allow inspection of all study-related documentation by authorized representatives. A site visit log is maintained at the study site to document all authorized inspection visits and audits.

On-site study monitoring is performed by site coordinators and the multisite coordinator. Monitoring includes verification of compliance with the consenting process and other human subjects guidelines; assessment of adherence to the study protocol, study-specific procedures manual, and local counseling practices; and confirmation of the quality and accuracy of information collected at the study site and entered into the study database.

All data forms are reviewed for accuracy and completeness by study staff before sending data to TUC, where data cleaning is performed. At TUC, errors identified during the data cleaning process are compiled into a quality control (QC) report and sent back to site study staff for corrections. QC reports are compiled and tracked quarterly.

Study Retention

As this study measures person-time on and off PrEP, retention for the full study period is not a primary goal. However, to encourage participants to access prevention services and facilitate PrEP adherence, study staff make every reasonable effort to follow participants for the entire study period. A study-specific appointment and tracking system is used to ensure completion of assessments and to facilitate management of participant tracking. Tracking methods include SMS text messages, voice calls, emails, and visits to participants' place of employment. Confidentiality for participants is maintained through outreach efforts including text messaging, phone calls, and emails that do not disclose any details of study participation and that are sent by outreach staff trained on maintaining confidentiality of participants and potential participants, using outreach method participants have selected as their preferred method (ie, SMS, voice, emails, or workplace visits).

Study staff have developed and implemented standard operating procedures for retention to minimize attrition. These procedures include thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit; collection of detailed contact information at the study enrollment visit, and active review and updating of this information at each subsequent visit; collection of locator information from each participant, so that the participant can be found if the phone number or address changes; creation of a retention plan to maximize the level of participation in study-required visits; use of appropriate and timely visit reminder mechanisms; and immediate and multifaceted follow-up on missed visits.

Compensation

Participants are reimbursed for their time and effort in this study and for their travel to study sites. Participants receive 1000 THB (US $35) per visit attended at 0 (baseline), 3, 6, 9, 12 months, and a courtesy award of 500 THB (US $17.50) for completing the final (12-month) visit. If the participant travels to the study site and is deemed ineligible during the screening process, he or she receives 1000 THB (US $35).

Participants receive cash compensation for responding to weekly SMS surveys. Each person receives 30 THB (US $0.83) for each SMS survey the participant completes. If a participant achieves a perfect response rate of 4 surveys per month, he or she receives a courtesy award of 100 THB (US $3.50) at the end of the fourth survey of the month.

In addition to the above compensation, participants who initiate PrEP receive 500 THB (US $17.50) at each monthly medication pickup.

To identify participants with potential acute HIV infection while being prescribed PrEP, participants with symptoms consistent with acute HIV infection are compensated 500 THB (US $17.50) if presenting to a study site before their next scheduled visit.

For participants who initiate PrEP, the total possible compensation for 1 year of follow-up is 14,360 THB (US $479), given an increased number of study visits for pill pickups. For those who choose not to initiate PrEP, the total possible compensation for one year is 8360 THB (US $279).

Statistical Considerations

Statistical analysis uses a person-time approach to compare HIV incidence during person-time on PrEP to HIV incidence during person-time not on PrEP.

Sample Size Calculation

This study focuses on the primary endpoint of incident HIV infection during follow-up, comparing person-time on PrEP and off PrEP. Participant uptake of PrEP, level of PrEP adherence, and cessation of PrEP use serve as secondary endpoints in this study.

As prospectively measured in the Bangkok MSM Cohort Study cohort [37], we expect that the participants will be a mixture of very high-risk MSM and TGW 18 to 24 years of age with an HIV incidence rate of 11 per 100 PY and high-risk MSM 22 to 26 years of age with an incidence rate of 5 per 100 PY. Assuming a 50/50 mixture, we expect an incident rate of 8.5 per 100 PY (range=7-10). On the basis of recent iPrEx open-label extension (iPrEx OLE) study, we assume a 50% reduction in incidence for the PrEP group versus off-PrEP group [38]. On the basis of empirical evidence, we expect that some 50% of the participants will choose to take PrEP.

The sample size of this study is 1240 participants based on the following assumptions: incidence without PrEP is 8.5 per 100 PY, a PrEP efficacy of 50%, time-on-PrEP of 50%, attrition of approximately 2% per month, power=0.8, α (one-sided)=.025, and inflation of the standard error of the hazard ratio by 0% to 20% after adjusting for confounding. From this assumption, we expect that a combined sample of 1240 (620 on PrEP and 620 not on PrEP) will be sufficient.

Data Analysis

Each week of study participation at risk for HIV for each participant falls into 1 of 4 mutually exclusive categories of person-time: (1) on PrEP, good adherence; (2) on PrEP, poor adherence; (3) off PrEP, recent PrEP discontinuation (in last 30 days); and (4) off PrEP, no recent PrEP exposure. Individuals are considered at risk for HIV until the first positive HIV test

result or until the last HIV negative test result in the case of administrative censoring, loss-to-follow-up, or another censoring event.

The primary outcome analysis will compare HIV incidence during person-time on PrEP (categories 1 or 2) to HIV incidence during person-time not on PrEP (categories 3 or 4), with a simplified analysis following the analytic methods used by other PrEP open-label studies, and a more complex analysis using marginal structural models to account for time-varying confounding. Secondary outcome analyses will explore whether HIV incidence differs between participants on PrEP with good versus poor adherence (category 1 vs category 2) and whether HIV incidence differs between participants not on PrEP who have recently discontinued PrEP use versus who do not have recent PrEP exposure (category 3 vs category 4).

A more complex primary outcome analysis will be conducted using marginal structural models, following the methods proposed by Robins et al [39] As participants self-select into the PrEP group, the difference in incidence between those on PrEP and not on PrEP may be biased due to confounding. Propensity score methods will be used for bias reduction for the estimation of the causal effect of being on PrEP on HIV incidence, an approach that is well documented in nonrandomized pharmacoepidemiologic studies [40]. This will be an as-treated analysis that will account for discontinuation of PrEP, and as PrEP initiation and cessation may occur over the course of follow-up, and participants may cease and restart sex work, potential confounders may be time-varying, further complicating the estimation of causal effects.

In marginal structural models, inverse probability of treatment and censoring weights (IPTCWs) will be used in weighted, pooled logistic regression models of HIV infection. The data for each participant are structured such that each record represents 1 person-week of time either on PrEP or not on PrEP [39]. The odds ratio from the weighted, pooled regression provides an estimate of the hazard ratio for HIV infection associated with PrEP initiation similar to Cox time-dependent regression [41,42]. The IPTCWs at time t_i incorporate the estimated probability of the observed treatment history and the estimated probability of prior censoring. Creating the IPTCWs requires estimating inverse probability of treatment weights (IPTWs), inverse probability of censoring weights (IPCWs), and stabilization weights.

To estimate the IPTWs, a series of logistic regression models will be used to estimate the propensity of transition from one treatment state at time t_{i-1} to a new treatment state at time t_i. These analyses will be limited to participants who were HIV-negative at time t_i, and the analyses will include time-invariant (ie, baseline) covariates, and time-varying covariates from time t_i or earlier. Potential confounders to be included in the propensity score models of treatment status will be identified based on existing knowledge and based on exploratory analyses. Factors associated with PrEP acceptability among Thai young MSM and TGW include STI history, frequency of anal intercourse, HIV testing history, PrEP awareness, and insurance status [13], and factors associated with PrEP acceptability in other populations include perceived risk for HIV, use of condoms, sexual identity, education, concerns about PrEP use, and sex with casual or exchange partners [43]. Based on the estimated coefficients, the predicted probability of the observed treatment will be estimated, and this estimate will be inverted to give the inverse probability of the observed treatment at time t_i, given the observed treatment at time t_{i-1}. Prior treatment history will be incorporated by multiplying the predicted probability of treatment by the probabilities of not receiving the observed treatment at each of the previous time points.

Stabilization weights will be similarly estimated, but, in contrast, they will be based on logistic regression models including only time-invariant covariates. The IPTWs will be multiplied by the stabilization weights to improve their performance. The IPCWs will be similarly estimated and stabilized, but using transition from observed to unobserved in place of transition between PrEP use and nonuse, and the covariates used for the censoring model may differ from the covariates used in the treatment model. Finally, the product of the stabilized IPTWs and the stabilized IPCWs will provide the IPTCWs that will be used in the pooled logistic regression model to estimate the hazard ratio of HIV infection during time on PrEP and time off PrEP. The pooled logistic regression will include all time-invariant covariates used to create the stabilization weights and additional time-invariant covariates may be identified through exploratory data analysis.

The estimated log-odds of HIV infection and the standard error of the estimate from the pooled logistic will be used to evaluate whether the hazard of HIV differs between time on PrEP and time off PrEP, with the null and alternative hypotheses evaluated using the Wald statistic.

> *H10: The hazard of HIV during time on PrEP will not differ from the hazard of HIV for time not on PrEP: HIV hazard ratio=1.*
>
> *H1a: The hazard of HIV during time on PrEP will differ from the hazard of HIV for time not on PrEP: HIV hazard ratio1.*

The simplified primary outcome analysis will be conducted using Poisson regression, following the methods used by Grant et al [38]. The simplified analysis will have the benefit of easier interpretation but lack the ability to control for time-varying confounders that may be both causes and consequences of PrEP use (eg, sexual risk behavior and risk compensation).

The Poisson regression model will control for baseline covariates and include a time-varying indicator for PrEP status. The outcome will be assessed using a person-time approach, assessing HIV incidence densities among young MSM and TGW on and off daily oral PrEP over follow-up. In the Poisson regression, the Wald statistic will be used to evaluate the coefficient for PrEP status to distinguish between the null and alternate hypotheses.

> *H10: The HIV incident rate during time on PrEP will not differ from the incident rate for time not on PrEP: HIV incident rate ratio=1.*

H1a: The HIV incident rate during time on PrEP will differ from the incident rate for time not on PrEP: HIV incident rate ratio 1.

Cost-Effectiveness Analysis

We will estimate the incremental cost of the intervention per DALY averted, with DALYs reflecting the present value of future years of healthy life lost to morbidity/disability and future years of life lost to premature mortality. The incremental cost will be the net total cost of the intervention, excluding the cost of standard-of-care comparison condition.

This study has a multifaceted intervention design, and the emphasis of the cost-effectiveness analysis will be on the incremental cost-effectiveness of PrEP use relative to the intervention components that are not tied to PrEP use. The cost-effectiveness analysis will be in accordance with the recommendations set forth in the US Public Health Service Panel on Cost-Effectiveness in Health and Medicine [32]. We will estimate the additional cost of PrEP use versus PrEP nonuse, number of infections averted through PrEP use, discounted treatment costs saved through PrEP use, and the discounted DALYs averted through PrEP use. On the basis of these estimates, we will determine whether the use of PrEP relative to the standard intervention is cost-saving, cost-effective, or not cost-effective using societal and provider perspectives [32,35,36].

Through the primary outcomes analyses, the number of infections averted will be estimated as the difference between the number of infections that would have been expected without PrEP treatment and the observed number of infections under PrEP treatment.

Treatment costs saved per infection averted will be based on national or local estimates of costs per year for ART in Thailand, including costs for first- and second-line ARVs, laboratory tests, facilities, staff time, and opportunistic infections [44]. Total lifetime treatment costs per HIV infection will be based on remaining life expectancy and disease progression and discounted at 3% per annum [32,45].

DALYs, calculated following the methods of Fox-Rushby and Hanson [46] and Larson [47], will capture the years of life lost and disability associated with HIV infection and will be based on both the difference in life expectancy with and without HIV infection and the difference in the quality of life during years of life not lost. Future DALYs averted will be discounted at 3% per year annum.

The incremental cost-effectiveness ratio (ICER) will be based on the estimation of incremental cost (difference between the additional intervention cost and the additional treatment cost averted) divided by the DALYs averted. The intervention will be considered cost-saving if the additional intervention cost is less than or equal to the additional treatment cost averted, considered highly cost-effective if the ICER is less than gross domestic product (GDP) per capita in Thailand, cost-effective if the ICER is between 1 and 3 times GDP per capita, and not cost-effective if ICER is more than 3 times GDP per capita [48].

For the various cost-effectiveness ratio components, uncertainty intervals will be established based on primary data collection, literature reviews, and expert opinion. One-way and multivariate sensitivity analyses will be used to examine the robustness of the cost-effective estimates. In these analyses, parameters will be varied within the uncertainly intervals, and the resulting estimates will be reported. These components are expected to include estimates of resources consumed, resource costs, discount rates, treatment costs, DALYs per HIV infection averted, and infections averted. In addition, some research procedures may conceivably contribute to an intervention effect, such as monthly PrEP pill counts and weekly SMS adherence surveys. The impact of these procedures on cost estimates and cost-effectiveness will also be evaluated in sensitivity analyses.

Ethical Review

The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents—and any subsequent modifications—have been reviewed and approved by the following institutional review boards (IRBs) and ethical committees (ECs): Thailand Ministry of Public Health Ethical Review Committee for Research in Human Subjects; The US CDC IRB; and The Johns Hopkins Bloomberg School of Public Health IRB. The Emory University IRB defers to the Johns Hopkins University IRB, which has been documented by letter to the principal investigator (PI). The study protocol is also reviewed and approved by the Prevention Sciences Review Committee of the Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH; Multimedia Appendix 1).

Safety Monitoring and Adverse Event Reporting

Study staff have established a data and safety monitoring plan. The staff ensure that interview protocols are followed, review all adverse event reports (if any) and ensure that confidentiality procedures are implemented. The larger project team meets regularly to discuss progress toward data collection goals. At these meetings, study staff prepare weekly reports on data collection and any emerging issues or potential problems regarding the Web-based survey data collection efforts.

The site PIs report in writing all serious adverse events associated with the study procedures and/or any incidents or problems involving the conduct of the study staff or subject participation, including problems with the consent processes, per IRB protocols. Drug-related adverse events described by study participants or identified during laboratory testing after initiation of Truvada (eg, nonbaseline abnormal creatinine levels) are collected and submitted to the Thailand MOPH EC, CDC IRB, and JHU IRB in accordance with individual IRB and EC requirements, and to the Thai Food and Drug Administration as per their requirements. Adverse events severity is graded following sponsor guidelines [49]. Study participants are provided instructions for contacting the study site staff to report any negative medical occurrences they may experience. Where feasible and medically appropriate, participants are encouraged to seek evaluation where a study clinician is based; in the event this is not possible, and participants receive care elsewhere, they are asked to follow-up

at SCC @TropMed for further evaluation and determination whether adverse-event reporting is necessary.

In the context of this effectiveness study of an approved drug (tenofovir and FTC) in Thailand, adverse events, should they occur, are likely to be the social harms associated with disclosure of status as an MSM or TGW, a sex worker, as having HIV infection or at risk for HIV infection, or as being on PrEP. The study team regularly assesses each of these social harms through the surveys, at monthly PrEP medicine pickups, and through regular meetings with the community advisory board. Study staff are trained on social harm counseling and monitoring before study initiation and undertake additional efforts to minimize social harms to participants. Study staff record information pertaining to the event on the Social Harm Case Report Form and provide counseling with proposed solutions or refer participants to personnel or organizations with this specific expertise. Study staff make every effort to provide appropriate care and counseling to the participant and offer referral to appropriate resources, as needed, for the participant's safety. Study staff follow up about the social harm event at every study visit and record updated information onto the Social Harm Case Report Form. Social harms that are determined by the study investigators to be serious or unanticipated are reported to the responsible IRBs, or according to their individual IRB requirements.

Results

Summary

As of January 2019, formative research has been conducted, and the intervention effectiveness study has launched in Bangkok. Community engagement and empowerment efforts also launched during the formative phase and are ongoing throughout the study.

Formative Research

Formative research has been conducted in Bangkok and is ongoing in Pattaya. A total of 41 young MSM, 21 young TGW, and 24 venue staff and managers have completed KIIs (Table 4). These interviews provided insight into the context of sex work and exchange sex in Bangkok and Pattaya, perceptions and understandings of PrEP use in these contexts, as well as informed recruitment methods and study implementation. Although qualitative research and analysis has been ongoing, debriefing sessions and notes have been used to inform study methods. Specifically, formative findings were considered in the development of the survey (length, mode of administration, terminology, and measures), study branding and marketing (logos, images, content, and media platforms), and recruitment/retention methods across subgroups and venue types.

Table 4. Characteristics of formative research participants for the Combination Prevention Effectiveness Study for young cisgender men who have sex with men and transgender women, Thailand (2015-2020).

Characteristics	MSM[a] (N=41)	TGW[b] (N=21)	Venue staff (N=24)
Age (years), median (range)	22 (18-26)	24 (20-26)	42 (21-52)
Completed education, n (%)			
Lower than primary	9 (22)	1 (5)	7 (29)
Primary/secondary	26 (63)	13 (62)	5 (21)
Vocational	4 (10)	1 (5)	3 (13)
BA or higher	2 (5)	6 (29)	9 (38)
Duration exchanging/selling sex, n (%)			
<1 month	0 (0)	1 (5)	—[c]
1-6 months	6 (15)	3 (14)	—
7-12 months	7 (17)	2 (10)	—
>12 months	28 (68)	14 (67)	—
No answer	0 (0)	1 (5)	—
Location of sex work/exchange, n (%)			
Internet only	7 (17)	6 (29)	—
Venue only	14 (34)	4 (19)	—
Street-based only	1 (2)	0 (0)	—
Individual financial support (*Sugar Daddy*)	1 (2)	1 (5)	—
Combination	18 (44)	10 (48)	—
Sexual orientation and gender identity (based on local terminology), n (%)			
Homosexual, gay cisgender	26 (63)	0 (0)	15 (63)
Homosexual, transgender	0 (0)	19 (91)	3 (13)
Heterosexual	8 (20)	0 (0)	4 (17)
Bisexual	5 (12)	0 (0)	1 (4)
Do not know/not sure	2 (5)	0 (0)	1 (4)
Other	0 (0)	2 (10)	0 (0)
Sexual role, n (%)			
Oral	3 (7)	0 (0)	—
Anal	4 (10)	2 (10)	—
Both oral and anal	34 (83)	19 (91)	—

[a]MSM: men who have sex with men.

[b]TGW: transgender women.

[c]Not applicable to venue staff as they do not participate in sex work.

Combination Prevention Intervention

As of February 2019, 445 participants (417 MSM and 28 TGW) have contributed approximately 168 PY with 95% (73/77) retention at 12 months. 74.2% (330/445) of enrolled participants initiated PrEP at baseline, contributing to 134 PY of PrEP adherence based on a measure of 4 or more pills within the last 7 days, 1 PY nonadherence, and 33 PY PrEP nonuse/noninitiation. Monitoring of unexpected events has identified 7 social harms, predominantly related to unintentional participant disclosure of PrEP use and peer stigmatization of PrEP and HIV.

Discussion

This novel open-label study design and analytic plan will allow evaluation of the effectiveness and cost-effectiveness of combination prevention intervention for people who sell or exchange sex.

The vast majority of cisgender MSM and TGW who exchange sex and participate in this study thus far are interested in PrEP, report taking sufficient PrEP, and stay on PrEP, though additional efforts are needed to address community misinformation and stigma. Given the high interest and uptake

of PrEP among young MSM and TGW who exchange sex, we anticipate that one limitation of the study will include the ability to enroll sufficient person-time of non-PrEP use. However, the high uptake, retention, and adherence that has not been observed in other PrEP demonstration projects may provide critical insights into method to improve the current PrEP continuum among MSM and TGW in other settings.

To our knowledge, this is one of the first studies to test the effectiveness of PrEP specifically for MSM and TGW who exchange sex. This study may answer important questions about the effectiveness of PrEP for those in high-risk contexts and the costs of providing such interventions. Furthermore, this study may identify optimal technology-based methods to support PrEP adherence among young populations with high transiency and occupations that would otherwise limit traditional in-person adherence support. In a setting where PrEP has received significant support by the government in HIV prevention and response, estimating the costs and cost-effectiveness of community-based implementation may have important implications for national approaches to bring PrEP to scale in Thailand.

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The findings and conclusions presented in this paper are those of the authors and do not necessarily represent the views of the NIH, the US CDC, and US Public Health Service.

Authors' Contributions

CB is the PI of this study. CB, PSi, THH, MCT, ALW, BWW, MRD, ED, TC, AV, PSu, SHHM, RV, and SDB collaborated in the design and oversight of the overall study. TC, AV, and SHHM led trainings of study team members and oversee data collection. ALW wrote the initial drafts of this manuscript. AA, representing the study sponsor, provided guidance to the ethical review and monitoring and evaluation components of the study as required by the NIH. JR, representing the manufacturer and donor of the study drug, contributed pharmaceutical QA/QC guidelines specific to Truvada. Neither AA nor JR had any further role in the scientific design and conduct of the study, or in the analysis and interpretation of study results. All authors reviewed and edited the manuscript, and all take responsibility for its integrity as well as the accuracy of the analysis.

Conflicts of Interest

The study drug, Truvada, was donated to the project by Gilead Sciences. Gilead Sciences had no role in the design of the study nor in the interpretation of study results. AW and CB also receive separate research funding support from Gilead Sciences and ViiV Healthcare. All other authors declare no conflicts of interest.

Multimedia Appendix 1
COPE4YMSM NIH summary statement (2015).
[PDF File (Adobe PDF File), 167 KB - resprot_v9i1e15354_app1.PDF]

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Abbreviations

ACASI: audio computer-assisted self-interview
APCOM: Asia Pacific Coalition on Male Sexual Health
ART: antiretroviral therapy
ARV: antiretroviral
CASI: computer-assisted self-interview
CBO: community-based organization
CDC: Centers for Disease Control and Prevention
COPE: Combination Prevention Effectiveness
DALY: disability-adjusted life year
DBS: dried blood spots
EC: ethical committee
eCrCl: estimated creatinine clearance
FTC: emtricitabine
GDP: gross domestic product
ICER: incremental cost-effectiveness ratio
IPCW: inverse probability of censoring weight
IPTW: inverse probability of treatment weight
IPTCW: inverse probability of treatment and censoring weight
IRB: institutional review board
KII: key informant interview
MOPH: Ministry of Public Health
MSM: men who have sex with men
NIAID: National Institute of Allergy and Infectious Diseases
NAAT: nucleic acid amplification test
NIH: National Institutes of Health
PI: principal investigator
PrEP: pre-exposure prophylaxis
PY: person-years
QC: quality control
RSAT: Rainbow Sky Association of Thailand
SCC: Silom Community Clinic
SEM: Social Ecological Model
STIs: sexually transmitted infections
SWING: Service Workers In Group Foundation
TDF: tenofovir disoproxil fumarate
TGW: transgender women
THB: Thai baht
TUC: Thai-US Collaboration
US CDC: United States Centers for Disease Control and Prevention

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Protocol

Understanding and Addressing Variation in Health Care–Associated Infections After Durable Ventricular Assist Device Therapy: Protocol for a Mixed Methods Study

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Abstract

Background: Durable ventricular assist device (VAD) therapy is reserved for patients with advanced heart failure who have a poor estimated 1-year survival. However, despite highly protocolized management processes, patients are at a unique risk for developing a health care–associated infection (HAI). Few studies have examined optimal strategies for HAI prevention after durable VAD implantation, despite variability in rates across centers and their impact on short- and long-term outcomes.

Objective: The objective of this study is to develop recommendations for preventing the most significant HAIs after durable VAD implantation. The study has 3 specific aims: (1) identify determinants of center-level variability in HAI rates, (2) develop comprehensive understanding of barriers and facilitators for achieving low center-level HAI rates, and (3) develop and disseminate a best practices toolkit for preventing HAIs that accommodates various center contexts.

Methods: This is a sequential mixed methods study starting with a cross-sectional assessment of current practices. To address aim 1, we will conduct (1) a systematic review of HAI prevention studies and (2) in-depth quantitative analyses using administrative claims, in-depth clinical data, and organizational surveys of VAD centers. For aim 2, we will apply a mixed methods patient tracer assessment framework to conduct semistructured interviews, field observations, and document analysis informed by findings from aim 1 at 5 high-performing (ie, low HAIs) and 5 low-performing (ie, high HAI) centers, which will be examined using a

mixed methods case series analysis. For aim 3, we will build upon the findings from the previous aims to develop and field test an HAI preventive toolkit, acquire stakeholder input at an annual cardiac surgical conference, disseminate the final version to VAD centers nationwide, and conduct follow-up surveys to assess the toolkit's adoption.

Results: The project was funded by the Agency for Healthcare Research and Quality in 2018 and enrollment for the overall project is ongoing. Data analysis is currently under way and the first results are expected to be submitted for publication in 2019.

Conclusions: This mixed methods study seeks to quantitatively assess the determinants of HAIs across clinical centers and qualitatively identify the context-specific facilitators and barriers for attaining low HAI rates. The mixed data findings will be used to develop and disseminate a stakeholder-acceptable toolkit of evidence-based HAI prevention recommendations that will accommodate the specific contexts and needs of VAD centers.

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KEYWORDS

heart failure; ventricular assist device; infection; cardiac surgical procedures; mixed methods

Introduction

Use of Durable Ventricular Assist Device to Treat Advanced Heart Failure

Heart failure affects nearly 5.7 million Americans and is a contributing cause of 1 in 9 deaths [1]. It is estimated that the prevalence of heart failure will increase by 46% from 2012 to 2030 [2]. The condition is the second costliest in terms of Medicare expenditures (approximately US $30.7 billion annually) [1]. Durable ventricular assist device (VAD) therapy is reserved for patients with advanced heart failure who have a poor estimated 1-year survival [3,4]. Technological advances using newer magnetically levitated centrifugal continuous-flow VADs have improved patient survival and decreased adverse event rates compared with older continuous-flow axial technology [5,6]. Currently, the estimated VAD survival is approximately 50% at 4 years, accompanied by significant improvements in functional status and quality of life [7,8].

Risk of Device-Related Health Care–Associated Infection

Patients with VADs are at a heightened risk for device-related and nondevice-related health care–associated infection (HAI) despite a highly protocolized perioperative and postoperative course. The nature of durable VAD therapy requires an uninterrupted external power source connected to the patient through a driveline (ie, a percutaneous lead to provide power and control to the implantable pump), which serves as a potential source for the development of HAIs given its connectivity between the patient and the external environment [9]. In addition, VAD therapy is frequently associated with other infections that are nondevice-related, including pneumonia and surgical site or bloodstream infections [10,11]. VAD patients are at a unique risk for HAIs given (1) the burden of multiple preoperative comorbid conditions; (2) the invasive nature of VAD implantation; (3) hemodynamic instability that often occurs at the time of device implantation; (4) a common feature of all devices, a percutaneous lead; (5) extended intensive care unit stays; and (6) concurrent need for invasive monitoring.

The majority of HAIs occur within 90 days after a VAD implantation, with a decreased but ongoing risk beyond the 90-day period [12-16]. More than 3000 patients undergo VAD implantation in the United States annually, with nearly 6 out of every 10 patients developing a HAI following the procedure [16-22]. Development of an HAI is associated with a 6-fold risk of 1-year mortality and incurs additional treatment expenditures (US $264,000-US $869,000 per patient) [23,24]. Notably, infectious complications secondary to VAD implantation are the second leading cause of death for this population (16% of all deaths) [25].

Variation in Health Care–Associated Infection and Preventive Strategies

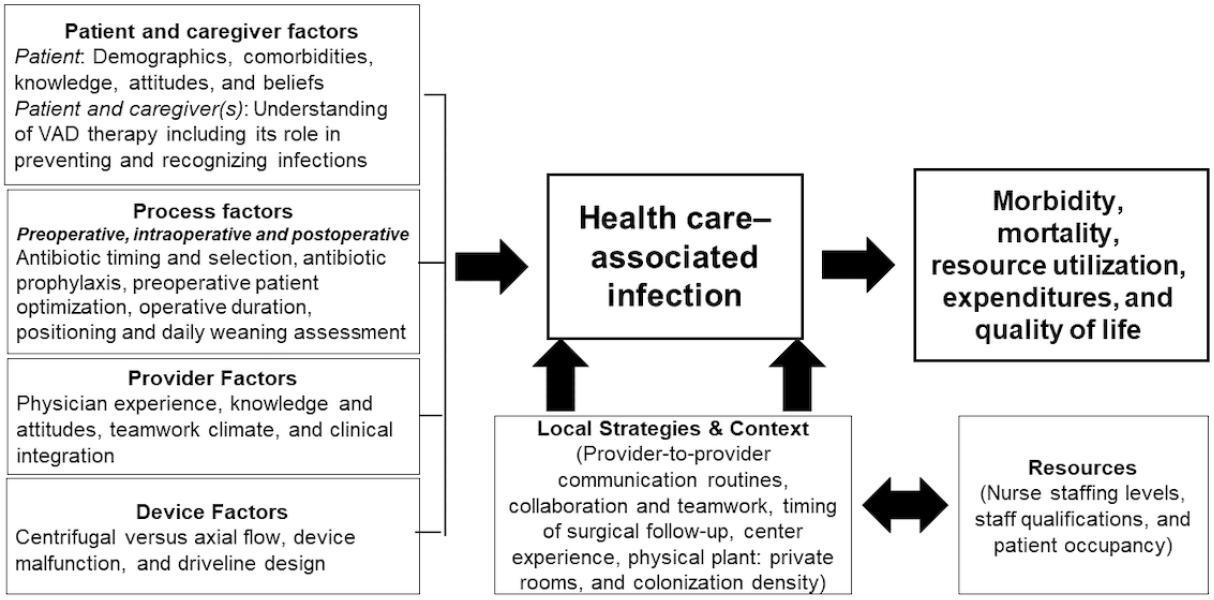
Large variation exists in both the rate of HAIs and, more notably, the adoption of preventive strategies (eg, checklists, effective teamwork, and unit and center leadership) across clinical centers [26,27]. A 2017 study noted significant variation in the choice and duration of antimicrobial prophylaxis across 20 VAD centers (ie, one that implants a VAD or treats a patient within 90 days of implantation of a VAD) [26]. Although researchers have reported the benefit of preventive strategies, adoption by the clinical community varies [28-33]. Researchers have noted improved outcomes among cardiac surgery patients being cared at health systems with stronger provider teamwork (as captured in the configuration of social networks among providers), suggesting that a high level of provider teamwork may promote the prevention of HAIs [33,34]. Moreover, a 2018 study reported reductions in HAIs with the adoption of evidence-based practices within the setting of coronary artery bypass grafting procedures [35]. However, further investigation is required to understand the optimal HAI prevention strategies that have been adopted and how high-performing centers (ie, those with lower HAI rates) enhance the implementation of these strategies relative to low-performing centers.

Conceptual Framework Guiding the Study

Figure 1 shows the conceptual framework illustrating the determinants of HAIs and informing the areas of investigation in this study. We hypothesized that patient and caregiver, process, provider, and device-related risk factors as well as a center's local strategies, context, and resources are associated with the development of HAIs. Moreover, we hypothesized that, after accounting for perioperative risk factors, a center's local strategies, context, and resources are associated with HAIs.

Centers with lower HAI rates may leverage resources (eg, infection prevention staff) to reduce barriers to and increase facilitators of infection prevention strategies (eg, antimicrobial prophylaxis regimen) to prevent HAIs. Furthermore, we envision that a modular, action-oriented HAI toolkit, taking into account a center's local strategies, context, and resources, could guide clinical teams (via evidence-based recommendations and educational tools) in preventing HAIs.

Figure 1. Conceptual model for health care–associated infection development and impact. VAD: ventricular assist device.



Rationale for the Study

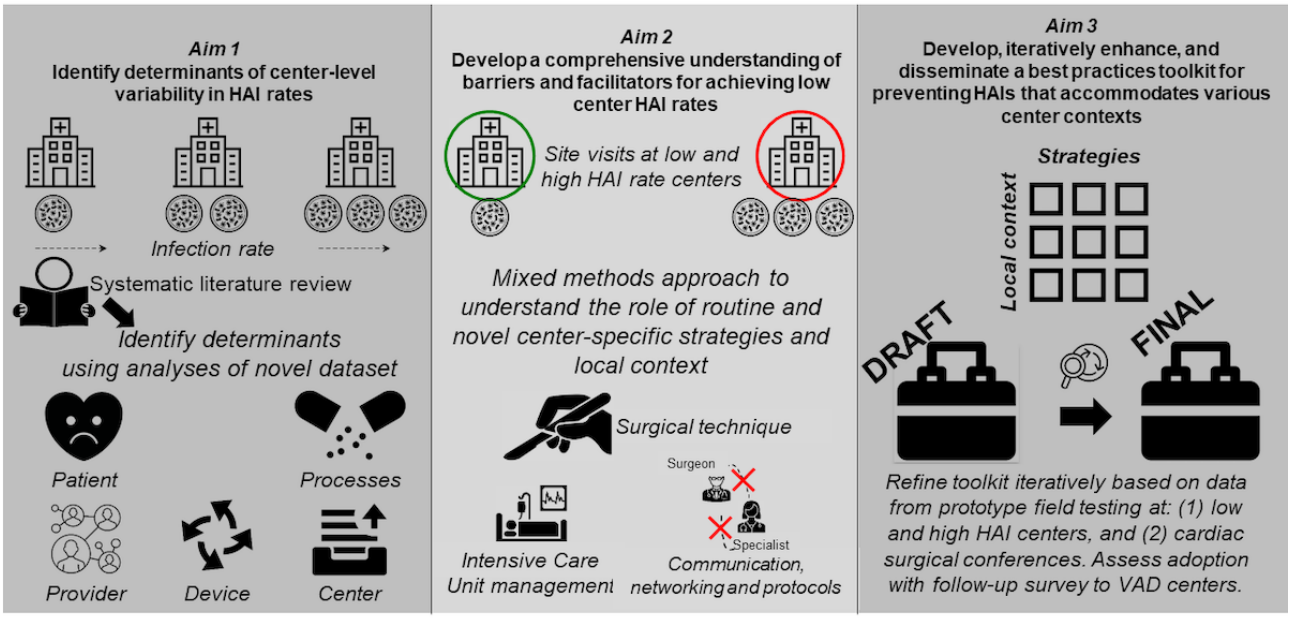
Few studies have focused on understanding both the optimal strategies for HAI prevention after VAD implantation as well as the approaches for enhancing the local adoption of these practices. Relying on administrative claims or clinical data is insufficient for identifying novel HAI practices, let alone understanding the characteristics of center- and unit-level strategies and contexts contributing to HAIs. To address this research gap, this mixed methods study seeks to identify recommendations for preventing the most clinically significant HAIs after VAD implantation. First, we plan to characterize key determinants of HAIs using quantitative approaches. Subsequently, we plan to identify context-specific promoters and barriers to preventing HAIs across low- and high-performing centers using qualitative approaches. More importantly, a multidisciplinary study team will use both findings to develop an action-oriented modular toolkit that provides evidenced HAI prevention recommendations, which accommodates the specific needs of individual centers. This project will contribute to research knowledge and interventions aimed at preventing HAIs by encouraging field-wide adoption of evidence-based practices.

Methods

Overall Study Design

As shown in Figure 2, we will use an explanatory sequential mixed methods design to address 3 aims: (1) identify determinants of center-level variability in HAI rates; (2) develop comprehensive understanding of barriers and facilitators for achieving low center-level HAI rates; and (3) develop, iteratively enhance, and disseminate a best practices toolkit for preventing HAIs that accommodates various center contexts. In aim 1, we will (1) conduct a systematic review of existing HAI prevention studies to compile a list of current prevention strategies and (2) conduct in-depth analyses using a unique merged dataset of all Food and Drug Administration (FDA)–approved VADs implanted in Medicare beneficiaries as well as an organizational survey administered to VAD centers. Our systematic literature review and analysis of provider social networks (including physician and nonphysician providers) will inform areas of investigation and identify the sample of high-performing and low-performing centers for aim 2. In aim 2, we will develop a comprehensive understanding of local facility and context-sensitive approaches contributing to variability in HAI rates through site visits at a sample of centers to reveal routine and novel HAI determinants and identify feasible solutions for ensuring local adherence to HAI prevention practices. In aim 3, we will (1) field test a prototype toolkit, (2) present an iteratively enhanced version to key VAD clinical stakeholders (eg, surgeons, clinical coordinators, nurses, and cardiologists) attending an annual conference in the field of cardiac surgery to optimize the toolkit's usability and acceptability before national dissemination, and (3) conduct a follow-up survey to assess the adoption of the proposed toolkit. The human subjects' applications for secondary use of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and Medicare data (HUM00155687) and for administration of center surveys (HUM00157335) have been approved by the institutional review board of the University of Michigan.

Figure 2. Overall study design. HAI: health care–associated infection; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support.



Aim 1: Identify Determinants of Center-Level Variability in Health Care–Associated Infection Rates

To address this aim, we will first conduct a systematic review of interventional HAI prevention studies. Second, we will supplement the clinical dataset with (1) data from an electronically distributed survey of VAD centers to identify HAI prevention strategies not already tracked through INTERMACS and (2) center-specific measures of provider social network configurations using a merged INTERMACS-Medicare dataset [7,36]. Third, we will calculate center-specific 90-day HAI rates. Fourth, we will model variability in and identify determinants of centers' HAI rates using this enhanced clinical dataset. We hypothesize that (after accounting for perioperative risk factors through INTERMACS) process, provider, device, and center- and unit-specific risk factors will be significant determinants of HAI rates. Findings will inform the sampling plan and focus on aim 2 activities.

Datasets Used for Aim 1

Center for Medicare and Medicaid Services Files

Given that Medicare is the largest US health care payer, Center for Medicare and Medicaid Services (CMS) is the sole national data source of exhaustive claims for noninstitutional and institutional providers. The CMS files contain data about (1) beneficiary (eg, age, diagnoses, and type of benefits); (2) institutional admissions; (3) provider services; (4) outpatient, hospice, home health agency, and skilled nursing facility services; and (5) prescription drugs (eg, heart failure medications). Each file contains data about the date and location of services and payments. We will characterize the social networks of providers (eg, nurse practitioners, physician assistants, and physicians) as a measure of provider teamwork. Following precedent from prior research on physician social networks, we will restrict these networks to specific provider specialties (eg, anesthesiology and surgery) that are most likely to be directly involved with the care of VAD patients [33,34,37-41]. Determination of relevant providers will be made through consultation with clinicians and through descriptive assessments of claims data.

American Hospital Association Survey

Data from this annual survey, to be merged with CMS files, contain center-specific structure and organizational measures (eg, size, urban or rural location, teaching status, affiliation with networks, training programs, ownership, staffing levels, and types of surgical services provided).

Interagency Registry for Mechanically Assisted Circulatory Support

INTERMACS is a multicenter, Joint Commission–recognized, nationally audited database of FDA-approved VADs. INTERMACS contains extensive data regarding (1) preimplant details (eg, age and comorbid diseases); (2) operative details (eg, device type and operative duration); (3) patient status until death, cardiac transplantation, or device removal; (4) adverse events (eg, device malfunctions); and (5) functional status, neurocognition, and health-related quality of life. INTERMACS monitors device-related (driveline, exit cannula, pump pocket, and pump interior) and nondevice-related (positive blood cultures, central line associated sepsis, pulmonary, urinary tract, mediastinum, peripheral wound, gastrointestinal) HAIs.

Center Survey

The survey, informed by a systematic review of the literature and prior work, will identify potential HAI determinants that are not available through existing data sources [42,43]. Independent of our network analysis, the survey will be designed to address determinants spanning the patient's full clinical trajectory (preoperative, implantation, postoperative, rehabilitation, and discharge). Surveys will be sent to the center's designated VAD coordinator, implanting surgeons, and heart failure cardiologists involved in the center's VAD

program. The use of Web-based survey software (ie, Qualtrics) will allow for the creation, distribution, storage, and analysis of survey instruments, with advanced features (eg, randomization of question ordering).

Preliminary survey drafts will be developed based on a conceptual framework and by our investigative team of clinical and research experts, with input from survey and decision science experts. We will test the draft survey instrument with key stakeholders at selected centers with low and high HAI rates to ensure readability, face validity, and completeness of response options. Interviews will be conducted by Web-based teleconference in real time as the draft survey is completed to solicit qualitative feedback on survey content. The survey will be revised based on this feedback.

We will use evidence-based strategies to maximize survey response rate and minimize nonresponse bias, especially as a function of a center's HAI rate. For example, the email invitation will be personalized, and the survey length will be limited. In addition, nonrespondents (VAD coordinator, surgeon, and cardiologist) will be contacted by the study team as necessary. Our team will provide respondents with a small gift card after completing the survey.

Sample Size

We project analyzing data among 9339 VAD patients receiving durable VAD from 2008 to 2017. We will administer surveys to potential respondents (VAD coordinator, surgeon, and cardiologist) from an estimated 153 VAD centers.

Analytic Approach

First, we will conduct a systematic review of the published literature to identify established HAI preventive practices [44,45]. Second, we will use survey responses to identify provider and institutional practices that contribute to center variability in HAI rates. Third, we will use our linked Medicare-INTERMACS datasets to identify preoperative, intraoperative, and postoperative factors that contribute to center variability in HAI rates.

Primary Endpoint

Our primary endpoint is any HAI 90 days after device implant. We will account for HAI competing risks (eg, death and device removal) and other censoring (follow-up less than 90 days) using time-to-event analysis. Furthermore, we will use 2 approaches for modeling HAI risk. First, we will use the Cox proportional hazards model. We will adjust for surgery year and season and investigate interactions by key biological variables (eg, patient age, sex, and race). We will account for patient demographics (eg, age and sex), disease characteristics (eg, pulmonary disease), and surgical history (eg, prior cardiac surgery) and study the effect of intraoperative care (eg, cardiopulmonary bypass duration) and postoperative care (eg, duration of intubation). We will use the Lasso variable selection method to assess variables for model inclusion [46]. We will handle the multilevel structure (eg, patients are nested within centers) using the robust sandwich variance–based inference or frailty model approach. On the basis of the final fitted model, effects of risk factors will be quantified by hazards ratios and tested by score tests. Second, we will use random survival forest, an extension of the random forest method to right-censored time-to-event data, to model the effects of risk factors nonparametrically [47-49]. The final model will be an ensemble average of fitted trees from bootstrap samples.

Exploratory Analyses

We will also conduct exploratory analyses for device-related and nondevice-related HAIs and their main components (to address heterogeneity of risk factors across HAI subtypes). We will quantify the importance of a group of factors in explaining center variability in HAI by fitting models with and without such factors and comparing how well the expected numbers from different models track with the observed numbers. Primary analyses will include all centers, and for the purpose of sensitivity analysis, we will also exclude low-volume centers. We will explore different center volume thresholds, trying to strike a balance between 2 considerations: stable estimate of HAIs rate (quantified by standard error) and number of centers remaining for analysis. We will use simple mean imputation, median imputation, or multiple imputation to account for anticipated missing covariates depending on their pattern and mechanism [50]. If the missing data itself are thought to be related to outcomes, then missing indicators will be used and modeled as independent variables as part of sensitivity analysis.

Teamwork and Communication as Quality Measurement

Provider social networks represent a measure of teamwork and communication that are associated with the quality of care [34]. In prior validation work, shared patients between providers, identified using unique provider identifiers found in claims data, have been found to correspond closely to surveyed provider network patterns [33,51]. We will characterize mapped VAD networks using a measure known as assortativity, which can capture the degree to which providers from different specialties and clinical disciplines are interconnected and, thus, better equipped for collaboration and teamwork [52]. We will incorporate this measure as a covariate in our statistical models [34]. Recent network research has drawn attention to several challenges in characterizing assortativity in social networks. First, global (ie, network level) measures of assortativity may mask considerable local (ie, node level) variation in cross-group (eg, specialty) interaction [53]. Second, common network data practices (eg, unipartite projection of a bipartite network) may lead to bias in values of standard assortativity measures [54]. To overcome these challenges, we plan to use state-of-the-art techniques for evaluating assortativity in social networks, including multiscale measures of assortativity (which allow for measuring assortativity at the node level) and comparison of assortativity on our observed networks with null (ie, random network) models.

Claims data do not map perfectly to true care patterns; therefore, our network measures may include false negatives and false positives. To assess for these biases, we will run several sensitivity analyses, motivated by prior work on missing data and thresholding techniques in the study of social networks [55-57]. Using Monte Carlo simulations, we will randomly drop increasingly larger fractions of providers and relationships in our observed networks, recompute our network measures, and then rerun our statistical models to assess bias attributed to false

negatives. In additional simulations, we will also gradually add larger fractions of random providers and relationships to our observed networks to assess sensitivity to false positives.

The approaches discussed above consider the time-to-event endpoint (ie, time to first HAI), which counts multiple HAIs from a single patient only once. Alternatively, we will consider the recurrent event endpoint, where multiple HAIs from a single patient are counted multiple times. We will use a counting process, Anderson-Gill model, to rerun the analysis using a recurrent event endpoint to help distinguish the 2 outcome scenarios [58].

Aim 2: Develop a Comprehensive Understanding of Barriers and Facilitators for Achieving Low Center Health Care–Associated Infection Rates

A mixed methods patient tracer assessment framework will be applied (adapted from the Joint Commission's tracer methodology) in aim 2 to examine center-level resources and local barriers and facilitators for achieving low HAI rates [59]. We will conduct semistructured interviews, field observations, and document analysis at 5 high-performing (ie, low HAI) and 5 low-performing (ie, high HAI) centers, which we will examine as a mixed methods case series to address this aim.

Sampling

A priori, we will use HAI rates derived from aim 1 to intentionally sample 5 high-performing centers with low HAI rates and 5 low-performing centers with high HAI rates for site visits. However, the sampling process will be further refined based on other criteria pending the nature of findings emerging from aim 1 and center-specific practices (eg, measures of provider teamwork).

Data Collection

We will conduct 2-day site visits at 5 high-performing and 5 low-performing centers. The mixed methods patient tracer assessment procedure focuses on the patient's trajectory from the index hospitalization to 90 days. Before site visits, we will conduct advanced analytics to examine performance features, measures, and other quantitative data that will inform qualitative data collection. During the center visits, the site-visiting team will systematically trace the patient's movement through the health system and investigate HAI risk factors or preventive strategies at each *stop* of the patient's trajectory (ie, transitions in care or changes in the patient's physical location). At each site, we will (1) conduct in-depth, semistructured interviews with relevant provider and nonprovider stakeholders and perform field observations of the environment and staff behaviors in the clinical unit and relevant operating room; (2) collect, discuss, and analyze relevant protocol documents; (3) learn local strategies used to enhance HAI prevention; and (4) gather toolkit design elements that would enhance its receptivity and local adoption. These findings will provide a robust understanding of the organizational resources and local facility barriers and facilitators for HAI prevention.

Semistructured Interviews

The site-visiting team will follow a patient's trajectory and conduct semistructured interviews with stakeholders impacting VAD patient care, including administrators (eg, chief medical or nursing officer, quality or safety officer, physician service chief, clinical unit manager, and hospital epidemiologist), physicians (eg, attending surgeon, intensivist, hospitalist, and medical consultants—pulmonologist and cardiologist), advanced practice providers (eg, nurse practitioner and physician assistant), and nurses (eg, ward and intensive care unit). Informed consent will be obtained from informants before starting each interview. Each interview, which will be conducted in private offices or conference rooms, will last for 40 min to 60 min. Stakeholder interviews will focus on answering questions from the advanced analytics, understanding perceptions of the center's resources and local strategies for HAI prevention, and eliciting key features that would enhance local toolkit adoption. Interviews will continue until reaching informational redundancy or saturation (ie, no new information is being identified) at each center. Following each interview, the study team will provide a gift certificate to each interviewee to acknowledge his or her contribution.

Observations and Field Notes

For each site visit, the site-visiting team will conduct direct observations of the clinical work environment and behavior within each *stop* of the patient trajectory. Quantitative observations regarding HAI determinants will be tracked using a structured data form. For example, we will track discrete process of care (eg, antibiotic prophylaxis regimens and preoperative optimization), provider practices (eg, location of driveline exit site), local context and strategies (eg, sink in every patient room and private vs shared patient rooms), and organizational resources (eg, nursing staffing levels). Qualitative observations will focus on examining (1) *context*—circumstances informing data collection (eg, recent line infection mortality); (2) *content*—factual data, locations visited, key process stakeholders, and ward layouts; and (3) *concepts*—hunches or theories about the environment that may help explain a center's HAI rate (eg, deviations from written protocols) [60].

Documents

During each site visit, we will collect relevant protocol documents and interview participants at the relevant transition point about the use of the documents, variations, or other volunteered information. Other relevant documents, patient education documents, postsurgical order sets, and variations by surgeons will be collected.

Analytical Approach

Qualitative Analysis

Preliminary analysis will begin with a research team debrief at the end of each day, which will reflect team members' field notes, impressions, and observations. These recorded conversations will provide an additional source of data for defining facility- and unit-level contextual characteristics. Debriefing sessions during day 1 will also identify areas of focus and inquiry for day 2. On day 2, we will explore questions raised on day 1 to develop an expanded understanding. At the end of day 2, the most current version of the toolkit will be presented to the sites for feedback.

Developing Case Studies

For each site, we will develop a case study following a structured outline that will have a sufficiently flexible format to accommodate site variation [61]. As the study summary for each site is completed, we will compare the findings with the other sites for the case series analysis. For each site case study, the summary will begin following each visit, when team members will review all qualitative and quantitative sources of data from each site. Team members will then begin the process of coding all the qualitative data including deidentified transcripts using qualitative analysis software (MAXQDA). Team members will convene regularly to compare independent coding of the qualitative data and revise the codebook iteratively until consensus is reached on codes, themes, categories, and coding criteria. This group consensus approach facilitates, enriches, and increases the rigor of data interpretation [62]. The study team will (1) develop findings by meeting regularly to review code summaries and memos created during prior meetings and (2) discuss and interpret the data across low- and high-performing centers. The analysis will occur by site, and findings or new questions will be iteratively explored after completion of each site visit.

Integration of Quantitative and Qualitative Analyses

All quantitative (aim 1 findings about the specific sites) and qualitative data (aim 2 findings) will be integrated into the case study for each site. Related findings from both data sources will be matched to provide a comprehensive understanding of each center's HAI prevention strategies. Multiple case series analyses will be performed. As appropriate for related findings, joint display analysis (ie, the process of iteratively creating, interpreting, and restructuring tables and figures that integrate the quantitative and qualitative findings) will be used to illuminate similarities and differences in HAI prevention strategies across centers and draw overall conclusions [63].

Member Checking

Member checking is the process of providing qualitative and mixed methods findings back to study participants to elucidate their input on the overall interpretation [64]. The case study summary for each site will be distributed back to participants who indicated an interest in reviewing the findings. These participants will be asked to indicate their overall agreement with the study findings and to make any corrections or clarifications they deem necessary. Any requisite correction or clarification will be incorporated into the final case study reports used in the case series analysis.

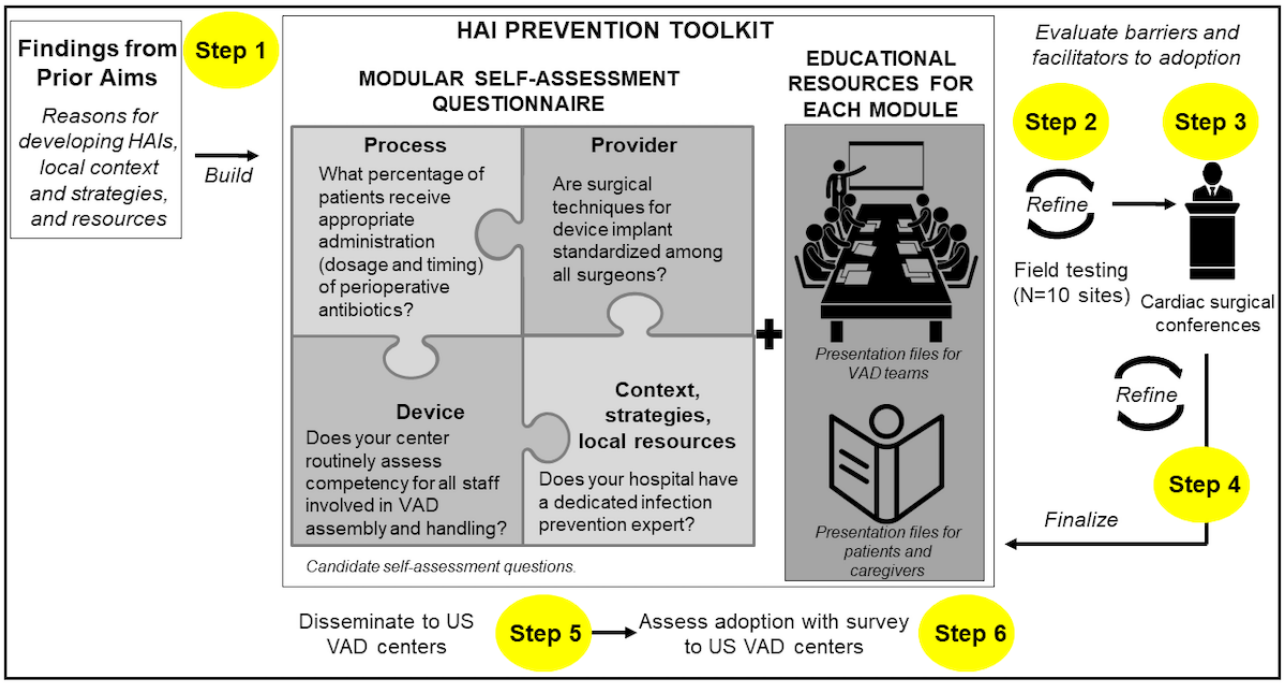
Aim 3: Develop, Iteratively Enhance, and Disseminate a Best Practices Toolkit for Preventing Health Care–Associated Infections That Accommodates Various Center Contexts

The study team will create a HAI preventive toolkit of evidence-based recommendations that may be customized to the context of each center. The development of the toolkit will be informed by the findings from aims 1 and 2. We will field test our prototype toolkit at the same 10 centers that participated in aim 2. This process will identify approaches for optimizing adoption (ie, fit and suitability for everyday use) as well as inform local context needs and any necessary modifications (eg, content, design, and options). The team will host a dedicated 90-min session at an annual cardiac surgical conference (eg, the International Society for Heart and Lung Transplantation) to elicit further user feedback about the toolkit's acceptability. We will use the feedback to develop a final toolkit, which will be distributed to US VAD centers. Finally, a follow-up survey will be electronically distributed to US VAD centers to assess national adoption rates of the toolkit.

Translation of Findings Into a Draft Toolkit

We will develop an initial version of a printed HAI prevention toolkit of evidence-based recommendations based on the Agency for Healthcare Research and Quality (AHRQ) guidelines [65]. In addition, we anticipate using the RE-AIM framework when considering the components of our toolkit as they relate to the likelihood of reach, efficacy, adoption, implementation, and maintenance [66]. The steps involved in the development of the toolkit are illustrated in Figure 3. The content of the toolkit will be informed by the findings from aim 1 (determinants of center's HAI rates) and aim 2 (center's strategies, context, and local resources). The toolkit will be designed to provide local customization to optimize adoption by individual centers. The toolkit will include a self-assessment questionnaire and corresponding educational resources. The self-assessment questionnaire will be designed to locally tailor evidence-based recommendations. The set of educational resources derived from stakeholder interviews will also address local, context-specific needs. We anticipate that the user-friendly toolkit will provide educational resources (eg, impact, prevention, pathophysiology, and epidemiology), prevention strategies (eg, concise summary of evidence-based recommendations with supporting literature).

Figure 3. Development of the health care–associated infection preventive toolkit. HAI: health care–associated infection; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; VAD: ventricular assist device.



Field Testing of the Toolkit

The prototype toolkit will be field tested at the same 10 centers that participated in aim 2. Study team members will conduct audio-recorded interviews of VAD clinical stakeholders to elicit user feedback regarding the toolkit's usability, acceptability, and likelihood of significant effectiveness for preventing HAIs using a *think out loud* approach [67]. Although primarily intended to identify approaches for optimizing adoption (ie, fit and suitability for everyday use), the interviews will inform local context needs and any necessary toolkit modifications (eg, content, design, and options). Study team members will analyze field notes and deidentified transcripts. Iterative versions of the toolkit will be developed and presented at subsequent centers, thus enhancing local stakeholder acceptability and usability. After iterative development across the 10 centers, a fully revised and enhanced version will be sent back to the centers for final review and feedback. A further refined version will be prepared for feedback and presentation at an annual cardiac surgical conference (eg, the International Society for Heart and Lung Transplantation).

Broad Ventricular Assist Device Stakeholder Input on the Toolkit

A moderated expert panel will be convened at an annual cardiac surgical conference (eg, the International Society for Heart and Lung Transplantation) to gather stakeholder input on the refined toolkit. During this session, we will share the rationale and intended use of the toolkit and highlight the toolkit's usability, acceptability, and likelihood of significant effectiveness. Attendees will use an audience response system to provide Likert-scaled responses to each question and will be invited to offer additional qualitative feedback concerning the reasons underlying their quantitative survey responses. Panelists (representing cardiac surgery, heart failure cardiology, infectious disease, and epidemiology) will be invited to respond to attendees' remarks. The entire session will be double audiotaped (with deidentified transcripts created thereafter). Analysis of the audience response system data and the themes emerging from the discussion for each item will be integrated to draw overall conclusions and inform final revisions of the toolkit. Thereafter, we will distribute the final version to US VAD centers.

Assessment of Toolkit Adoption

A follow-up survey intended to assess toolkit adoption rates among US VAD centers will be developed and electronically distributed using the same approach as the center survey described in aim 1. The survey will be pretested to assess face and content validity, comprehensibility, time to completion, and ambiguity. The survey is anticipated to solicit information using a mixture of multiple-choice responses (eg, awareness of the toolkit, roles of those involved with local adoption, identified surgeon champion, types of resource support provided to the adoption team, and frequency of team meetings) and open-ended responses (eg, method used to implement the toolkit, perceived barriers and facilitators for implementation, ongoing quality improvement initiatives to enhance local adoption, and perceived effectiveness of the toolkit).

Results

The project was funded by the AHRQ in 2018 and enrollment for the overall project is ongoing. We are conducting a systematic review of interventional HAI prevention studies and developing the survey concerning HAI determinants across US VAD centers. We anticipate that survey data collection will begin in November 2019. Findings from aims 1 and 2 will be

used to develop a toolkit of evidence-based HAI prevention practices that may be adopted to the local contexts and across VAD centers. The first results are expected to be submitted for publication in 2019.

Discussion

Strengths

Although current emphasis is placed on surgical technical competence and checklists, further improvements in patient safety and outcomes may only be achieved with greater attention to optimizing the organization of clinical practice to reliably deliver safe and effective care. Our mixed methods study has several strengths. First, we will employ network analytic tools to assess whether provider teamwork is a determinant of variation in center-level HAI rates. This analytic method will enable us to account for differences in collaboration and communication across provider teams that would not be captured through traditional patient risk factors. Second, we will employ a novel patient tracer mixed methods assessment in which center-specific outcomes inform our qualitative investigation as we follow a hypothetical patient through each critical transition (or stop) of the patient's care trajectory. Using this novel technique, we will identify potentially modifiable contexts, communication, and practices that could be missed if solely relying on quantitative approaches. Third, we will enhance our toolkit's adoption by field testing a prototype during site visits to assess end-user usability and adoption, incorporating broad provider community input at an annual cardiac surgical conference (eg, the International Society for Heart and Lung Transplantation) before national dissemination and conducting follow-up surveys to assess the uptake of the toolkit.

Limitations

Although unlikely, there are a few unanticipated challenges with this study. First, it is possible that we will not identify determinants of HAI across centers. There is a possibility that we will not find distinct HAI determinants across centers. However, given the documented center variability in anticoagulation practices and pump implant techniques, we anticipate ample variability related to HAI prevention practices [68]. Second, in the case of unobserved variability in HAI rates, we may have to adjust our qualitative sampling frame to include other relevant characteristics where variability is likely. However, we will use maximum variation sampling among the 5 low-performing and 5 high-performing centers to adjust the selection of sites to incorporate other selection criteria (eg, center volume and strength of provider network) [62]. Third, we may encounter unanticipated issues regarding the toolkit receptivity by US VAD centers. However, we will use the iterative stakeholder testing process to incorporate context-specific elements and ensure broad generalizability of the toolkit.

Conclusions

This study seeks to elucidate determinants of HAI across clinical centers using quantitative approaches and identify context-specific facilitators and barriers for attaining low HAI rates using qualitative approaches. We will use these findings to develop and disseminate a stakeholder-acceptable toolkit of evidence-based HAI prevention recommendations that will accommodate the specific needs of VAD centers and address AHRQ patient safety guidelines [65]. The overall mixed methods approach may offer an investigative model for evaluating and improving clinical care, particularly in the area of complex surgical procedures.

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Conflicts of Interest

None declared.

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Abbreviations

AHRQ: Agency for Healthcare Research and Quality
CMS: Center for Medicare and Medicaid Services

FDA: Food and Drug Administration
HAI: health care–associated infection
INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support
NHLBI: National Heart, Lung, and Blood Institute
NIH: National Institutes of Health
VAD: ventricular assist device

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Protocol

Examining the Ethical Implications of Health Care Technology Described in US and Swedish PhD Dissertations: Protocol for a Scoping Review

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Abstract

Background: The development of new biomedical technologies is accelerating at an unprecedented speed. These new technologies will undoubtedly bring solutions to long-standing problems and health conditions. However, they will likely also have unintended effects or ethical implications accompanying them. It may be presumed that the research behind new technologies has been evaluated from an ethical perspective; however, the evidence that this has been done is scant.

Objective: This study aims to understand whether and in what manner PhD dissertations focused on health technologies describe actual or possible ethical issues resulting from their research.

Methods: The purpose of scoping reviews is to map a topic in the literature comprehensively and systematically to identify gaps in the literature or identify key evidence. The search strategy for this protocol will include electronic databases (eg, ProQuest, PubMed, Diva, SwePub, and LIBRIS). Searches will be limited to PhD dissertations published in the United States and Sweden in the last 10 years. The study will be mapped in 5 stages: (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) retrieving and charting the data, and (5) collating, summarizing, and reporting the results.

Results: The findings of this study will indicate if and how researchers, PhD students, and their supervisors are considering ethics in their studies, including both research ethics and the ethical implications of their work. The findings can guide researchers in determining gaps and shortcomings in current doctoral education and offer a foundation to adjusting doctoral research education.

Conclusions: In a society where technology and research are advancing at speeds unknown to us before, we need to find new and more efficient ways to consider ethical issues and address them in a timely manner. This study will offer an understanding of how ethics is currently being integrated into US and Swedish PhD dissertations and inform the future direction of ethics education at a doctoral level.

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KEYWORDS

ethics; biomedical; technology; dissertation; doctoral education; scoping review; protocol

Introduction

Background

The importance of understanding the ethical implications of new health technologies is more important now than ever owing to the accelerated speed in which it is developing. Having insight into the possible ethical implications of new health technologies enhances research and development, thereby increasing the likeliness of successful implementation in clinical practice. It may be presumed that the findings presented in dissertations

have been evaluated from an ethical perspective; however, evidence that this is the case is scant. This review protocol is developed to evaluate to what extent and how ethical issues are being addressed in PhD dissertations that focus on health technologies. This can give insight into and steer what ethical and moral education would prepare future researchers and academics for recognizing and addressing ethical issues. The proposal builds on a 2-year grant that focused on evaluating and integrating ethics when developing new health technologies [1].

The development of new technologies is accelerating at an unprecedented speed. It is predicted that in the next century, our earth will experience as much change as we have in the preceding 20,000 years [2]. These technological changes will also include medical advances such as electronic health, robotics, genomics, bioinformatics, nanotechnology, and numerous others [3,4]. This will undoubtedly bring solutions to long-standing problems and health conditions. However, they will likely also have a shadow side in the form of unintended effects or ethical implications accompanying them [5]. Owing to the rate at which technology is advancing, bioethics is falling further and further behind in staying current with new evolving issues. This is mainly because examining ethical issues has historically occurred retrospectively, which is a slow process [6,7]. Developers of new health technologies should thus be integrating ethical discernment early on in the development and research phase.

Much has been written, discussed, and taught about the importance of performing health research involving human subjects in an ethical manner and in accordance with strict guidelines [8-10]. In addition, medical and health journals should no longer publish research that has not gone through an ethical review by an independent ethics board [11]. These ethical review boards limit their review to the ethics of the study itself by reviewing issues such as informed consent, coercion, and risks or benefits to study participants. Research ethics and the role of the ethical review boards limit themselves exclusively to the ethical nature of research studies and do not consider possible ethical and unintended effects resulting from the research findings after the study has been completed. Efforts have been made in teaching and socializing [12] ethical and moral thinking and behaviors as a part of doctoral education [13-15]; however, the impact of those efforts remains to be determined. A number of studies have focused on the extent that research ethics is discussed in PhD dissertations and found deficiencies in the extent that the ethics pertaining to the *study method* was addressed [16-18]. The primary focus of this study is to evaluate the extent to which PhD students have addressed the *ethical implications* of their work, not only limited to the study method.

To be proactive in anticipating and understanding the ethical implications of these new developments, research ethics should be considered from each study's conception. A researcher's awareness of possible ethical implications will allow him or her to respond proactively and address issues at an early stage, which points toward the importance of developing this awareness and capability to respond already during the postgraduate training of new researchers. To obtain an understanding of this practice, this study will analyze dissertations that pertain to health technology and analyze to what extent ethical implications are discussed and how they are addressed. As PhD students work with advisors/supervisors and dissertation committees, the findings from this study will also give a general insight into how senior academic researchers understand and value the ethical implications of research. Thus, this study does not intend to be a comprehensive overview of specific ethical issues in health technologies nor offer a comprehensive overview of all technologies; instead, it will focus on giving preliminary insights into what extent doctoral students are incorporating ethics in their work. This information is essential to identify if educational changes need to be made in doctoral education to allow for a more proactive approach to identifying the ethical and unintended effects of one's research.

Objective

This study aims to understand in what manner and whether PhD dissertations focused on health technologies describe actual or possible ethical issues resulting from their research. This study will examine US and Swedish PhD dissertations with the future objective of showing the applicability of the protocol in other countries.

Methods

Study Design

The method of inquiry for this study will be a scoping review based on a study by Arksey and O'Malley [19] comprising 5 stages: (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) retrieving and charting the data, and (5) collating, summarizing, and reporting the results.

Stage 1: Identifying the Research Question

In the context of scoping reviews, maintaining a broad approach in the first instance improves the possibility to generate a breadth of coverage and allows setting parameters based on the scope and volume of references generated. For this scoping study, the overarching research question is the following:

> *Are US and Swedish PhD dissertations researching health care technologies addressing possible ethical implications of their research findings, and if so how?*

Answering this question will not only require a thorough examination of the extent to which PhD students are considering possible ethical issues during the design phase of their study but also if and how the ethical implications of their research findings are discussed in their dissertation.

For this study, we will use the definition of *technology* as defined by Jacques Ellul as the underlying ethical framework and theory [20]. Ellul argues that the basis of all technologies are techniques, systems that make a process more efficient [20]. Technologies are typically devices or systems that automate 1 or more techniques. On the basis of this view, this proposal considers *technology* to be broader than mere electronic devices and equipment and also include *techniques* such as health economics, risk management, health quality assurance, and genomics [20]. The importance of understanding the impact of

techniques and technology, such as the ethical implications, is thus crucial in fully comprehending the full effect of new technologies. A list of technologies (Textbox 1) presented in the World Health Organization (WHO) report, "Human Resources for Medical Devices, the Role of Biomedical Engineers" [21], will be used to identify current technologies and techniques used worldwide. The WHO listing was selected because of the comprehensive nature and scope of technologies and techniques. The list includes not only devices but also techniques to help manage health care delivery, which is in line with the definition of technology and technique as identified by Ellul [20]. To confirm the validity of using these terms concerning ethics and health care technologies, we will perform a search among all original peer-reviewed publications written in English and listed in PubMed in the period 2009 to 2019. The search will explore to what extent publications are mentioning ethics accompanying technologies. The following searches will be performed:

1. Term of technology in title or abstract
2. Term of technology + ethics or unintended effects in text
3. Term of technology + ethics or unintended effects in title or abstract in text.

Findings will be entered into a matrix describing the number of articles identified by each search combination. A total of 168 searches (56 terms x 3 searches) will be performed during this stage.

Stage 2: Identifying Relevant Studies

To identify dissertations as comprehensively as possible for answering the research question of this study, the search strategy will involve searching broadly via multiple sources. Electronic databases will primarily be used, but other sources will be considered in the context of practicability. The following databases will be prioritized, based on topic and coverage:

- US PhD dissertations:
  - ProQuest Dissertations and Theses—contains dissertations and theses from over 1000 North American and European universities (only a limited number of Swedish universities are indexed in ProQuest and the use of ProQuest will be limited to US dissertations).
- Swedish PhD dissertations:
  - LIBRIS—the national catalogue for Swedish PhD dissertations covering a substantial part of all the books and periodicals published in Sweden from the 16th century onward.
  - SwePub—contains references to research publications from approximately 40 Swedish universities and other publication databases. Selection and extent vary among contributing universities and authorities.
  - DiVA portal—an institutional repository for research publications and student theses written at 47 universities and research institutions in Sweden.

To identify dissertations that refer or mention ethics in relation to technology or techniques defended in the US and Sweden during the last 10 years, each database will be searched for the terms used by WHO in the report, "Human Resources for Medical Devices, the Role of Biomedical Engineers" [21] (Textbox 1). The following search strategy will be used:

1. Term of technology
2. Term of technology + ethics in title or abstract
3. Term of technology + ethics in text

Stage 3: Selecting Studies

Unlike systematic reviews, inclusion and exclusion criteria in scoping reviews are developed posthoc, once there is familiarity with the literature. However, all dissertations written in a language other than English or Swedish will be excluded. Our focus is on PhD dissertations researching a technique or technology intended to improve or impact the health of individuals or a population. This will include health treatments, diagnostic and testing equipment, health monitoring systems, and quality assurance and health economics systems. Even though we anticipate most dissertations to be from health sciences such as medicine, nursing, and physical therapy, other disciplines will also be included as indicated to assure an accurate and comprehensive overview.

Stage 4: Retrieving and Charting the Data

The process for classifying and synthesizing the data retrieved involves 2 steps: first, to map how the dissertations are distributed according to the search terms, that is, technology and technique terms and ethics, and second, to map in relevance to the research question.

Charting the data retrieved will involve classifying and synthesizing the data identified in the dissertations. The steps for mapping the data will be the following:

1. Step 1.0—Map the distribution of dissertations among the 56 search terms (from the WHO human resources for medical devices report) for technologies and techniques
2. Step 2.0—Map publication years, disciplines, and names of universities
3. Step 2.1—Map dissertations into groups describing different topic areas
4. Step 2.2—Map the extent of mentioning and elaboration of ethics in the dissertations.

Textbox 1. Subspecialisms of biomedical engineering.

Research and development

1. Biomechanics
2. Biomaterials
3. Bioinformatics
4. Systems biology
5. Synthetic biology
6. Bionics
7. Biological engineering
8. Nanotechnology
9. Genomics
10. Population health or data analytics
11. Computational epidemiology
12. Intellectual property innovation
13. Theranostics
14. Biosignals

Rehabilitation

15. Artificial organs
16. Neural engineering
17. Tissue engineering or regeneration
18. Mechatronics
19. Assistive devices
20. Rehabilitation software
21. Prosthetics

Application and operation: clinical engineering

22. Technology management
23. Health quality assurance
24. Health regulatory assurance
25. Health education and training
26. Ethics committee
27. Clinical trials
28. Disaster preparedness
29. eHealth
30. Telemedicine
31. mHealth
32. Wearable sensors
33. Health economics
34. Health systems engineering
35. Health technology assessment or evaluation
36. Health informatics
37. Service delivery management
38. Field service support
39. Heath and security
40. Heath and privacy

41. Heath and cybersecurity
42. Forensic engineering or investigation
43. Manufacturing QMS
44. Manufacturing GMP
45. Medical imaging
46. Project management
47. Robotics
48. Virtual environments
49. Risk management
50. EMI compliance
51. EMC compliance
52. Technology Innovation strategies
53. Population- and community-based needs assessment
54. Engineering asset management
55. Environmental health
56. Systems science

Selected and included dissertations will be manually assessed by using a self-developed Dissertation Ethics Assessment Tool recording; 1) year, 2) discipline, 3) name of University, 4) topic area, 5) discussion of research ethics "Quotations of texts", 6) discussion of unintended effects of ethical issues of the research findings "Quotations of texts", 7) suggestions regarding ethics or unintended effects offered "Quotations of texts", and 8) comments. Data coding and categorization will be performed by 2 researchers independently, and findings will be compared and discussed. When there is a difference in assessment, the researchers will discuss to come to a consensus. If no consensus is achieved, the dissertation will be excluded from the study.

Stage 5: Collating, Summarizing, and Reporting the Results

Processing of the results in a scoping review does not emphasize the level or quality of evidence presented, but instead develops a thematic framework based on the existing literature relating to the research question. This study will focus on the sections found in the dissertations that pertain to (1) research ethics and (2) ethical implications of the research that are described.

This will be qualitatively analyzed by using the Web-based research tool, Covidence. Any sections from dissertations that mention *ethics* will be entered into Covidence for coding and analysis purposes. After the data are entered, data analysis will be based on the work of Cobin et al [22,23]. First, qualitative data analysis will focus on identifying codes, phrases, or words with an objective to organize the data. Second, a unified coding system will be developed, and codes will be collapsed into categories while continuing to code the data when relevant. Finally, the categories will be abstracted into themes, and narrative descriptions will be written for each theme. The Covidence tool was selected as it allows for several researchers to code and analyze the same dataset simultaneously and is specifically intended for use for this type of research. The authors will follow and adapt Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines for systematic reviews to accurately report the analysis process and the outcomes from the study [24].

Results

The findings of this study will indicate how far researchers, PhD students, and their supervisors are considering ethics in their studies, including both research ethics and the ethical implications of their work. The importance of our findings is to help understand what deficits exist in the discussion of ethics in peer-reviewed research publications and in US and Swedish PhD dissertations. The findings can guide researchers in determining gaps and shortcomings in current doctoral education. These findings will offer a foundation for adjusting doctoral research education to meet the needs of a society in which research and technological advancement is accelerating at a rate previously unknown. The awareness of ethical issues will allow ethical implications to be addressed more responsively and to start thinking and addressing ethical implications at the beginning of a research project. Some limitations to the interpretations and applicability of the study are (1) the technologies researched will be based on the WHO classification, this might not be all-inclusive, (2) articles and dissertations that are relevant for this study might be missed, (3) discussion and education regarding ethics might occur during the PhD education without being reflected in the dissertations, and (4) studies might discuss ethics without using the term *ethics* and hence might not be captured in this study.

Discussion

In an era where technology and research are advancing at speeds unknown to us before, we need to find new and more efficient ways to consider these issues and address them in a timely manner. This study could offer ways of starting an ethical analysis earlier and making it a part of every researcher's

foundation. Not only will addressing ethical issues during the education of future researchers increase their knowledge, but it will also instill a higher level of accountability for how their research could be used in unethical ways.

This study will give insights into and steer what ethical education might prepare future researchers for joining the community of academics by completing a PhD. This study will contribute to the goal of teaching and embedding ethical thinking and moral discernment as part of PhD education to meet the needs of a world that is changing at an accelerating pace.

Conflicts of Interest

None declared.

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Abbreviations

WHO: World Health Organization

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