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Protocol

Optimizing the Context of Support to Improve Outcomes of Internet-Based Self-help in Individuals With Depressive Symptoms: Protocol for a Randomized Factorial Trial

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Abstract

Background: Internet-based self-help interventions for individuals with depressive symptoms, in which the main component is often a web-based self-help program, have been shown to be efficacious in many controlled trials. However, there are also trials on self-help programs showing no significant effect when delivered in routine care, and some studies report high dropout and low adherence rates. Research suggests that these findings do not emerge primarily due to the specific content of a self-help program. It seems more important how a program is embedded in the context of human and automated support before and during the use of a self-help program.

Objective: This study aims to better understand the effects of 4 supportive contextual factors on outcomes of and adherence to a web-based self-help program for depressive symptoms. In a factorial experiment, 2 of 4 supportive factors, for which there is evidence for their role on outcomes and adherence, are realized during the intervention—personal guidance and automated email reminders. The other 2 factors are realized before the intervention—a diagnostic interview and a preintervention module aimed at increasing the motivation to use the program with motivational interviewing techniques.

Methods: The study is a full factorial randomized trial. Adults with mild to moderate depressive symptoms (Patient Health Questionnaire–9 score: 5-14) are recruited from the community through the internet and conventional media. All participants receive access to a web-based self-help program based on problem-solving therapy. They are randomized across 4 experimental factors, each reflecting the presence versus absence of a supportive factor (guidance, automated reminders, diagnostic interview, preintervention module) resulting in a 16-condition balanced factorial design. The primary outcome is depressive symptoms at 10 weeks post assessment. Secondary outcomes include adherence to the program, anxiety, stress, health-related quality of life, possible negative effects, and treatment satisfaction. Potential moderators and mediators (eg, treatment expectancy, problem-solving skills, working alliance with the study team) will also be investigated.

Results: Ethical approval was received on January 20, 2020. The study was initiated in February 2020, and 240 participants have been enrolled in the study as of November 1, 2020. Recruitment for a total of 255 participants is ongoing. Data collection is expected to be completed by May 2021.

Conclusions: A better understanding of relevant supportive factors in the dissemination of web-based interventions is necessary to improve outcomes of and adherence to web-based self-help programs. This study may inform health care systems and guide decisions to optimize the implementation context of web-based self-help programs for depressive symptoms.

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KEYWORDS

depression; self-help; adherence; internet-based intervention; factorial design; problem-solving therapy; online; mental health; multiphase optimization strategy; digital health

Introduction

Depression is one of the most common mental disorders that burdens society and individuals psychologically and financially [1,2]. Psychological consequences of depression include lower quality of life and more years lived with disability [3,4]. Although psychotherapy is an established evidence-based treatment option for depression [5], people often do not receive adequate care [6-8]. Internet-based self-help interventions are promising to reduce the burden of depression. During the last two decades, several research groups intensively studied the efficacy of internet-based self-help interventions and concluded that they effectively reduce depression [9-12].

Internet-based self-help interventions complement existing interventions in health care, addressing some of their limitations. Potential advantages of internet-based self-help interventions include that they are easily accessible, provide a high degree of anonymity, can be used independently of time and place, and can be provided to many people simultaneously. Hence, many authors suggest internet-based self-help interventions as a possibility to complement face-to-face psychotherapy to improve mental health care [13].

Although internet-based self-help interventions effectively reduce depressive symptoms, their potential might not be fully exploited. For example, studies [10] about internet-based self-help interventions for depression report a wide range of effect sizes (Hedges g=0.02-1.56). One study [14] that investigated widely used internet-based self-help interventions for depression failed to transfer the established effects into other settings, such as primary care. Further challenges of internet-based self-help interventions are low uptake rates (ie, logging into an intervention) and low levels of adherence (eg, completing modules of an intervention) [15,16].

One reason for diverging outcomes and adherence seems to be the degree of human support and guidance provided before and during the use of a self-help program. Current literature suggests that unguided internet interventions without human support at any stage tend to be associated with high dropout rates [17], lower adherence [18], and lower effects [11]. In a review [19], the authors suggested there were positive effects from guidance during the treatment on outcome in depressive patients. Additionally, several meta-analyses [9,12,20,21] report larger symptom reductions in guided self-help interventions with therapist support during the treatment compared to unguided self-help interventions without therapist support during the treatment. However, the differences between guided and unguided interventions may also be related to other factors such as the scope of diagnostic assessments or the length and content of a self-help program. These and other factors may confound the association between guidance, adherence, and outcomes. It is worth mentioning that in some studies [22,23] directly comparing self-help interventions with and without guidance, no significant differences were reported about the outcomes and number of modules completed.

In the review [19], the authors propose that other forms of human interaction (such as pretreatment contact) might also be beneficial for the treatment with internet-based self-help interventions. In a study [24] with patients that have social anxiety disorder, a diagnostic telephone interview conducted before an internet-based intervention significantly improved adherence to treatment and secondary outcomes of depression and stress.

Other aspects that potentially improve internet-based self-help intervention outcomes and adherence can be automated and realized without human contact. There is limited evidence that automated email reminders may improve adherence and outcomes of internet interventions. For example, a study [25] that compared semistandardized email feedback with fully standardized email feedback did not find a difference in the 2 conditions indicating that fully automated emails may be as effective as semistandardized feedback. Furthermore, in a transdiagnostic intervention, email reminders resulted in better outcomes for participants who had elevated co-occurring symptoms of anxiety and depression [26]. However, this did not apply to participants with elevated symptoms of either just anxiety or depression. In the same study [26], the reminders increased the number of people completing the intervention. Consistent with this finding, some participants mentioned that they experience email reminders helpful for adhering to the intervention [27].

Another possibility for increasing outcomes of and adherence to internet-based self-help interventions is to enhance the motivation of participants. A well-known method in face-to-face treatments to address ambivalence and enhance motivation is motivational interviewing [28]. High effect sizes and increased adherence were observed in a study [29] with motivational interviewing prior face-to-face psychotherapy treatment. A study [30] on an internet-based self-help intervention for social phobia was able to replicate these findings for internet-based self-help interventions to some extent—whereas participants of the group that received an additional motivational interviewing–based intervention did not show a higher magnitude of improvement, these participants were more likely to complete the treatment. Furthermore, for patients with depressive symptoms, a brief informational video about internet-based self-help interventions significantly increased the acceptance of internet-based self-help interventions [31].

Thus, several supportive contextual factors have been associated with better outcomes and increased adherence. Yet, it is not entirely clear which factors are crucial for a significant enhancement of internet-based self-help interventions. Consequently, clear guidelines for how to optimally embed

internet-based self-help interventions into a context of supportive factors are missing. To fully exploit the potential of internet-based self-help interventions, dismantling studies are needed to understand how and which supportive factors are essential when disseminating internet-based self-help interventions. Often, studies that investigated the influence of a specific supportive factor such as guidance had other factors in their study design that potentially confounded the effect of guidance (eg, a diagnostic interview). Therefore, only conclusions about the whole treatment package (eg, internet-based self-help intervention, diagnostic interview, and guidance combined) and not about individual supportive factors (eg, either diagnostic interview or guidance) were possible. This entanglement limits insight into both the main effect of a given factor and possible interactions with other factors.

One reason for limited insight into essential supportive factors may be reliance upon RCTs in internet-based self-help intervention research. Although RCTs are the gold standard for establishing the efficacy or effectiveness of an intervention, they are not suited for investigating the effects of single supportive factors or specific treatment components. Because RCTs only compare the whole multifactorial intervention (treatment package) with another intervention or a control group, specific mechanisms are confounded with one another. Therefore, it is only possible to draw conclusions about the whole treatment package and not about the main and interactive effects of specific factors [32].

A new approach to getting more insight into how treatments work is the multiphase optimization strategy, which integrates perspectives, approaches, and concepts of various sciences [33]. Collins and Kugler [33] suggest that behavioral intervention research has focused too much on establishing the efficacy of treatments rather than understanding how treatments work and how they could be optimized. The multiphase optimization strategy's fundamental idea is to optimize interventions to meet specific criteria such as effectiveness, economy, or scalability. Interventions can be optimized by making decisions based on findings about which intervention components work and which intervention components do not work, which ones work well together, or which ones adversely affect each other.

The multiphase optimization strategy presents several experimental designs to optimize interventions. The most frequently used in behavioral sciences is the factorial design [34-36]. This design allows investigating multiple factors simultaneously within one trial. It can reveal which factors are active or inactive in influencing the desired outcomes. More specifically, factorial experiments allow exploring the main effects of and possible interactions between factors. Consequently, the findings of a factorial design study are suited to optimize a given intervention because they provide information about which factors can be kept and which factors can be omitted. Note that Collins and Kugler [33] do not claim that RCTs can be replaced with factorial designs. Rather, they suggest an integrative strategy that focuses both on optimizing interventions (for which there are better designs than RCTs) and establishing efficacy or superiority of interventions (for which RCTs are still the best option).

This study aims to further clarify the optimal context of support of internet-based self-help interventions for depressive symptoms. It uses a factorial design to test the impact of 4 factors and their combinations. These factors are (1) a diagnostic interview conducted before the intervention, (2) a preintervention module using techniques of motivational interviewing accessible before the intervention, (3) human guidance during the intervention, and (4) automated email reminders during the intervention.

Methods

Study Design

The study, including assessments and the self-help intervention, will be conducted online. Participants will not receive any financial reimbursement for taking part in the study. The study consists of a full factorial trial that includes 4 experimental factors. Each factor will be evaluated at 2 levels (either present or absent), resulting in a 16-condition (2×2×2×2) balanced full factorial design (Table 1). Factorial designs allow for reliably estimating all main effects and 2-factor interactions. To do so, the full sample (ie, participants from all 16 conditions) are used. Thereby, power remains associated with all participants as half of the participants are in a condition with a specific factor active, and half of the participants are in a condition with a specific factor inactive. This makes the factorial design efficient with respect to sample size and power.

Table 1. Overview of the 16 experimental conditions of the full factorial design—every factor is balanced; therefore, each is present and absent an equal number of times.

Condition	Diagnostic interview	Preintervention motivational interviewing module	Guidance	Email reminders
1	✓[a]	✓	✓	✓
2	✓	✓	✓	—[b]
3	✓	✓	—	✓
4	✓	✓	—	—
5	✓	—	✓	✓
6	✓	—	✓	—
7	✓	—	—	✓
8	✓	—	—	—
9	—	✓	✓	✓
10	—	✓	✓	—
11	—	✓	—	✓
12	—	✓	—	—
13	—	—	✓	✓
14	—	—	✓	—
15	—	—	—	✓
16	—	—	—	—

[a]Factor is present.

[b]Factor is absent.

Participant Eligibility

Eligible participants are German-speaking residents of Switzerland, Germany, Austria, and Lichtenstein. Inclusion criteria are (1) being at least 18 years of age; (2) meeting criteria for mild to moderate depression (score between 5 to 14 on the Patient Health Questionnaire–9) [37]; (3) providing written informed consent; (4) having access to the internet as well as an email account; and (5) providing an emergency contact before treatment. The study allows participants to take part even if they currently receive constant antidepressant medication or psychotherapy treatment. Exclusion criteria are (1) having a history of a psychotic or a bipolar disorder and (2) having increased suicidal tendencies (a score >7 on the Suicide Behaviors Questionnaire-Revised)[38,39].

Study Procedure

Interested participants can leave an email address on our study website [40]. Participants will automatically receive study information and an informed consent sheet (by email). After providing informed consent, participants are invited to complete the baseline assessment. Study eligibility is assessed and if included in the study, participants must wait 2 weeks before they can start with the intervention. Depending on which condition participants are randomized to, during these 2 weeks, participants either wait, are diagnostically interviewed, receive access to the preintervention motivational interviewing module, or receive both the interview and the preintervention motivational interviewing module (see Table 2).

Table 2. Study flow and overview of study variables.

Study activity	Study period and timepoint					
	Allocation		Postallocation			Follow-up
	Week 0, T0	Week 0-2	Week 2, T1	Week 4, T2	Week 10, T3	Week 16, T4
Enrollment						
Registration	✓	—[a]	—	—	—	—
Informed consent	✓	—	—	—	—	—
Eligibility screening	✓	—	—	—	—	—
Randomization	✓	—	✓	—	—	—
Treatment						
Internet intervention	—	—	✓	✓	✓	✓
Factors						
Diagnostic interview	—	(✓)[b]	—	—	—	—
Motivational interviewing module	—	(✓)	—	—	—	—
Guidance	—	—	(✓)	(✓)	(✓)	—
Automated emails	—	—	(✓)	(✓)	(✓)	—
Surveys						
Patient Health Questionnaire–9[c]	✓	—	✓	✓	✓	✓
Generalized Anxiety Disorder–7	✓	—	—	—	✓	✓
Patient Health Questionnaire–Stress	✓	—	—	—	✓	✓
Short Form health survey–12	✓	—	—	—	✓	✓
Suicide Behaviors Questionnaire–Revised	✓	—	—	—	✓	✓
Social Problem-Solving Inventory–Revised	✓	—	—	—	✓	✓
Client Satisfaction Questionnaire	—	—	—	—	✓	—
Working Alliance Inventory for Guided Internet Interventions	—	—	—	✓	✓	—
Credibility/Expectancy Questionnaire	✓	—	✓	✓	—	—
Inventory for the Assessment of Negative Effects of Psychotherapy	—	—	—	—	✓	✓
System Usability Scale	—	—	—	—	✓	—

[a]The study activity was not applied at this point.

[b]Parentheses indicate that factors apply to half of the participants.

[c]Primary outcome.

If individuals are excluded, they can make use of the intervention outside of the study. However, participants reporting suicidal ideation first need to confirm that they are in touch with their emergency contact or a psychotherapist. We offer to provide a contact for professional psychological help in case participants are severely depressed.

Recruitment

Participants are recruited through depression-related websites, radio interviews, self-help groups, Facebook groups, Google ads, and the website of the University of Bern (Switzerland). The description of our study includes a link to the study website. Written informed consent to participate in the study is obtained from all participants.

Intervention

The web-based self-help program *Herausforderungen meistern (overcoming challenges)* (HERMES) is based on problem-solving therapy [41]. The first, second, and last author developed the online program at the University of Bern. The problem-solving therapy intervention includes an introductory module and 3 toolkits: (1) Feeling, (2) Thinking, and (3) Acting. Problem-solving therapy shares various assumptions of cognitive behavioral therapy but focuses more explicitly on problems causing distress and problem-solving skills. We recommend that participants use the intervention approximately 1 hour per week and complete each module or toolkit within 2 weeks. This results in 8 weeks of recommended program use. An online problem-solving therapy intervention has previously been

investigated in a 3-arm RCT [42]. Results indicated that, compared to a waiting list control group, the online problem-solving therapy intervention was as effective as an online cognitive behavioral therapy intervention in reducing symptoms of anxiety and depression [42].

Within the factorial design, 4 factors are realized. The first factor consists of a diagnostic telephone interview conducted before the self-help program. The second factor is a preintervention module based on motivational interviewing presented before the self-help program. The module aims at initiating a reflection process about one's motivation for using the intervention [29]. The third factor is human support during the self-help program with personalized weekly emails. Guidance contains answering questions from participants within 3 working days and giving regular feedback on progress once a week. It is carried out by trained Master and PhD students who are supervised by licensed psychotherapists. The fourth factor is a set of weekly automatically sent emails during the self-help program. The emails inform participants on how far they should be in the program approximately, suggest content to work on next, and remind participants that they take part in a study. In contrast to human support (guidance), these emails are not individualized and contain the same information for all participants. In addition to these emails, prompts are sent to participants who have not logged in for 1 week. Our research focuses on investigating the context of human and automated support when providing web-based interventions. This implies that all participants receive the same main intervention with all program components of HERMES and that the main intervention is not changed throughout the whole study.

Study Outcome Measures

All outcome measures will be assessed online with validated German versions of the original questionnaires.

Primary Outcome Measure

Symptoms of depression will be assessed with the self-reported measure Patient Health Questionnaire–9 [37]. The Patient Health Questionnaire–9 has good diagnostic validity, sensitivity, and specificity and is a commonly used measure to assess and monitor depression severity [43].

Secondary Outcome Measures

Adherence is defined as the extent to which participants use the intervention. Following the suggestion of Donkin et al [44], a composite score encompassing time spent in the intervention, number of modules completed, number of exercises completed, number of log-ins, and number of clicks in the intervention will be used to measure adherence to the intervention. The composite score will be created by averaging the *z* scores of these indicators. Furthermore, and for exploratory purposes, we will also run the analyses with each of these indicators of adherence. Symptoms of anxiety will be assessed with the Generalized Anxiety Disorder–7 [45]. Symptoms of stress will be assessed with the stress subscale of the Patient Health Questionnaire [45]. Health-related quality of life will be assessed with the Short Form Health Survey–12 [46,47]. Suicidal ideation will be assessed with the Suicide Behaviors Questionnaire–Revised [38,39]. Problem solving will be assessed with the Social Problem Solving Inventory-Revised [48,49].

Treatment Characteristics

Possible adverse effects of the intervention will be assessed with the Inventory for the Assessment of Negative Effects of Psychotherapy [50]. Client satisfaction will be measured with the Client Satisfaction Questionnaire [51,52]. System usability will be assessed with the System Usability Scale [53,54].

Moderators and Mediators

Demographic information about participants will be assessed at baseline. Treatment expectancy will be assessed with the Credibility/Expectancy Questionnaire [55]. Working alliance with the online coaches will be assessed with the Working Alliance Inventory for Guided Internet Interventions [56].

Randomization

The online platform Qualtrics (Qualtrics XM) randomizes participants in 2 steps. First, after T0 and before any contact with the study team, participants are randomized automatically to 1 of 4 groups (1, diagnostic interview and motivational interviewing module; 2, diagnostic interview; 3, motivational interviewing module; 4, no factor). The first randomization is stratified (either mild or moderate depressive symptoms). Second, after 2 weeks and completing T1, participants are randomized to 1 of 4 groups (1, guidance and email reminders; 2, guidance; 3, email reminders; 4, no factor). Both times, block randomization ensures a balance in sample size across groups over time. A schedule of enrollment and participation is shown in Table 2.

Data Collection, Management, and Analysis

Participants complete questionnaires at all 5 time points online via Qualtrics. We manually invite participants to complete the baseline questionnaire (T0). The 4 subsequent time points (after 2, 4, 10, and 16 weeks) are automatically triggered once T0 is completed. We try to limit the amount of missing data from survey attrition by reminding participants after 5 and 10 days to complete the questionnaires.

Statistical Analysis

Statistical reporting will follow CONSORT [57] and CONSORT-EHEALTH standards [58]. We will conduct primary analyses using intention-to-treat. The primary outcome is the change in Patient Health Questionnaire–9 score from baseline to 10 weeks and 16 weeks. Dropout rates are examined per condition. Before the 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.

To test for the main and interaction effects of treatment components on primary and secondary outcomes, linear mixed model analysis of variance will be used. This approach uses all available data on each subject and does not involve the substitution of missing values but estimates parameters about missing values. However, sensitivity analyses will explore the impact of the imputation of missing values before computing the mixed models. The main effects and interactions will be

based on aggregates across experimental conditions. The purpose of the factorial experiment is not to compare the 16 conditions to each other but to estimate the main effects of the 4 factors and interactions between the factors. For example, the main effect of the diagnostic interview will be estimated by comparing the mean of the experimental conditions in which this factor is present (conditions 1-8 in Table 1) versus the mean of the experimental conditions in which this factor is not present (conditions 9-16 in Table 1). No adjustment for multiple testing will be applied in the estimation of statistical significance because, in the optimization phase of the multiphase optimization strategy framework, the emphasis is on deciding what components will make up the optimized intervention [33]. Only a future RCT can then establish the superiority of the optimized intervention over other conditions.

Power Analysis

We conducted an a priori power analysis for small-to-medium effect sizes (Cohen *d*=.35) for main effects and interactions between 2 factors (eg, guidance and diagnostic interview) on change in depressive symptoms (G-Power 3.1). From a clinical perspective, smaller effects are considered to be less relevant [59]. For type I error α=.05, with a common power of .80 to detect effects. Based on previous studies, we assume that our measurements regarding pre, post, and follow-up correlate at approximately *r*=.60. For a factorial design, this signifies a sample of n=204 to detect effects. Because we expect a dropout rate of about 20%, the planned sample size is n=255. For every condition, roughly 15 participants are required.

Results

The study was registered at ClinicalTrials.gov (NCT04318236). The ethics committee of the canton of Bern (*Kantonale Ethikkommission Bern*) approved the study on January 20, 2020 (2019-01795). Recruitment started in February 2020. As of November 1, 2020, out of 1480 interested individuals, 409 individuals have completed T0, and 240 participants have been enrolled in the study.

Discussion

Overview

The primary outcome is depressive symptoms 10 weeks after baseline. Several secondary outcomes will be measured, such as symptoms of anxiety and stress, health-related quality of life, suicidal ideation, and problem solving. Possible moderating (age, gender, and adherence) and mediating (treatment expectancy, therapeutic alliance) effects will be tested. Furthermore, negative effects of psychotherapy, treatment satisfaction, system usability, and dropout rates will also be measured and inspected. This study builds on a wealth of encouraging efficacy studies of internet-based self-help. It promises to provide a more detailed insight into which supportive context factors enhance outcomes of and adherence to internet-based self-help interventions for depressive symptoms. Furthermore, the study may also inform about possible mediation and moderation effects that could provide more information about how or why internet-based self-help interventions for depressive symptoms work.

Strengths and Limitations

Our study has been designed to shed more light on the supportive context of internet-based self-help interventions. It deconstructs a treatment package and explores active and inactive supportive factors. Understanding which factors do and do not work will help us get closer to the goal of delivering internet-based self-help interventions optimally. According to the guidelines of multiphase optimization strategy, a future RCT should test an intervention providing an optimal supportive context based on our findings, against an intervention providing a context that is usual in studies about internet-based self-help interventions (eg, an intervention with guidance). With such a study, the possible superiority of the optimized context could be established.

Limitations of this study are comparable to those of the majority of studies about internet-based self-help interventions. The sample of this study is self-selected and participants become aware of our study through the internet. This limits the generalizability of possible findings to regular clinical settings or individuals that rarely use the internet.

Conclusion

To improve outcomes to future internet-based self-help interventions for depression, this study could provide recommendations on how to optimize the context of human and automated support. Based on findings of active and inactive factors and the interactions thereof, recommendations could be made for future research and the implementation and dissemination of internet-based self-help interventions in routine care.

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Authors' Contributions

OTB and TB designed the study. OTB is responsible for the data collection. OTB wrote the first version of the manuscript. TK, SM, JPK, and TB read the manuscript and provided suggestions for improvements. All authors approved the final version of the manuscript.

Conflicts of Interest

JPK received funding for clinical trials (German Federal Ministry of Health, Servier), payments for presentations on internet interventions (Servier), payments for workshops and books (Beltz, Elsevier, Hogrefe, and Springer) on psychotherapy for chronic depression and on psychiatric emergencies. Other authors declare no conflicts.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
HERMES: Herausforderungen meistern (overcoming challenges)
RCT: randomized controlled trial

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Protocol

A Brief Mobile-Augmented Suicide Prevention Intervention for People With Psychotic Disorders in Transition From Acute to Ongoing Care: Protocol for a Pilot Trial

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Abstract

Background: People with serious mental illnesses (SMIs) are at exceptionally high risk for lifetime suicidal ideation and behavior compared with the general population. The transition period between urgent evaluation and ongoing care could provide an important setting for brief suicide-specific interventions for SMIs. To address this concern, this trial, SafeTy and Recovery Therapy (START), involves a brief suicide-specific cognitive behavioral intervention for SMIs that is augmented with mobile phone interactions.

Objective: The primary aim of this pilot trial is to evaluate the feasibility, acceptability, and preliminary effectiveness of the intervention.

Methods: A 6-month pilot trial with 70 participants with a diagnosis of bipolar disorder, schizophrenia or schizoaffective disorder, and current active suicidal ideation were randomized to START or START with mobile augmentation. START consists of 4 weekly sessions addressing early warning signs and triggers, symptoms influencing suicidal thinking, and social relationships. Recovery planning is followed by biweekly telephone coaching. START with mobile augmentation includes personalized automated cognitive behavioral therapy scripts that build from in-person content. Participants were evaluated at baseline, 4 weeks (end of in-person sessions), 12 weeks (end of telephone coaching), and 24 weeks. In addition to providing point estimates of feasibility and acceptability, the primary outcome of the trial was the change in severity of suicidal ideation as measured with the Scale for Suicide Ideation (SSI) and secondary outcome included the rate of outpatient engagement.

Results: The trial is ongoing. Feasibility and acceptability across conditions will be assessed using t tests or Mann-Whitney tests or chi-square tests. The reduction of SSI over time will be assessed using hierarchical linear models.

Conclusions: The design considerations and results of this trial may be informative for adapted suicide prevention in psychotic disorders in applied community settings.

Trial Registration: ClinicalTrials.gov NCT03198364; http://clinicaltrials.gov/ct2/show/NCT03198364

International Registered Report Identifier (IRRID): DERR1-10.2196/14378

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KEYWORDS

prevention; mental health services; psychosis; technology

Introduction

Suicide in Serious Mental Illnesses

The burden of suicide is exceptionally high in serious mental illnesses (SMIs) such as bipolar disorder and schizophrenia. The lifetime risk of suicide in people with SMIs is 5% to 10% [1,2], which is 12 times the rate in the general population [3]. Recent evidence indicates that direct interventions (ie, those that specifically target suicidal thoughts, such as cognitive behavioral therapy [CBT] techniques) are more effective in reducing suicide risk than indirect interventions (eg, those that target depressive symptoms and promote treatment engagement) [4,5]. Unfortunately, most clinical trials of direct interventions exclude patients with psychotic symptoms or disorders [4,6]. Only a handful of trials of psychosocial interventions have been evaluated for their impact on suicidal ideation or behavior in schizophrenia (some of which are suicide-specific CBT [7,8]), and data on psychosocial interventions in suicide prevention are *virtually nonexistent* in bipolar disorder [9].

Intervention Targets for Suicide Prevention in People With SMIs

To address these gaps, the 2 key questions are as follows: (1) How might the content of suicide prevention interventions be adapted for people with SMIs? (2) Where and when would such interventions fit within the care continuum? One adaptation consideration is that people with SMIs appear to have some unique characteristics of suicidal ideation and behavior as well as the transition between them. For example, in psychotic disorders, suicidal ideation may be intertwined with hallucinations, suicidal ideation appears to be less transient [10], and suicidal ideation is more likely to be associated with suicide attempts than in people without psychosis [11]. The means used to attempt suicide are also different, and a history of psychosis is overrepresented in those with severe attempts [12]. Moreover, social support is frequently limited in SMIs [13], and people with SMIs may be less likely to self-initiate the use of suicide prevention services such as crisis lines [14]. Finally, although psychotherapeutic interventions such as CBT are effective for SMIs, they are typically adapted to accommodate aspects of these illnesses that may interfere with skill acquisition, such as cognitive impairments [15,16].

There are also unique considerations for fitting suicide prevention interventions into the care continuum in SMIs. A higher proportion of service use is in acute and outpatient specialty mental health services compared with primary care. Furthermore, services tailored to people with SMIs are increasingly tailored to reduce barriers to access given the high rates of disengagement from care. One emerging site of potential deployment for brief suicide prevention interventions for people with SMI is walk-in or *same-day* clinics. Walk-in clinics provide access to immediate unscheduled psychiatric evaluation and are the best practice in both the Zero Suicide framework [17] and for service engagement of people with SMIs [18]. These clinics aim to increase access to mental health care and provide an access point to initiate ongoing psychiatric outpatient care [19,20]. However, only a minority of patients seen in urgent care for suicidal ideation actually go on to engage in follow-up outpatient care [21].

SafeTy and Recovery Therapy

To address the gaps described earlier, we developed a brief suicide-specific intervention adapted for SMIs called SafeTy and Recovery Therapy (START). The intervention builds from prior work in CBT for suicide and SMIs. START consists of 4 sessions intended to fit within a typical gap period between urgent and ongoing care and to successively build suicide-specific skills. Furthermore, this brief in-person individual psychotherapeutic intervention is integrated with an automated mobile intervention. Emerging research has examined mobile health and telemonitoring interventions in suicide prevention [22-24], although less so in SMIs. Ecological momentary interventions (EMIs) couple brief in-person CBT with automated mobile assessment linked with personalized intervention content in SMIs [25-28] and deliver automated therapeutic content that extends the content of in-person CBT to everyday life. The role of EMIs in START is to promote recall and engagement in personalized, adaptive thoughts and behaviors aimed at suicide prevention by employing content collaboratively developed during in-person sessions.

To evaluate the START intervention, we developed a pilot clinical trial using a deployment-focused approach. The goals of this pilot trial were to evaluate the feasibility, acceptability, and preliminary effectiveness of the intervention. Here, we report our study design, intervention approach, and related considerations, which we hope will be informative for research on suicide-specific interventions for SMIs. Of particular interest, may be, design decisions in suicide-specific intervention clinical trials on SMIs, informed by guidance from the National Institute of Mental Health [29]. This study has the following aims:

- Aim 1: to refine intervention content and safety protocol with input from community stakeholders.
- Aim 2: to evaluate feasibility, engagement, impact, and preliminary comparison of START with Mobile Augmentation versus START alone.

Methods

Study Deployment Planning

This study is deployed in the public mental health system in San Diego, California. Study deployment relied on collaborative meetings with leadership, triage, and outpatient clinicians. Key components of these meetings included (1) a review of the draft manuals, study materials, and mobile app; (2) specifications of research team community communication plans, roles, documentation, and reporting protocols; and (3) emergency and safety planning for participants, research staff, and clinicians delivering the intervention. Front-line staff were afforded the opportunity to suggest and improve the approach, for example, where same-day clinics were in separate locations from outpatient centers, a suggestion was to split the sessions across these sites to allow participants the opportunity to transition sites and become comfortable with the outpatient clinic. To reduce the burden on sites and to increase the likelihood of consistent appropriate referrals, we held additional meetings

with triage providers during in-services and created a *pocket guide* detailing the study inclusion or exclusion criteria and procedures.

Recruitment Sites and Screening

Usual care in walk-in settings involves a diagnostic interview or intake with a triage provider (typically a social worker) and a psychiatric evaluation, which includes a standardized screening for suicidal thoughts and behavior. The outcome of these evaluations may include acute stabilization or hospitalization but is most frequently the initiation of medication treatment, linkage to resources, and an outpatient follow-up appointment for psychosocial care. The focal population of these clinics are people with SMIs, and individuals who do not meet the criteria for SMIs are referred to as primary care. To fit within these high acuity settings, our research screening is kept minimal and includes only the basic eligibility criteria, diagnostic screen, and recent and lifetime suicide history screening with the Columbia Suicide Severity Rating Scale (CSSR-S), lifetime version [30].

Eligibility

Participant inclusion criteria are as follows: (1) aged 18-65 years, (2) *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* diagnoses of bipolar disorder, schizoaffective disorder, or schizophrenia (confirmed by the Mini International Neuropsychiatric Interview [31]), and (3) suicidal ideation, defined as CSSR-S≥2 in the past 1 month and/or a suicide attempt in the past 3 months as identified by the CSSR-S. Additional inclusion criteria are as follows: (1) plans to remain in the region for ≥6 months and pending appointment for outpatient mental health treatment initiation and (2) capable of informed consent. Exclusion criteria are as follows: (1) not English speaking, (2) inability to complete the assessment battery, (3) insufficient visual acuity or manual dexterity to navigate a touch screen, (4) current intoxication requiring immediate detoxification or an outpatient plan directed to substance use disorder (not mental health) services, and (5) under conservatorship requiring proxy consent. Given that the population is vulnerable to impaired decisional capacity, we confirm the capacity to consent with a brief measure [32].

A key consideration for inclusion criteria was the floor and ceiling for suicide risk. We selected a floor for our suicidal ideation measure at active thoughts or higher (≥2 on CSSR-S), consistent with a recent clinical trial [33]. As our study is embedded in an urgent screening setting, triage provides a *ceiling* which is voluntary or involuntary hospitalization on the day of evaluation. Finally, due to high base rates in the population, we included people with active substance use disorder, provided that they do not require acute detoxification as a next step following triage, and we also included those with unstable housing.

Therapist Training

Therapists for the study are employees of the San Diego County mental health system and include triage evaluators and case managers. Therapists complete a 4-hour training with 5 components: (1) intervention model and rationale, (2) safety procedures, (3) trial protocol, (4) fidelity monitoring procedures, and (5) mobile intervention deployment. Embedded in the training are role-plays of specific skills, including redirecting sessions to suicide-specific concerns and conducting risk assessments or documentation of adverse events. Therapists are required to complete role-plays concerning safety assessment, describing the treatment model, and re-establishing focus on suicide-related concerns in sessions.

Randomization, Masking, and Trial Design Considerations

Participants are randomized to START with mobile augmentation or START alone. Randomization schedules are compiled by an independent statistician, and research assessors are kept masked to the assignment. Participants and the study therapists are not blinded to the assignment. Several factors led to our decision to include 2 active conditions in this pilot trial. First, we were encouraged by our prior trial that identified a statistically significant augmentative benefit of a mobile intervention immediately posttreatment with a comparable sample size, albeit in a somewhat different population. Second, we considered the primary success criteria for this pilot phase to start the absence of sustained changes in suicidal ideation (in aggregate) and secondary comparisons across the mobile-augmented and nonaugmented conditions were designed to yield information about preliminary differences in feasibility, acceptability, and hypothesized mediators of change (eg, recall of safety plans). Third, we considered a no-treatment control condition, but this design was not preferred by our stakeholder community partners. Moreover, due to the timing of the intervention to the gap period between urgent and ongoing care, a waitlist control would be impossible.

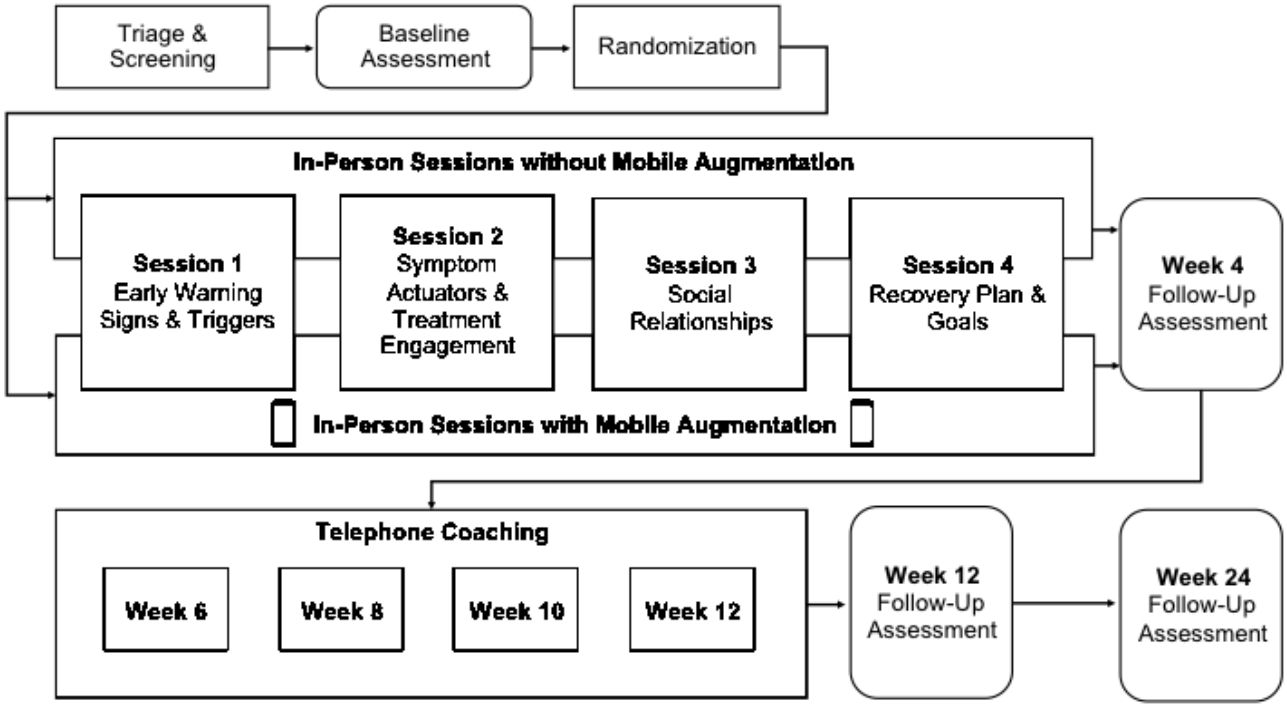
The primary success criteria for this pilot trial of START are sustained changes in suicidal ideation (in aggregate), and secondary comparisons across the mobile-augmented and nonaugmented conditions were designed to yield information about preliminary differences in feasibility, acceptability, outcomes, or hypothesized mediators of change (eg, outpatient engagement, recall of safety plans). Owing to the pilot nature of the trial, we may not have adequate power to detect modest differences between START and START with mobile augmentation conditions; however, we considered that the absence of detectable differences between conditions on any of the dimensions of feasibility, acceptability, mediators, and preliminary outcomes in the presence of sustained improvement in the primary outcome (suicidal ideation) would indicate that mobile augmentation may not be warranted in future deployment of START.

Interventions

After baseline assessment, participants were scheduled for 4 consecutive weekly sessions with a study therapist in the walk-in facility. We opted for individual sessions (vs group) to enhance the likelihood of personalization and to reduce the potential for wait times to reach group capacity. Each session is structured with a demonstration and practice of a coping skill (10 min), skill focus on 1 of 4 topics (20 min), and personalization of implementation intentions surrounding a topic area (30 min). The structure of sessions is highly comparable between START with mobile augmentation and START-alone conditions, as

both conditions involve compiling implementation intention statements in a workbook. Participants in the START-alone condition are instructed to record homework completion, and those in the mobile augmentation condition are instructed to respond to queries on the mobile app as described below. Figure 1 outlines the study flow.

Figure 1. Study flow.



Session 1: Content (Early Warning Signs and Triggers, 90 Min)

After establishing the ground rules, participants are led through a brief grounding technique called *look, point, name*. Then, an interactive description of the generic cognitive model is provided (ie, that thoughts, feelings, and behaviors are related), thoughts and feelings are identified and labeled, and patients complete exercises demonstrating how dysfunctional beliefs can impact feelings and behavior. Suicidal thoughts are discussed in this framework, and education is provided about the high frequency of such thoughts among people with SMI diagnoses. The concept of early warning signs (internal experiences) and triggers (external factors) are introduced in relation to suicidal thoughts. Participants are also presented with the idea of adaptive versus unhelpful responses; participants then form implementation intention statements based on adaptive responses. The session concludes with an agreement regarding the focus of work together in diminishing vulnerabilities to suicidal thinking, with parameters around safety planning, crisis contacts, and one commitment to reduce access to means. In the START with mobile augmentation condition, participants were provided with a 15- to 20-minute overview of interactive responding on the phone, and in the START-alone condition, the session concludes (see below for mobile content).

Session 2: Content (Symptom Actuators and Treatment Engagement, 60 Minutes)

In this session, the therapist first elects from 1 of the 2 symptom *actuators* of suicidal thoughts from early warning signs (mood or psychotic symptoms), with modules focused on these symptom clusters as they create vulnerabilities to suicidal thoughts. Evidence is used to challenge unhelpful beliefs, such as the uncontrollability or permanence of symptoms, and each is coupled with a behavioral suggestion or experiment that can be employed to test assumptions. The therapist and participant decide to focus on mood symptoms or voices, depending upon which is most associated with suicidal thinking. Participants delineate *portable* coping strategies for 3 levels of severity of depressed mood (and manic symptoms, if present) or for common dysfunctional beliefs about voices (eg, uncontrollability). In addition, the role of treatment in managing these symptoms is discussed, which is linked with intentional (eg, *treatment won't work*) and unintentional (eg, forgetting) barriers and facilitators to treatment adherence.

Session 3: Content (Social Relationships, 60 Min)

This session begins with progressive muscle relaxation. Content then addresses the role of social relationships and beliefs about others as factors in coping with or exacerbating suicidal thinking. Unhelpful, generalized, or extreme beliefs about social interactions are reappraised (eg, *there are some people who are on my side*), and the role of social isolation in suicidal thinking is discussed. Potential behaviors that promote social contact are elicited, including the use of crisis-oriented resources. Barriers to asking for help are elicited, including appraisals and predictions about disclosing suicidal thoughts to others and behaviors that are linked with help-seeking that resulted in benefits.

Session 4: Content (Recovery Plan and Goals, 60 Min)

This session begins with a Loving Kindness meditation to increase positive affect and addresses recovery goals and future-oriented thinking; a recovery plan is developed around

personal values and a linked single, attainable short-term goal consistent with personal values. Participants and the therapist worked within the START goal framework and delineated 2 relevant goals and steps aligned with the selected goals. Next, the therapist and participants reviewed the topics and content generated in sessions 1 to 4 and revised and added to statements that were previously generated. Plans for subsequent contacts were made for follow-up phone contacts.

Rationale for START Foci

The therapeutic targets were selected to address short-term risk and protective factors in a brief intervention format, and as such, do not directly address all of the risk factors for suicide in SMIs. For example, we do not directly target substance abuse, although participants do have the freedom to select substance use as a trigger or unhelpful coping strategy. We also do not directly involve caregivers, such as family members. We will use postintervention follow-up satisfaction data to identify potential modifications to the protocol.

Follow-Up Telephone Coaching

Participants are contacted via phone by the study therapist every at weeks 6, 8, and 10 or until they are established in outpatient care (ie, attend an intake appointment). Follow-up telephone coaching consists of a concise scripted interaction to briefly check in (target 10 min) with a focus on the following: (1) safety and utilization of strategies developed in the 4 in-person sessions; (2) assessing and problem solving around barriers to outpatient engagement; and (3) in the mobile augmentation condition, troubleshooting, and requests for adapting any elements of the device interaction [34-36].

Mobile Augmentation Procedures

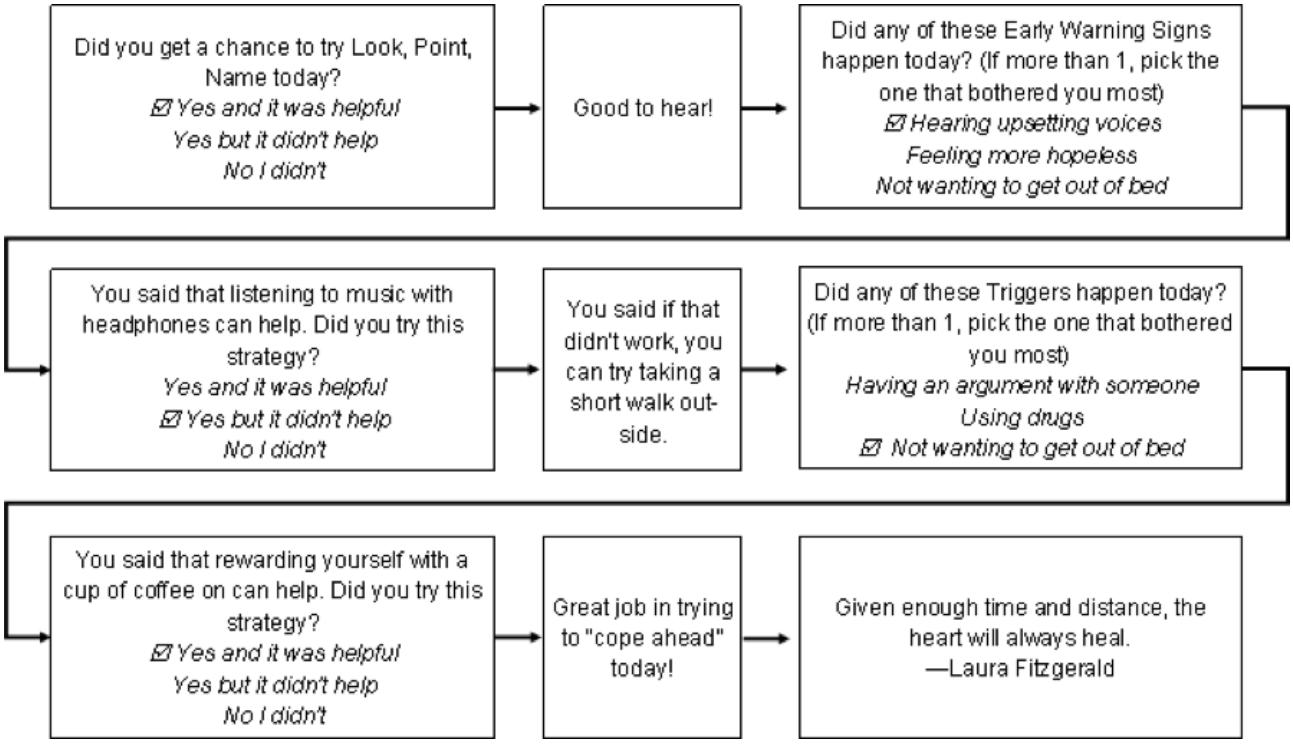
Mobile Devices and Training

Participants can opt to either use their mobile phone device or, if they do not use a personal mobile phone device, obtain a provisional one during the 12-week period with support for accessing free or low-cost mobile devices. In either case, the interactive content is delivered through an EMI app called Illumivu. Personalized content is delivered through this app, and deidentification is made possible by a mobile code that is unique to each participant. In Session 1, participants receive training that is individually tailored to their learning needs on how to respond to questions and response choices, procedures for charging the device, and responding to outreach.

Mobile Intervention Content

Surveys scaffold onto in-person content and successively add modules according to the following schedule—*Session 1*: Early Warning/Triggers; *Session 2*: Symptom Actuators and Treatment Engagement; *Session 3*: Social Relationships; and *Session 4*: Recovery Plan/Goal tracking. In each survey, participants are asked whether they practiced relaxation skills. They are then asked to respond to *first-layer* ecological momentary assessment (EMA) questions that assess current state (eg, past 24-hour presence of triggers or early warning signs, severity of depressed mood). In the *second layer*, content is branched to address endorsement of maladaptive beliefs pertaining to first-layer questions, and the *third layer* contains 2 questions on participants' adaptive cognitions or behaviors developed in session and their implementation intentions for these. Each of these layers contains a set of possible responses derived from content that was personalized in the in-person sessions. If no triggers or early warning signs or symptoms are endorsed, participants select from personalized adaptive beliefs and actions pertinent to the maintenance of wellness. Participants are then queried about their intention to engage in the behavior and the survey concludes with a quote on recovery, adapted from public sources or from anonymous prior participants. See Figure 2 for a sample mobile session. During in-person contact with study therapists, participants can request to alter content, add, remove, and/or update their responses. In addition to the *pushed* surveys, participants can access content (eg, recovery goals) on demand.

Figure 2. Sample mobile session for early warning signs and triggers.



Rationale for Mobile Augmentation

Our group and others have completed trials that indicate that patients will use mobile devices for EMIs up to 12 weeks or more when coupled with in-person therapies [26,37]. On the basis of prior research suggesting that only 50% of participants initially engaged with outpatient care, there is reasonable concern that without additional intervention, participants may disengage from this care during the 6-month period of this study [38]. Given that there is no staff cost to continue an automated mobile intervention through 6 months after establishment in outpatient care and the content reinforces ongoing participation in care, the automated intervention is available in perpetuity.

Safety Procedures

In collaboration with stakeholders, plans have been developed to systematically monitor and address safety. At *screening*, participants are seen on the same day as the triage assessment, in which plans for outpatient follow-up are set by the triage provider. Our research screening included crisis resources for all screened participants. If screening cannot occur on the same day as triage, we follow the protocol for baseline assessments. At baseline and follow-up assessments, we developed a suicide safety monitoring protocol that uses the CSSR-S to identify *increases* in ideation or new interim behavior since the time of screening (or in case of delay, urgent evaluation is initiated if CSSR-S scores are >2). During *in-person START sessions and telephone contacts*, the study therapist administers the CSSR-S at the end of each session. If an increase in ideation or new interim suicide behavior is identified, it activates urgent evaluation, connection with resources, and arrangement of notification of providers and hospitalization. We also elected not to directly query about suicidal ideation via the device, as the understanding of the use of remote technologies in querying suicidal risk and safety response is in its infancy [39,40].

Measures

The measurement battery for this pilot trial was brief and restricted to study constructs related to acceptability and preliminary outcomes (Table 1).

Table 1. Study measures.

Timing and measure	Specific aim	Construct assessed
Screening		
MINI[a] DSM-5[b] interview	Inclusion	Diagnosis
CSSR-S[c]	Inclusion	Suicide risk inclusion
Baseline and follow-ups		
Scale for Suicide Ideation or CSSR-S Interval	Primary outcome	Suicidal ideation severity
Outpatient follow-up	Secondary outcome	Treatment engagement post-triage
Composite suicide-related crises	Secondary outcome	Suicidal behavior or psychiatric hospitalization for suicidal ideation
Beck Hopelessness Scale	Mechanism	Hopelessness
Coping Self-Efficacy Scale	Mechanism	Self-efficacy
EMA[d] Adherence or Outcomes	Acceptability: secondary outcome	Response rate to mobile surveys: mood or psychotic symptoms
Tablet routines questionnaire	Secondary outcome	Medication adherence
BPRS-24[e]	Secondary outcome	Global psychopathology
Treatment Rationale Scale	Acceptability	Treatment expectancy
Timeline Followback Scale	Moderator	Substance abuse
Follow-ups only		
Intervention Satisfaction Questionnaire	Acceptability	Satisfaction with intervention
Recovery plan and safety plan recall	Mechanism	Accuracy of recall

[a]MINI: Mini International Neuropsychiatric Interview.
bDSM-V: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition.
[c]CSSR-S: Columbia Suicide Severity Rating Scale.
[d]EMA: ecological momentary assessment.
[e]BPRS-24: Brief Psychiatric Rating Scale–24 item.

Suicidal Ideation Severity and Behavior (Primary Outcome)

We administer the interview-rated version of the *Scale for Suicide Ideation*, a 21-item widely used measure that predicts completed suicide [41,42] in addition to the interval CSSR-S, which queries the timing, severity, and characteristics of suicidal ideation and behavior [30].

Our study addresses changes in suicidal ideation and is underpowered to detect the impact on the risk of suicidal behaviors. Our rationale for change in suicidal ideation as our primary outcome was that for a suicide-specific intervention to be potentially effective, it must be feasible, acceptable, and associated with significant and sustained reductions in suicidal ideation to move on to a confirmatory trial. If the target of suicidal ideation was not moved, then we would not proceed to a confirmatory trial. We recognize that people may experience a reduction in suicidal ideation severity as part of natural regression to baseline. However, we note that people with SMIs are more likely to have chronic ideation than people without psychosis and therefore would be less likely to experience natural reductions in ideation [43]. Moreover, people with SMIs are more likely to have recurrent suicidal ideation, and as such, we added follow-up assessments at 12 and 24 weeks. Finally, we used the minimally important clinical difference of 0.5 SD as a threshold for meaningful reduction and power analyses. We will investigate whether the SSI score is skewed or kurtotic using the convention of +3 investigate skew and, if evident, will dichotomize the variable.

Outpatient and Crisis Service Utilization (Secondary Outcome)

We extracted electronic medical record (EMR) encounter data regarding attendance at the first follow-up appointment and rate of follow-up outpatient contacts. It is possible that participants may use out-of-county institutions not captured in the EMR; therefore, the *Cornell Service Use Index* [44] is administered for service use not recorded in the EMR to facilitate a comparison of augmented and nonaugmented arms.

Global Psychopathology (Secondary Outcome)

Global psychopathologic severity is evaluated using the *Brief Psychiatric Rating Scale–24-item expanded version 4.0* (BPRS-24) [45], a clinician-rated measure with 24 items that

cover depression, anxiety, mania, suicidality, delusions or hallucinations, and unusual behavior.

Medication Adherence (Secondary Outcome)

Self-reported adherence is assessed with the *Tablet Routine Questionnaire* [46], which asks about the proportion of psychotropic medication taken over the past week and month.

Electronic Adherence and Targets (Secondary Outcome)

A wealth of EMA data will be generated, including adherence data (eg, response rate=the number of responses/number of queries) and patterns of adherence over time. In our completed trial, treatment response was associated with greater adherence; thus, we will also explore this association. We structured the EMA protocol to provide day-to-day data on the early warning signs or triggers, symptoms, medication use, socialization, and contextual influences. These data will inform hypotheses about determinants or contexts of suicidal thoughts in SMIs [47].

Substance Use Frequency or Intensity (Moderator)

We assessed substance abuse as an exploratory moderator of attrition, adherence, and response. To quantify alcohol and drug use, we selected the 30-day *Timeline Followback Scale* [48].

Therapeutic Mechanisms Variables

We examined mechanistic targets for the START intervention that map on to therapeutic content: *Treatment Engagement*, *Coping Self-Efficacy (CSE) Scale* [49] and *Beck Hopelessness Scale* [50].

Safety and Recovery Plan Recall (4, 12, and 24 weeks only)

Modeled after recent research on recall of elements of CBT for bipolar disorder [51] and our research in schizophrenia [15], we administer a knowledge or recall measure that corresponds to elements in the safety plan generated in Session 1 as well as the recovery plan in Session 4. Participants are asked to recall broad elements discussed (eg, responding to early warning signs) and the individual responses of their own plan once prompted (eg, specific responses to early warning signs). Participants' written responses are coded as fully accurate, partially accurate, or not accurate in regard to recalled elements of the safety and recovery plans.

Acceptability Measures

At baseline, participants are administered the *Treatment Rationale Scale* [52], a 3-item self-report that garners perceived credibility and anticipated benefit. Participants also completed seven 5-point Likert-type and 4 open-ended questions (modified from Kimhy et al [53] and used in our prior research [54]) focused on greater intervention satisfaction, barriers and suggestions concerning the intervention, the therapist, and the manual, and for the mobile health condition, experiences with the device and suggestions for future usability.

Fidelity

We systematically address the relevant components of treatment integrity: *Competence*, *Therapist and Participant Adherence, and Treatment Differentiation* [55]. *Competence* is addressed by initial training of the study therapists who meet minimum competence standards (see above) and in an ongoing fashion by audiotape-rated delivery of the intervention, supported by weekly supervision. *Therapist Fidelity* to the manualized protocol is assessed via 100% of session recordings rated by the therapist and research team on an adapted version of the Cognitive Therapy Rating Scale for Psychosis (CTS-Psy) [56]. *Participant adherence* is assessed by session attendance or telephone contacts and objectively via device-obtained data. *Treatment differentiation* is assessed by blinded random selection of 25% of audio-taped sessions rated by masked raters, with a running quarterly calculation of discrepancies between conditions evaluated to determine if content delivered varies between the 2 conditions; retraining occurs if differences in CTS-Psy scores are >0.5 SD.

Sample Size Determination

Our pilot trial's sample size is derived based on the nexus of 3 goals, guided by work on optimization of pilot studies [57]: (1) to obtain point estimates of feasibility, acceptability, and test the impact of the intervention compared with population base rates for engagement and crisis service utilization; (2) to be powered to test a clinically significant within-subjects reduction (d>0.5) in the SSI score; and (3) to evaluate the preliminary impact of augmentation. Intent-to-treat analyses with 70 patients, with an alpha of .05, will have 95% power to evaluate whether the sample estimates differ from population estimates (eg, 50% no-show rates) [58] and 77% power for each of the individual arms. On the basis of the General Linear Multivariate Model Power and Sample Size program [59], there is >0.80 power across 24 weeks to detect a 0.5 SD pre-post change in SSI score. We have considerably less power to detect augmentation effects, but following recent research on sample size estimation in pilot trials and confidence intervals [60,61], the preliminary impact of augmentation will be assessed by defining a minimally clinically significant augmentative effect for a future trial.

Analysis of Feasibility and Acceptability

Point estimates of feasibility and acceptability included the following: (1) triage clients screened, (2) screened clients eligible, (3) eligible clients enrolled, (4) enrolled clients completing 4 sessions and follow-up calls, and (5) percentage of participants reporting being somewhat or very satisfied with the overall intervention. Comparative data regarding feasibility and acceptability are our completed trials, which enable us to examine whether indicators of feasibility in the triage setting are similar to general outpatient populations. Each of these estimates, in addition to Treatment Rationale and Satisfaction scores, will be contrasted across conditions with t tests or Mann-Whitney tests or chi-square tests.

Analysis of Within-Person Changes

Distributions for the SSI score may be skewed (with overdispersion due to persons with no present ideation) and, if so, zero-inflated negative binomial models will be employed. We will use hierarchical linear models (HLMs) in which time will be tested as a categorical time-varying predictor of SSI score and subjects are a random effect, with significant reduction in SSI over time indicated by a statistically significant time effect. We expect that by the 24-week time-point, SSI will have

at least a medium effect size decrease ($d \geq 0.5$) as measured by HLM linear-estimated change. To evaluate augmentation, we will examine group×time interactions, with estimated standardized differences considered supportive of the augmentation inclusive of minimal clinical significance CI>0.80. We will evaluate secondary continuous outcomes (eg, BPRS) variables in the same way.

Analysis of Mechanisms

For analysis of binary mechanisms (outpatient engagement) and outcomes (crisis service use), we will use chi-square analyses to examine associations at 24 weeks. For the continuous time-varying mechanism (CSE), we will examine a mechanistic association between changes in CSE and SSI scores using the Macarthur framework [61]. We will use generalized estimating equations to evaluate the prediction of crisis service use by within-subjects change in CSE and then repeat these analyses within mobile-augmented and nonaugmented arms. We will also contrast the Safety or Recovery Plan recall at weeks 4, 12, and 24 using *t* tests or Mann-Whitney U tests.

Results

The trial is ongoing and recruitment is active, with anticipated completion of the baseline sample randomization target of 70 participants by the close of 2020.

Discussion

Principal Findings

This trial focuses on evaluating a novel brief suicide prevention intervention for SMI, addressing the imbalance between the low number of empirically supported interventions for SMI and the high rates of suicide in people with bipolar disorder and psychotic disorders. Key considerations in developing and deploying an intervention to fit the needs of people with SMI were in the design of the intervention content and the setting and timing of the intervention within the typical American community mental health care continuum. This approach could yield potential benefits to both suicide prevention and operational efficiency by improving follow-through with scheduled outpatient appointments and reducing lost productivity due to *no shows* at follow-up appointments. This experimental treatment approach is an augmentation of the standard transition from a walk-in clinic to outpatient care follow-up and is not fully integrated into care. The likelihood of future adoption may depend upon a demonstrated reduction of suicide and cost recovery due to the reduced rate of missed appointments.

A trial focus is also on the relative additional value of integrating mobile interventions with in-person appointments. The additional mobile intervention content is meant to augment the recall and implementation of personalized intervention content derived from in-person sessions. In this community-based trial of a suicide-specific intervention, we did not have a no-treatment control condition, and this trial design decision was due in part to the community partner's preference against a no-treatment condition. We note that future developmental trials of suicide-specific interventions may face a similar dilemma and alternative designs (eg, SMART designs) may provide useful means of detecting mobile augmentation effects.

Lessons Learned

Key lessons learned to date include the importance of frequent deployment meetings that emphasized co-design among staff training and leadership to enable referral, recruitment, and safety protocol refinement. We also based our safety protocol on published guides [29]; these guides have yet to be specifically adapted for SMIs but provide a reasonable starting point for clinical trials in suicide prevention in SMIs. We also opted not to include direct questions about suicidal ideation or behavior during automated mobile communications that augment in-person appointments, due to the lack of specific evidence of acceptability in SMI to date. The trial is currently ongoing, and we anticipate that data collected will further inform research and practice in suicide prevention interventions adapted for SMIs.

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Conflicts of Interest

EG reported consulting fees from Otsuka America Pharmaceutical, Inc.

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Abbreviations

BPRS-24: Brief Psychiatric Rating Scale–24 item
CBT: cognitive behavioral therapy
CSE: coping self-efficacy
CSSR-S: Columbia Suicide Severity Rating Scale
CTS-Psy: cognitive therapy rating scale for psychosis
EMA: ecological momentary assessment
EMI: ecological momentary interventions
EMR: electronic medical record
HLM: hierarchical linear model
SMI: serious mental illnesses
SSI: Scale for Suicide Ideation
START: SafeTy and Recovery Therapy

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Protocol

Evaluation of an Intergenerational and Technological Intervention for Loneliness: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Social integration and mental health are vital aspects of healthy aging. However, close to half of Canadians older than 80 years report feeling socially isolated. Research has shown that social isolation leads to increased mortality and morbidity, and various interventions have been studied to alleviate loneliness among older adults. This proposal presents an evaluation of an intervention that provides one-on-one coaching, is intergenerational, provides both educational and socialization experiences, and increases technology literacy of older adults to overcome loneliness.

Objective: This paper describes the protocol of a randomized, mixed-methods study that will take place in Ontario, Canada. The purpose of this study is to evaluate if an intergenerational technology literacy program can reduce social isolation and depression in older adults via quantitative and qualitative outcome measures.

Methods: This study is a randomized, mixed-methods, feasibility trial with 2 conditions. Older adults in the intervention condition will receive 1 hour of weekly technological assistance to send an email to a family member, for 8 weeks, with the assistance of a volunteer. Participants in the control condition will not receive any intervention. The primary outcomes are loneliness, measured using the University of California, Los Angeles Loneliness Scale, and depression, measured using the Center for Epidemiologic Studies Depression scale, both of which are measured weekly. Secondary outcomes are quality of life, as assessed using the Older People's Quality of Life-Brief version, and technological literacy, evaluated using the Computer Proficiency Questionnaire-12, both of which will be administered before and after the intervention. Semistructured interviews will be completed before and after the intervention to assess participants' social connectedness, familiarity with technology, and their experience with the intervention. The study will be completed in a long-term care facility in Southwestern Ontario, Canada. Significance was set at $P<.05$.

Results: This study was funded in April 2019 and ethical approval was obtained in August 2019. Recruitment for the study started in November 2019. The intervention began in February 2020 but was halted due to the COVID-19 pandemic. The trial will be restarted when safe. As of March 2020, 8 participants were recruited.

Conclusions: Information and communication technology interventions have shown varying results in reducing loneliness and improving mental health among older adults. Few studies have examined the role of one-on-one coaching for older adults in

addition to technology education in such interventions. Data from this study may have the potential to provide evidence for other groups to disseminate similar interventions in their respective communities.

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KEYWORDS

seniors; communication technology; social isolation; computers; intergenerational; older adults; mobile phone

Introduction

Social integration and mental health are fundamental indicators of healthy aging and represent significant public health concerns among Canadian older adults. Unfortunately, up to 50% of the Canadians older than 80 years report feeling socially isolated [1]. Similarly, 10%-15% of the Canadian older adults living in the community experience depression, and 44% of older adults in residential care have a diagnosis of depression or symptoms of depression [2,3]. Social isolation has significant detrimental effects on older adults, and previous research has shown an association between loneliness and depression [4-6]. Social isolation and higher levels of depressive symptoms, in turn, uniquely and jointly, are associated with increased morbidity and mortality, including reduced quality of life, decreased mental health, cognition, and function, and increased hospitalizations [1,7-12].

Multiple factors have been posited to influence loneliness, including health factors such as chronic diseases, in addition to cognitive and functional decline that may lead to difficulties in communication and mobility [1,13,14]. Structural factors that affect social isolation include relocation and separation from family and friends [15]. Given the multidimensional nature of loneliness, preventing and reducing loneliness is a top priority in Canadian public health care policy [1].

Growing evidence supports the use of intergenerational programs in improving various indicators for both older adults and younger cohorts. Interventions to reduce loneliness and improve mental health in older adults have traditionally consisted of group-based and individual-based interventions [16-19]. These include support groups, outreach volunteers, and animal therapy. In addition, previous studies have investigated information and communication technology methods such as internet-based videoconferencing and the overall impact of internet usage to maintain contact with family and friends, with varying levels of efficacy [20-22]. Previous mixed-methods intervention studies have identified improvements in social behavior, social interaction, quality of life, and mood in older adults [23]. These studies include production of art (eg, puppets or music), group reading, and shared spaces to gather with loved ones and friends [24-27].

Quantitative evidence also supports the use of intergenerational programs with older adults and youth, demonstrating efficacy via measures in geriatric depression scales, life satisfaction scales, quality of life, and self-esteem scales [28-34]. Examples of such studies include electronic gaming, student volunteer programs, and reminiscence therapy [29,35,36]. However, given the inherent social support that underlies intergenerational programs, it would be expected that improvements in the outcomes above are potentially mediated by reductions in social isolation and loneliness. Despite this, few studies have examined the role of intergenerational programming via a mixed-methods approach to reduce social loneliness [37-40]. As such, programs of this nature serve to improve not only relationships between older adults and younger adults but also the technological literacy and connectivity of older adults to family and friends via the internet—a multi-modal strategy to reduce social isolation and loneliness.

Addressing perceived social isolation or loneliness by using technology requires that older adults have a certain level of information and communication technology literacy, which is defined as the ability to locate, evaluate, and communicate information using a digital platform [18]. However, many older adults have low information and communication technology literacy, yielding a “digital divide” between older adults and younger adults in Canada, wherein older adults are less likely to use the internet as compared to younger adults [41]. Previous research has shown that compared to other age groups, older adults have less confidence in using technology and often need support for setup and use [42]. To target this, the enTECH Computer Club (enTECH) was founded in 2015 at the University of Waterloo. enTECH student volunteers provide one-on-one education to support older adults living in long-term care homes to use technology to keep in contact with their families, stay connected to their communities, and generally browse the internet. This student club consists of around 30 student volunteers from the undergraduate to graduate level who volunteer to work in service retirement homes and long-term care facilities in Southern Ontario. enTECH presents an opportunity for intergenerational learning.

This study is being conducted to determine the feasibility and effects of the educational program of enTECH for older adults on the levels of loneliness and depression reported by older adults. We hypothesize that our intervention will reduce loneliness and depression in older adults.

Methods

Managing Stakeholders

The organization implementing the intervention is a student club affiliated with the student union at the University of Waterloo, Ontario, Canada. We received funding through an internal funding opportunity. In order to proceed with this study, permission was required from both the student union and the institution’s research ethics board. The student union acknowledged that they lacked the resources and infrastructure to host the study and study funds, and thus, they requested that

study funding and logistics be managed exclusively by a research team. This delineation has made managing the study easier by eliminating redundant paperwork, thereby allowing finances to be managed by research staff experienced in the required procedures and documentation.

Study Design

This study is a mixed-method, randomized feasibility trial with 2 conditions. Participants in the intervention condition will receive assistance in sending an email to a designated family member once a week. This program will be carried out by experienced enTECH volunteers who have been trained in teaching older adults how to use technology. Participants in the control condition will continue interacting with their family as they do now (ie, not via information and communication technology). Participants in the control group also have access to 3 public computers in the facility and recreational therapists if they require support.

Inclusion and Exclusion Criteria

As the focus of this study is specifically older adults who do not currently communicate with their family members in text by using technology, this is one of the key factors when determining the eligibility to participate. Potential participants are asked to confirm that they do not currently contact their family members using technology, including email, text message/iMessage, or any other digital text-based messaging platform (eg, WhatsApp, WeChat, Facebook Messenger). No exclusion criteria on the basis of computer proficiency will be applied, as the club provides support to people, regardless of their computer skills.

As this study is asking older adults to communicate with family members, participants were asked, prior to the consent process, if they had a family member who would agree to respond to an email from them weekly. No contact information will be collected at this time. There are no age or physical ability requirements to participate in this study, as long as the potential participant resides in a long-term care home. There are no exclusion criteria based on previous information and communication technology experience or expertise. If a participant is unable to physically use the technology to send an email, a member of the research team will assist them with doing so. Staff at the location will be asked to both identify potential participants and residents of that location who may not be a good fit to participate. Participants will be excluded if they have cognitive impairment with the inability to consent. Participants who are unable to speak English will be excluded from this study.

Ethics Approval

This study was approved by the University of Waterloo Office of Research Ethics as of September 2019. The study ID is ORE #41104.

Randomization and Blinding

After the consenting process, participants will be randomized to either the intervention or the control group by using a computer-generated allocation sequence in a 1:1 ratio. If randomized to the intervention group, researchers will work with the participants to obtain a family member's email address for use in the study. Owing to the nature of the study, participants cannot be blinded to allocation. Two separate research teams will facilitate the study. The clinical team will be carrying out the intervention, while the research team will be conducting the interviews and administering the scales. In order to maintain participant confidentiality and anonymity to the interviewers, participants will be assigned a participant ID number via the allocation sequence described above. This number will be known to both the clinical team and the research team; however, the research team will not be able to see the participants in the intervention group or those in the control group. When data are entered into the computer, the data will be associated with the participant IDs alone.

Recruitment

Location Recruitment

Recreation facilitators at the nursing home will be contacted and asked for permission to run the study at their location via the location recruitment letter (Multimedia Appendix 1). Recreation facilitators will be contacted by email using a secure email specific for study purposes, in addition to informal communication methods (eg, in-person conversations) between the recreation facilitator and the study team.

Participant Recruitment

Participants will be recruited through a long-term care home in Southern Ontario. Recreational facilitators will assist in recruiting participants for the study. Moreover, brochures, pamphlets, and flyers (Multimedia Appendix 2) will be placed in the study location by the team, in addition to a town hall advertising the study. Potential participants will be asked 2 questions to determine eligibility: if they currently use email/texting/messaging to contact family members and if they believe a family member would be willing to respond to an email sent by them once a week (Multimedia Appendix 3). Collecting the contact information of the participants' family members requires balancing of respect for the participants' autonomy, along with their potential comfort with the study's subject matter. After consenting, participants will be presented with 2 options so that the research team can contact their family members. One option will consist of the participant providing the research team with a ranked list of family members to potentially receive emails from the participant, along with their phone numbers. The other option will consist of providing the participants with an information sheet, written in layperson terms, which they can use to describe the study to the family members to ask if they would like to participate. Members of the research team will follow up after 3 days to see if the participants were able to contact their family members or to provide support to facilitate this contact. The research team will then offer to contact the family member on their behalf, and at such time will record the contact information of up to 3 family members and contact them using the telephone script (Multimedia Appendix 4). Recruitment for the study started in November 2019. We expected to enroll approximately 20 participants, 10 in each condition. We successfully enrolled 8 participants before the study was forced to halt due to the COVID-19 pandemic (Multimedia Appendix 5).

Student Recruitment

The study team will consist of 10 students from the University of Waterloo who are volunteers in the enTECH Computer Club. Student volunteers were recruited through school club advertisements, course announcements, and through social media. Student volunteers were interviewed and trained to provide technology education through in-house lesson plans and simulations.

enTECH Intervention and Study Procedure

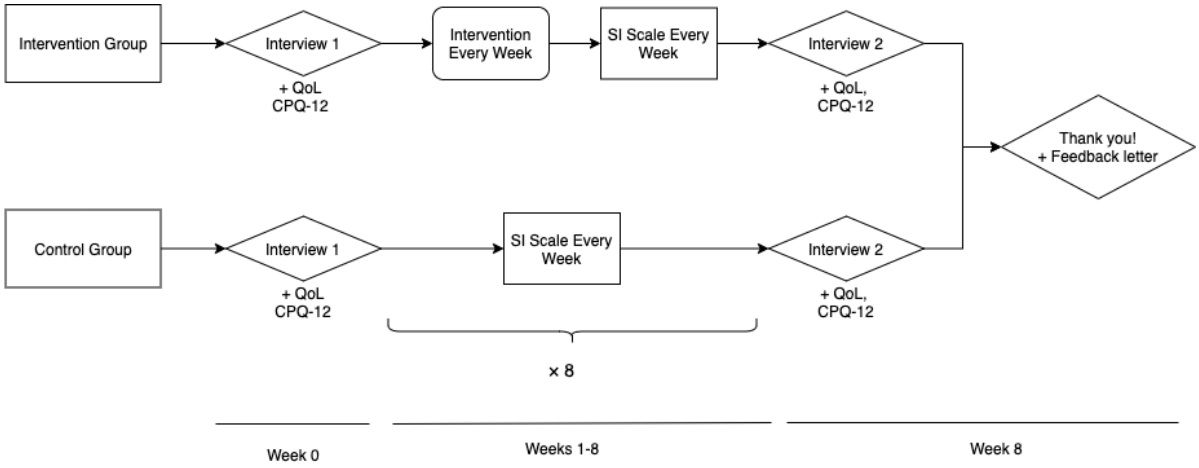
After obtaining informed consent, demographic information will be collected (Multimedia Appendix 6) and participants will be randomized as described above. The intervention outline is described below and detailed in the study flow chart of Figure 1.

Week 0: Members of the study team will conduct semistructured interviews with participants (Multimedia Appendix 7) and complete the Computer Proficiency Questionnaire-12 (CPQ-12) and the Older People's Quality of Life-Brief version (OPQOL-Brief) questionnaire, which will be measured before and after the study period.

Weeks 1-7: Participants in the intervention group will complete the enTECH program. Trained enTECH volunteers will help older adults use either our laptops or participants' own technology systems to email their family members. These sessions will take place in group settings in a public area in the long-term care facility accessible to all participants. Both the Center for Epidemiologic Studies Depression scale (CES-D) and the UCLA (University of California, Los Angeles) Loneliness Scale (version 3) will be measured each week in the intervention and control groups.

Week 8: Participants in both groups will complete their final session of the intervention, and they will then be asked to complete the CPQ-12, the OPQOL-Brief, the CES-D, and the UCLA loneliness scale. Participants in the intervention group will also be invited to complete a second interview discussing their experiences using technology to communicate with a family member (Multimedia Appendix 8).

Figure 1. Diagram detailing the timeline for the study components. QoL: quality of life; CPQ-12: Computer Proficiency Questionnaire-12; SI scale: social isolation scales (Center for Epidemiologic Studies Depression Scale and University of California, Los Angeles Loneliness Scale version 3).



Outcomes

Primary outcomes: The primary outcomes of this study are loneliness and depression. Loneliness will be assessed using the UCLA Loneliness Scale-version 3 [43]. The scale is a 20-item measure using a 4-point Likert scale and has been validated for use with older adults [44]. Depression will be measured using the CES-D [45]; this is a 20-item scale, each with 4 response items ranked from 0 to 3 based on the frequency of symptoms associated with depression over the past week. A cut-off of over and equal to 16 has been used in multiple validation studies [46].

Secondary outcomes: The secondary outcomes of this study are quality of life and computer proficiency. Quality of life will be measured using the OPQOL-Brief and a 13-item Likert scale from 1 to 5. This scale has been validated in older adults [47]. Technological proficiency will be measured using the CPQ-12, a 12-item measure using a 1-5 Likert scale and has been well-studied in older adults [48].

Feasibility outcomes: The feasibility outcome measures of this study will include the number of participants that we are able to enroll in the study, adherence to the intervention (frequency of contact with the family and attendance to the program), and the rate of attrition [49]. We also intend to determine the challenges faced by the site and volunteers as a result of our intervention, in particular, the restrictions of having only university student volunteers as well as the restrictions of the daily schedules for the residents of the facility. These will both be determined quantitatively (eg, total number of participants, adherence) and qualitatively, where participants will be asked about their experiences with the program. We do not expect any adverse events as a result of our intervention.

Qualitative interviews: Semistructured interviews will be conducted with older adults prior to and following the 8-week intervention. Interviews will be continued with all the participants before the study and those in the intervention condition after the study has concluded. Interviews will be digitally audio recorded and transcribed verbatim, and pseudonyms will be assigned to participants. A thematic analysis methodology will be used to code the qualitative data. Two independent investigators will conduct line-by-line coding. The preintervention and postintervention questionnaires are provided

in Multimedia Appendix 7 and Multimedia Appendix 8, respectively. Qualitative interviews will provide context in the role that the enTECH program provides for older adults living in long-term care facilities as well as how they currently socialize with others. By assessing participants both before and after the intervention, we hope to provide narrative data on how the enTECH program may have changed the way participants socialize in their community, determined changes in their knowledge with technology, and provided insight into their experience with the program. In addition, by understanding the goals participants have by enrolling in the program, future modifications to the program may allow for more tailored technology and social interventions.

Statistical Analysis

Statistical Software

Participant demographic data will be tabulated for both intervention and control groups with their respective means and standard deviations. Participant dropouts will also be considered, and an intent-to-treat analysis will be completed. All data will be analyzed using GraphPad Prism 9 (GraphPad Software, Inc).

Primary Outcomes

The UCLA Loneliness Scale and the CES-D Scale will be analyzed using a repeated measures approach, as these measures will be collected weekly. The normality of the data will be assessed using the Shapiro-Wilk test; if the data are nonparametric, a Q-Q plot will be performed to identify skewness of the data. A Brown-Forsythe test will be used to determine equal variance. If the data are determined to be normally distributed and equal variance is observed between the groups, a repeated measures analysis of variance test will be used to detect between-group and within-group differences. If normality cannot be established or unequal variance is observed within the data, the Friedman test will be used to detect between-group and within-group differences. If the data are nonnormal with unequal variance, a Box-Cox transformation will be performed to obtain equal variances. For all tests, statistical significance will be set at $P<.05$.

Secondary Outcomes

The OPQOL-Brief and the CPQ-12 will be analyzed by comparing changes in the scores between the intervention group and the control group. The normality of the data will be assessed using the Shapiro-Wilk test, and equality of the variances between the groups will be assessed via a Q-Q plot and the Brown-Forsythe test. The differences between prestudy and poststudy period assessments in the intervention and control groups will be assessed using pooled variances and a one-sided *t* test. If normality cannot be established or unequal variance is observed within the data, a Q-Q plot will be used to determine the appropriate test (eg, Sign test, Wilcoxon-Signed Rank Test, or Wilcoxon Rank-Sum Test). For all tests, statistical significance will be set at $P<.05$. Quantitative feasibility outcomes (eg, adherence and attrition) will be reported as descriptive data and compared using a one-sided *t* test or a nonparametric equivalent (Mann-Whitney *U* test). All evaluation outcomes will be integrated in a joint display.

Power

This study was designed as a feasibility study for investigating the feasibility of a student-run initiative to reduce loneliness in older adults. A component of this study will be understanding recruitment and retention, which may have significant variability in our sample size. Based on previous studies on interventions to reduce loneliness in older adults, with an effect size of approximately 0.2 and alpha of .05 and 80% power, we expect our sample size to be 196 [43,50-54]. Accounting for attrition rates in other intergenerational programs would be approximately 10%, and the sample size would be 216 [20,55,56]. Since the nature of this study is a feasibility study, which we aim to use to guide a future randomized controlled trial, this feasibility trial is not registered.

Results

Participant Recruitment

Recruitment started in November 2019. As of March 2020, we have recruited 8 participants. This study was halted as per the University of Waterloo Office of Research Ethics in accordance with public health guidelines. We expect that recruitment will be resumed once the long-term care facility can offer the program for older adults, in conjunction with approval from the ethics board to ensure safety for both students and participants. Gantt charts are provided detailing our progress to date Figure 2, which details our progress to date (Figure 2) and the expected timeline once permitted to resume (Figure 3).

Figure 2. Gantt chart for currently completed pilot.

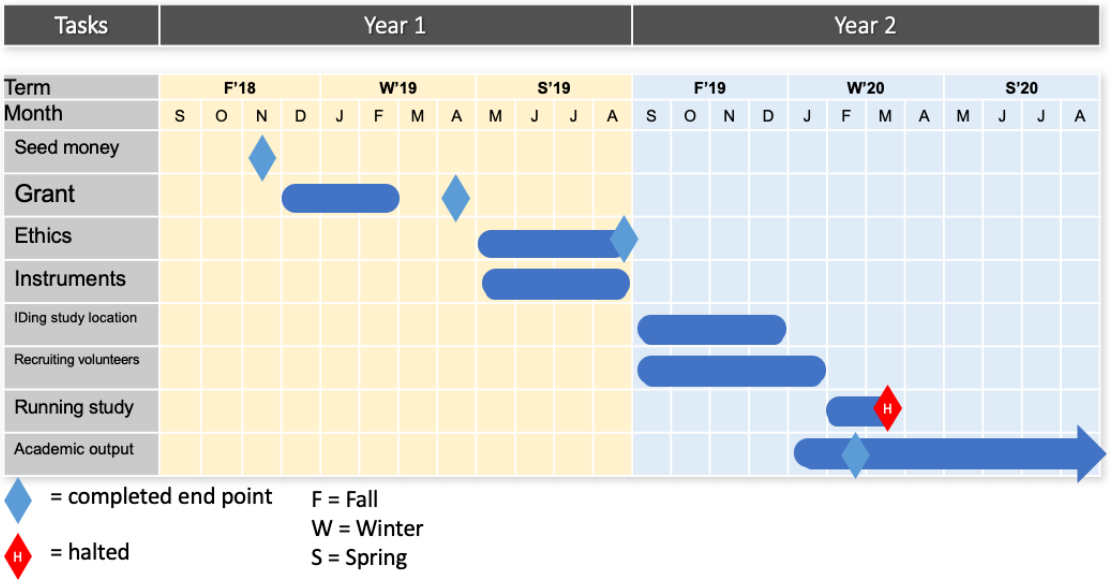
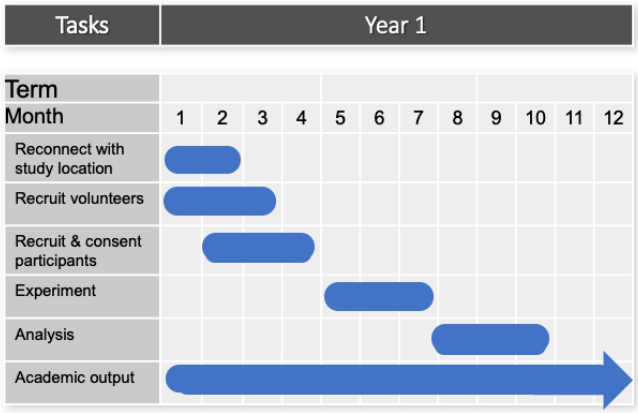


Figure 3. Gantt chart for when the pilot will be restarted.



Evaluation Outcomes

Demographic outcomes will be tabulated, as shown in Table S1 of Multimedia Appendix 9. A joint display will be used to integrate qualitative and quantitative data [57,58]. This joint display will present test statistics for the 4 variables measured as well as exemplary quotes from the intervention group before and after the study (Table S2 of Multimedia Appendix 9). There will also be a column to highlight the results of integrating the qualitative and quantitative data. Feasibility outcomes will be displayed, as shown in Table S3 of Multimedia Appendix 9.

Discussion

Overview of the Study

We were able to recruit 8 participants, before the study was forced to halt due to the COVID-19 pandemic, in accordance with institutional and public health guidelines. A large component of this study involves coordinating the schedules of student volunteers, older adults, and staff at the long-term care home. This presents a number of challenges as in-person classes lead to students generally being available only in the evenings, older adults often have busy schedules, and staffing shortages are prevalent in Canadian long-term care locations [59]. Scheduling is anticipated to be a problem, which will be resolved through extensive dialogue and trial-and-error scheduling.

The enTECH Computer Club in this study is a club with the Waterloo Undergraduate Student Association (WUSA), which does not have the infrastructure to manage the awarded research funding. Additionally, club activities require approval from the WUSA. In consultation with WUSA, the decision was made to run this study independent of WUSA, so as to use existing university research infrastructure. The club was referenced to establish a basis for this study to indicate the program used and the expected backgrounds of the research assistants, but this does not indicate that the club is otherwise affiliated with this study.

Principal Results

This study will contribute to a deeper understanding of intergenerational technology programs for older adults living in long-term care homes. We hope that these data will allow for stronger advocacy efforts for the benefits these programs can provide for older adults, especially in improving their mental health and reducing their feelings of loneliness. We also hope that this protocol will allow others who wish to study university

club programs as a starting point on how to do so. Navigating the requirements for university clubs, which are generally affiliated with university student unions, as well as university research requirements, including institutional review board approval, is a first-time occurrence for our institution from our understanding.

Limitations

Obtaining a sufficiently large sample to observe statistical significance for the measures used is anticipated to be a challenge, as resource limitations necessitate that this study is only run at 1 location. Should additional funding be secured, there is a potential for this study to be run at multiple sites.

Conclusions

We hope that the results of this study will highlight the need for increases in innovative technologically focused programs for older adults and the need for additional resources to be directed to promoting the value of this program to older adults.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Location recruitment letter.
[PDF File (Adobe PDF File), 141 KB - resprot_v10i2e23767_app1.pdf]

Multimedia Appendix 2
Advertisement to older adults.
[PDF File (Adobe PDF File), 2884 KB - resprot_v10i2e23767_app2.pdf]

Multimedia Appendix 3
Screening questions.
[PDF File (Adobe PDF File), 507 KB - resprot_v10i2e23767_app3.pdf]

Multimedia Appendix 4
Email script for phone call with family member.
[PDF File (Adobe PDF File), 36 KB - resprot_v10i2e23767_app4.pdf]

Multimedia Appendix 5
CONSORT 2010 flow diagram for the study.
[DOC File , 51 KB - resprot_v10i2e23767_app5.doc]

Multimedia Appendix 6
Demographics questionnaire.
[PDF File (Adobe PDF File), 34 KB - resprot_v10i2e23767_app6.pdf]

Multimedia Appendix 7
Preprogram interview guide.
[PDF File (Adobe PDF File), 63 KB - resprot_v10i2e23767_app7.pdf]

Multimedia Appendix 8
Postprogram interview guide.
[PDF File (Adobe PDF File), 44 KB - resprot_v10i2e23767_app8.pdf]

Multimedia Appendix 9
Proposed tables for recording evaluation outcomes.
[DOCX File , 16 KB - resprot_v10i2e23767_app9.docx]

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Abbreviations

CES-D: Center for Epidemiologic Studies Depression scale
CPQ-12: Computer Proficiency Questionnaire-12
OPQOL-Brief: Older People's Quality of Life-Brief version
UCLA: University of California, Los Angeles
WUSA: Waterloo Undergraduate Student Association

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Protocol

Evaluating a Mobile Phone–Delivered Text Message Reminder Intervention to Reduce Infant Vaccination Dropout in Arua, Uganda: Protocol for a Randomized Controlled Trial

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Abstract

Background: Globally, suboptimal vaccine coverage is a public health concern. According to Uganda's 2016 Demographic and Health Survey, only 49% of 12- to 23-month-old children received all recommended vaccinations by 12 months of age. Innovative ways are needed to increase coverage, reduce dropout, and increase awareness among caregivers to bring children for timely vaccination.

Objective: This study evaluates a personalized, automated caregiver mobile phone–delivered text message reminder intervention to reduce the proportion of children who start but do not complete the vaccination series for children aged 12 months and younger in select health facilities in Arua district.

Methods: A two-arm, multicenter, parallel group randomized controlled trial was conducted in four health facilities providing vaccination services in and around the town of Arua. Caregivers of children between 6 weeks and 6 months of age at the time of their first dose of pentavalent vaccine (Penta1; containing diphtheria, tetanus, pertussis, hepatitis B, and Haemophilus influenzae type b antigens) were recruited and interviewed. All participants received the standard of care, defined as the health worker providing child vaccination home-based records to caregivers as available and providing verbal instruction of when to return for the next visit. At the end of each day, caregivers and their children were randomized by computer either to receive or not receive personalized, automated text message reminders for their subsequent vaccination visits according to the national schedule. Text message reminders for Penta2 were sent 2 days before, on the day of, and 2 days after the scheduled vaccination visit. Reminders for Penta3 and the measles-containing vaccine were sent on the scheduled day of vaccination and 5 and 7 days after the scheduled day. Study personnel conducted postintervention follow-up interviews with participants at the health facilities during the children's measles-containing vaccine visit. In addition, focus group discussions were conducted to assess caregiver acceptability of the intervention, economic data were collected to evaluate the incremental costs and cost-effectiveness of the intervention, and health facility record review forms were completed to capture service delivery process indicators.

Results: Of the 3485 screened participants, 1961 were enrolled from a sample size of 1962. Enrollment concluded in August 2016. Follow-up interviews of study participants, including data extraction from the children's vaccination cards, data extraction

from the health facility immunization registers, completion of the health facility record review forms, and focus group discussions were completed by December 2017. The results are expected to be released in 2021.

Conclusions: Prompting health-seeking behavior with reminders has been shown to improve health intervention uptake. Mobile phone ownership continues to grow in Uganda, so their use in vaccination interventions such as this study is logical and should be evaluated with scientifically rigorous study designs.

Trial Registration: ClinicalTrials.gov NCT04177485; https://clinicaltrials.gov/ct2/show/NCT04177485

International Registered Report Identifier (IRRID): DERR1-10.2196/17262

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KEYWORDS

immunization; vaccination; reminder system; mHealth; short message service; text messages; cell phone; mobile phone; vaccination dropout; vaccination timeliness

Introduction

Vaccination Coverage

Although global childhood routine vaccination coverage has increased markedly since the inception of the Expanded Program on Immunization (EPI) in 1974, coverage has plateaued since 2010, with rates of the third dose of diphtheria being between 84% and 86% [1]. According to Uganda's 2016 Demographic and Health Survey (DHS), 49% of children aged 12 to 23 months received all recommended vaccinations by 12 months of age. Despite high coverage (95%) for the first dose of pentavalent vaccine (Penta1; containing diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type b antigens), which is given at 6 weeks of age, vaccination coverage for the third dose of pentavalent vaccine (Penta3), which is given at 14 weeks of age, was found to be 79% for a Penta1-Penta3 dropout of 17% [2]. Timely dosage of these vaccines remains low, threatening the health of Ugandan children with morbidity and mortality from vaccine-preventable diseases.

Innovative ways are needed to increase coverage, including increasing the recall rates of caregivers to bring children for timely vaccination [3]. Prompting health-seeking behavior via mobile technology interventions has been shown to improve health intervention uptake, particularly in high-income countries [4]. However, only a limited number of studies have evaluated the role of reminders sent by mobile phone text messages to increase vaccination coverage in low- and middle-income countries (LMICs).

Background on Texting Reminders for Vaccination in LMICs

A few studies in LMICs [5-8] have assessed coverage improvements from the implementation of electronic immunization registers (EIRs) that had an automated text message reminder feature. The study designs varied in terms of scientific rigor and each concluded that coverage increased; however, it was not possible to assess the impact of text message reminders alone, as the EIRs provided the additional intervention of improving the tracking of individuals.

Other studies [9-14] enrolled participants between birth and Penta1 and followed them through Penta3, or in some cases through 12 months of age. Most of these studies focused on coverage at 2 to 4 weeks after the scheduled Penta3 date, as compared with the Kenya cluster randomized controlled trial (cRCT) [13], as it assessed coverage at 12 months of age, which is a typical EPI indicator. This cRCT study did not find the text message reminder intervention alone to significantly improve vaccination coverage at 12 months of age, likely due to high coverage in the control group. However, other studies concluded that text message reminders significantly improved vaccination coverage.

In addition, a few studies have focused primarily on the acceptability of text message reminders for vaccination [15-17]. Crawford et al [15] and Brown et al [16] found the acceptability to be high (99% and 95%, respectively); however, one study in Nigeria [17] found that only 69% of caregivers were willing to receive text message reminders.

Despite a body of research focused on vaccination reminders, there is still a deficit of scientifically rigorous studies evaluating the impact and scalability of text message reminders in LMICs. With 74% of households reported to have mobile phones [2], this research builds upon a growing mobile health (mHealth) system in Uganda to use personalized, automated text messages to remind caregivers of upcoming vaccination visits, which is hypothesized to reduce vaccination dropout (defined as starting but not completing the recommended vaccination schedule) in children under 12 months and to eventually contribute to reductions in morbidity and mortality due to vaccine-preventable diseases. With the goal of being scalable if shown to be effective, this intervention is designed to assess the impact of text message reminders using an mHealth platform already implemented in Uganda.

Study Objectives

Primary objective:

- To evaluate a personalized, automated caregiver text message reminder intervention to reduce vaccination dropout for children aged 12 months and younger in select health facilities in Arua district

Secondary objectives:

- To measure the impact of a personalized, automated caregiver text message reminder intervention to increase the probability that children will receive Penta3 within 12 weeks of Penta1 receipt and MCV by 10 months of age.

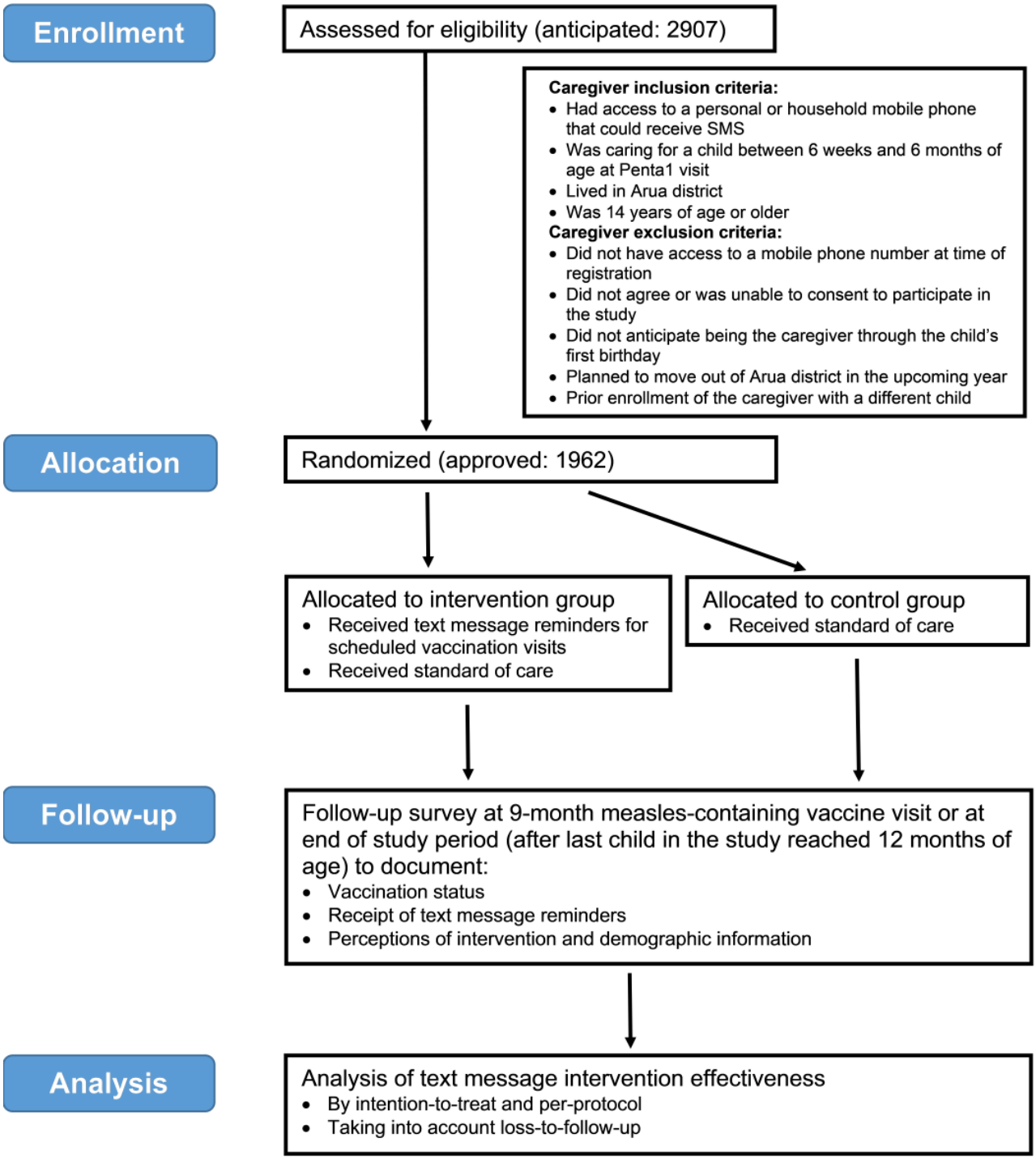
- To assess caregiver acceptability of a personalized, automated caregiver text message reminder intervention
- To determine the cost-effectiveness of a personalized, automated caregiver text message reminder intervention from the provider (Ministry of Health [MOH]) perspective

Methods

Study Design

A two-arm, multicenter, parallel group randomized controlled trial (RCT) was conducted in 4 health facilities providing vaccination services in and around the town of Arua. Caregivers were recruited at the time of their children's Penta1 vaccination visit. Caregivers and their children were randomized to either the intervention arm or the control arm and followed until the exit interview, which took place at the health facility during the children's measles-containing vaccine (MCV) visit or outside the health facility (generally at the caregiver's home) after the last child in the study completed 1 year of age. If the original caregiver was not available at the exit interview, another caregiver was consented and interviewed if available. The protocol was designed taking into consideration criteria described by the Consolidated Standards of Reporting Trials (CONSORT) [18], and the diagram of the study design is shown in Figure 1.

Figure 1. Diagram of study design.



Setting and Participants

Districts located in Uganda but outside the city of Kampala were considered for inclusion in the study if they had the following characteristics:

- Penta1 administrative coverage ≥80% (calculated as the number of children vaccinated with Penta1 vaccine divided by the total number of eligible children)
- Penta1-MCV administrative dropout rate ≥10% (calculated as the number of children vaccinated with the Penta1 vaccine minus the number of children vaccinated with MCV, divided by the number of children vaccinated with Penta1)
- Interest from District Health Office
- Both urban and rural populations

Among the districts under consideration, Arua district was selected as the study area because it had a Penta1 administrative coverage of over 80% and a Penta1-MCV dropout rate greater than 10%. We used this parameter for dropout because 10% is considered the programmatic threshold for unacceptable dropout [19]. In December 2014, we conducted a site visit to the health facilities in and around Arua town, where we found that 18 out

of 25 caregivers (72%) either had mobile phones with them or knew the phone numbers of their family phones. In addition, most caregivers indicated that they had village-level mobile phone reception as well as an electrical source to charge their phones (most typically solar charge).

Arua district is in northwest Uganda and borders the Democratic Republic of Congo in the west. Arua has an estimated population (2014) of 782,077, with an under 1-year-old target population of 28,605 [20]. Arua has 72 health facilities with varying levels of health services that are provided, including 3 hospitals.

To maximize study personnel efficiency, the 4 largest health facilities in and around Arua town were approached, and they agreed to participate as enrollment sites. Of these 4 facilities, 2 vaccinated every day, 1 vaccinated twice per week, and 1 vaccinated once per week. All 4 facilities provided outreach vaccination on an irregular basis.

During the enrollment period (February-July 2016), all caregivers who attended one of the selected health facilities for their children's Penta1 vaccinations were approached to determine if they met the inclusion criteria and were willing to participate.

Caregiver participant inclusion criteria were as follows: had access to a personal or household mobile phone that could receive text messages; caregiver for a child between 6 weeks and 6 months of age at the time of Penta1 vaccination visit; lived in Arua district; and was 14 years of age or older.

Caregiver participant exclusion criteria were as follows: did not have access to a mobile phone number at the time of enrollment; did not agree or was unable to consent to participate in the study; did not anticipate being the caregiver through the child's first birthday; planned to move out of Arua district in the upcoming year; prior enrollment of the caregiver with a different child.

Illiterate caregivers who were interested in participating, gave informed consent, and met the other inclusion criteria were enrolled. The understanding was that illiterate participants would have family members or friends read the text messages to them.

Study Arms

The study consisted of 2 arms: a control arm and an intervention arm. The control arm received the standard of care in the selected health facilities, defined as health workers providing child vaccination home-based records (HBRs), known as Child Health Cards in Uganda, to caregivers, as available and providing verbal instruction of when to return for the next visit. The intervention arm received the standard of care as well as personalized, automated text message reminders sent to participants for each of their 3 subsequent vaccination visits, as per the Uganda National EPI schedule [21] (Table 1).

Table 1. Uganda National Expanded Program on Immunization schedule in 2016-2017.

Vaccination visit	Age	Vaccines
0	Birth	• Bacillus Calmette-Guerin Vaccine • OPV[a] birth dose
1	6 weeks	• Penta1[b,c] • OPV1 • PCV1[d]
2	10 weeks	• Penta2 • OPV2 • PCV2
3	14 weeks	• Penta3 • OPV3 • PCV3 • IPV[e,f]
4	9 months	• MCV[g]

[a]OPV: oral polio vaccine.

[b]Penta1: pentavalent vaccine first dose.

[c]Pentavalent vaccine contains diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type b antigens.

[d]PCV1: pneumococcal conjugate vaccine first dose.

[e]IPV: inactivated polio vaccine.

[f]IPV was introduced in April 2016.

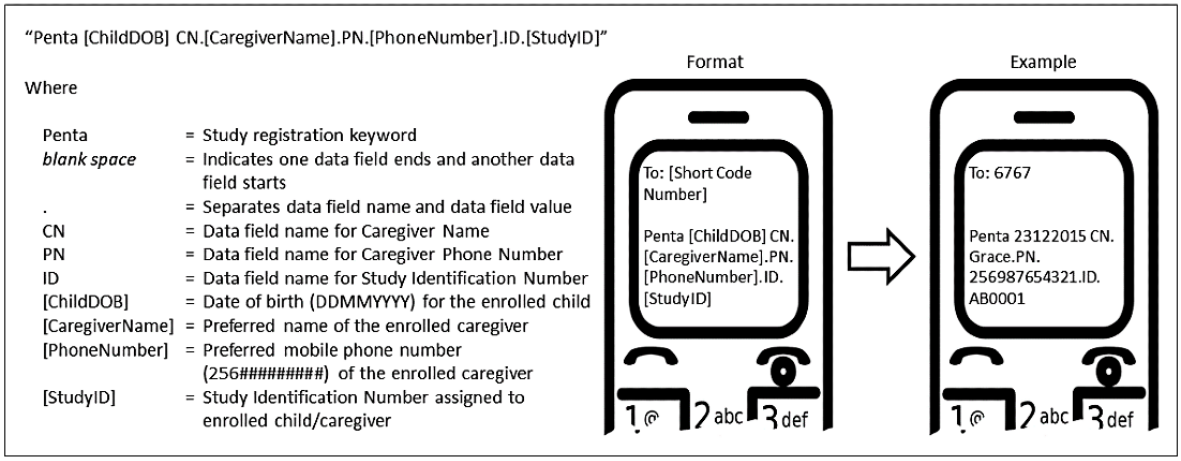
[g]MCV: measles-containing vaccine.

Enrollment, Randomization, and Blinding

Study personnel were stationed in the 4 selected health facilities and recruited caregivers of children between 6 weeks and 6 months of age who presented for their Penta1 vaccinations. Study personnel explained the study, obtained consent, and enrolled the eligible caregivers who agreed to participate in the study. Study participants responded to a brief preintervention

questionnaire to collect basic demographic information and locating information. The health facility staff vaccinated the children, filled out the health facility immunization register, and filled out the children's HBRs per standard practice in Uganda [22]. For each study participant, the study personnel sent a text message to a designated short code number with information that included the caregiver's preferred first or last name, caregiver's mobile phone number, child's date of birth, and the participant study ID in the following format: "Penta [ChildDOB] CN.[CaregiverName].PN.[PhoneNumber].ID.[StudyID]" (Figure 2).

Figure 2. Screenshot of mobile phone displaying data registration format used at health facility study sites in Arua, Uganda.



The information in the text message populated a centralized immunization registry database in a District Health Information System 2 (DHIS2) Software (version 2.26) Tracker Module instance created for this study. In addition, the mobile phone number of the study personnel who registered the study participant and the date that the registration text message was sent (which also served as the date of Penta1 vaccination) were recorded in the database. At the end of each day, study participants who were registered that day were randomized by computer using stratified permuted block randomization to either the control or the intervention arm, which was then recorded in the database as well. For randomization assignment, study participants were matched in order of registration to a sequence generated by nonfield study personnel before the start of enrollment. Stratification and blocking occurred at the health facility level; blocks of random size were used (lengths=2, 4, and 6) to minimize the ability to predict the next assignment. The health worker, study personnel, and participants were blinded to the randomization at assignment. However, unblinding of the intervention group occurred when they received the first text message reminder. The control group became unblinded, as they realized that they were not receiving text message reminders. On occasion, study participants shared their intervention status with health workers and field-level study personnel, thus unblinding them to the status of some caregivers. Nonfield staff study personnel who managed the database had access to intervention status after randomization assignment.

Texting Reminder Intervention

Following the Uganda EPI schedule and accounting for health worker practices in Arua, the DHIS2 Tracker instance was programmed to automatically schedule follow-up vaccination visits at 30 days after Penta1 (for the visit to receive Penta2, oral polio vaccine [OPV] dose 2, and pneumococcal conjugate vaccine [PCV] dose 2), 61 days after Penta1 (for the visit to receive Penta3, OPV3, and PCV3), and 274 days after the child's date of birth (for MCV). For each scheduled follow-up vaccination visit, the DHIS2 Tracker queued text message reminders to be sent on 3 different dates. At 7 AM on the scheduled dates, the DHIS2 Tracker delivered the messages to an SMS text message aggregator in Uganda, which then routed the messages to the appropriate Uganda telecommunications service providers, which in turn sent the messages to the appropriate participants. Every intervention group participant received the reminder in both English and Lugbara (the most common local language spoken in Arua). Penta2 text message reminders were sent 2 days before, on the day of, and 2 days after the scheduled vaccination visit. Penta3 and MCV text message reminders were sent on the scheduled day of vaccination and five and seven days after. Compared with the Penta2 text message reminders, the Penta3 and MCV text message reminders were sent later because at the time of reminder scheduling, the exact due dates for Penta3 were unknown (because Penta2 had not yet been received) and MCV (because DHIS2 Tracker could only schedule in terms of days, not months). Later reminders were preferred to reduce the possibility that caregivers would present too early for vaccination. As an automated intervention, text message reminders were sent regardless of whether the caregiver had already visited the health facility. Ideally, the visit for Penta3, OPV3, and PCV3 should have been scheduled 30 days after the visit for Penta2, OPV2, and PCV2. However, as the DHIS2 Tracker instance was not updated after vaccination visits, we had to schedule the visit in reference to the date of the visit for Penta1, OPV1, and PCV1.

Before study enrollment, consensus decision making with caregivers and health workers in Arua district and partners at the national level took place to finalize the pattern, timing, and exact wording of the text messages (Table 2). As some text message reminders would be automatically sent to caregivers either before the child was due for vaccination or after a

completed visit, we emphasized in the text messages that the caregiver refer to the child's HBR to confirm the date of the next vaccination.

Table 2. Content and timing of mobile phone text message reminders sent to intervention group participants' mobile phones.

Vaccination visit, scheduled vaccination visit[a], and message timing	Message[b]
Vaccination visit 2: Penta[c,d] dose 2; OPV[e] dose 2; PCV[f] dose 2	
30 days after vaccination visit 1 (Penta1, OPV1, and PCV1)	
2 days before scheduled visit	"[CaregiverName], please bring your child for immunisation this week. Confirm the date in your child health card."
On the day of the scheduled visit	"[CaregiverName], don't forget to immunise your child this week. Confirm the date in your child health card."
2 days after the scheduled visit	"[CaregiverName], don't forget to immunise your child this week. Confirm the date in your child health card."
Vaccination visit 3: Penta3, OPV3, PCV3	
61 days after vaccination visit 1 (Penta1, OPV1, and PCV1)	
On the day of the scheduled visit	"[CaregiverName], please bring your child for immunisation. Confirm the date in your child health card."
5 days after the scheduled visit	"[CaregiverName], please bring your child for immunisation. Confirm the date in your child health card."
7 days after the scheduled visit	"[CaregiverName], please bring your child for immunisation. Confirm the date in your child health card."
Vaccination visit 4: measles-containing vaccine	
274 days after the child's date of birth	
On the day of the scheduled visit	"[CaregiverName], please bring your child for measles immunisation this week. Confirm the date in your child health card."
5 days after the scheduled visit	"[CaregiverName], don't forget to immunise your child against measles. Confirm the date in your child's health card."
7 days after the scheduled visit	"[CaregiverName], don't forget to immunise your child against measles. Confirm the date in your child's health card"

[a]Vaccination visits subsequent to the Penta1 visit were scheduled in the District Health Information System 2 Tracker at the time of registration. As such, vaccination visit 3 (Penta3, OPV3, and PCV3) was scheduled based on the date of vaccination visit 1 (Penta1, OPV1, and PCV1).

[b]Messages were sent in both English and Lugbara.

[c]Penta: pentavalent vaccine.

[d]Penta contains diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type b antigens.

[e]OPV: oral polio vaccine.

[f]PCV: pneumococcal conjugate vaccine.

Data Collection

Data were collected using a variety of tools: pre- and postintervention questionnaires, immunization data extraction form, and health facility record review form. At the time of enrollment, study personnel administered the preintervention questionnaire to participants (at the Penta1 visit) to gather basic demographic and locating information. At the time of the MCV visit, study personnel administered the postintervention questionnaire to participants to gather information on the acceptability of the text message reminder intervention, knowledge, attitudes, and beliefs regarding vaccination practices, and demographic information. Participants who did not return for MCV were interviewed at their homes. In some cases, the study personnel met the participants in another location that was convenient to them and reimbursed them for their transportation costs. In some other cases, the study personnel interviewed participants by phone because it was not feasible to interview in person. As part of the postintervention questionnaire, study personnel reviewed the HBRs of the child participants to extract vaccination data.

Every day during the enrollment period, study personnel completed the health facility immunization system record review form to capture service delivery process indicators (eg, vaccination sessions held, antigens administered). In addition, study personnel extracted vaccination data on the child participants from the immunization register.

Data Management and Analysis

Initially, data collectors completed the participant interviews on paper and then entered the data into a REDCap electronic capture tool [23] on a tablet. After becoming comfortable with the tablet, data collectors entered the data directly into the tablet. Data were stored on a cloud-based server that used a 256-bit

encryption. The server backed up the data daily and was only accessible through a secure password-protected website, which had individual log-ins only for authorized users. Data were removed from the server once the project was completed.

Data quality control was addressed at multiple stages. The first stage of quality control was the data collectors themselves. Adequate training minimized the risk of procedural errors. Furthermore, questionnaires were formatted electronically, which limited the amount of missing data, as logic patterns required the study personnel to enter all required fields. The electronic tools required the data collector to input values for each field. The second level of control was the local study coordinator. During data collection, the study coordinator ensured proper sampling and interviewing through daily periodic spot checks during data gathering. The study coordinator reviewed the data entered by the data collectors and then locked each record, after which it was no longer modifiable by the data collectors. The third level of control was the principal investigator who reviewed the data to ensure that (1) the sample size was reached, (2) the eligibility requirements of each participant were met, and (3) blanks or partially completed forms were minimized.

For the primary objective, a logistic regression model with fixed effects at the health facility level will be used to analyze differences between intervention and control groups in Penta3 and MCV coverage at 12 months of age. For the assessment of timeliness, a logistic regression model with fixed effects at the health facility level will be used to analyze differences between intervention and control groups in Penta3 coverage 12 weeks after receiving Penta1 and MCV coverage at 10 months of age. In addition, Cox proportional hazards models with fixed effects at the health facility level will be used to analyze time-to-event (ie, timeliness) outcome data. The primary analyses will be based on intention-to-treat, but per-protocol analysis will also be conducted. Dates of vaccination from HBRs will be used for analysis, supplemented with dates from the immunization register extraction if HBR dates are unavailable. In addition to logistic regression, log-binomial regression models will be used to estimate risk ratios. Data will be analyzed using statistical software such as STATA, SAS, or R.

Sample Size

On the basis of administrative data from 2013 to 2014, we assumed a 16% Penta1-MCV dropout rate for the nonintervention group and calculated a sample size with a power of 90% and confidence level of 95% with the ability to detect a 5% decrease in dropout rate in the intervention group compared with the control group. A one-sided test was used for the sample size calculations.

Anticipated coverage of the control group was as follows: Penta1: 100% (Penta1 is an eligibility requirement); MCV: 84% (16% dropout).

Anticipated coverage of the intervention group was as follows: Penta1: 100% (Penta1 is an eligibility requirement); MCV: 89%.

We calculated the sample size based on the following formulas [24]:

and

where n' is the sample size of each group if we ignore the continuity correction; n is the sample size of each group, accounting for the continuity correction; P_1 is the proportion found in the first sample (0.84); P_2 is the proportion found in the second sample (0.89); Q_1 is 1 minus P_1 (0.16); Q_2 is 1 minus P_2 (0.11);  is the average of P_1 and P_2 (0.865);  is the average of Q_1 and Q_2 (0.135); z_α *is* the z-score for a one-sided test with a level of significance of .05 (1.645); z_β *is* the z-score for power of 90% or $z_{0.10}$ (1.28).

To detect a change in MCV coverage, the sample size per arm (without attrition) needed was 838. Of these 838 per arm, we anticipated a 10% loss to follow-up for caregivers who do not return to the same health facility for MCV and who cannot be found at the end of the study or who have lost their HBRs. In addition, for the purposes of quality control, approximately 100 participants (about 5%) were recruited and contacted by mobile phone after their scheduled visits to assess the reliability of the intervention at sending text messages and having those messages received by the intended individual. Thus, an adjusted sample size of 1962 participants was necessary for enrollment.

Among caregivers approached during their children's vaccination visit 1 (Penta1, OPV1, and PCV1), we anticipated an eligibility rate of 75% and a study refusal rate of 10%, thus estimating that study personnel would need to screen 2907 caregivers in order reach the sample size.

According to administrative data from the operational year 2013 to 2014, the 3 largest health facilities in and around Arua town administered a total of 9292 doses of Penta1 during the course of 1 year. On the basis of the number of caregivers that needed to be screened (2907) and the number of doses the 3 health facilities provided in a year (9292), we estimated that 16 weeks would be necessary for enrollment. After the first 2 months of study recruitment (February-March 2016), enrollment was found to be lower than expected, so a fourth health facility was added as a study site.

Ancillary Research Objectives

In addition to the RCT study design to address the principal research objectives, we also conducted focus group discussions (FGDs) to more thoroughly assess caregiver acceptability of a personalized, automated caregiver text message reminder intervention. At the end of the study, study personnel conducted 8 FGDs with caregivers and spouses who were originally randomized into the intervention group from one of the select health facilities. A total of 4 types of FGDs were conducted:

1. Female caregivers who received messages on their personal phones and whose children were up to date with vaccinations

2. Female caregivers who received messages on their personal phones and whose children were not up to date with vaccinations
3. Female caregivers' spouses who received messages on their personal phones and whose children were up to date with vaccinations
4. Female caregivers' spouses who received messages on their personal phones and whose children were not up to date with vaccinations

The FGDs were audiorecorded, and 2 research assistants translated and transcribed (1 step) discussions into English. Thematic content analysis will serve as a strategic analytical approach. Codes will be identified and then refined through additional reviews of the data. The main themes will be identified, reviewed, further refined, categorized, and subcategorized; matrix analysis will be used to organize themes and assess patterns. Data will be analyzed using word processors, spreadsheets, and qualitative data analysis software.

In addition, we will conduct an economic analysis that will focus on evaluating the incremental costs and cost-effectiveness of the personalized, automated caregiver text message reminder intervention compared with standard practice. Costs will be evaluated from the provider (MOH) perspective and will include the start-up costs of developing the system and operational costs of delivering the text messages (including costs related to data charges for message deployment, system maintenance, and troubleshooting). For the calculation of incremental cost-effectiveness ratio (ICER), coverage data from the questionnaire will be an important determinant in evaluating the value for money in adopting the caregiver text message reminder strategy. Effectiveness will be measured by the cost per additional fully immunized child at 12 months of age in the intervention arm. Furthermore, we will estimate the costs of scaling up the proposed intervention by the MOH to cover the entire country using data on the expected catchment areas for health facilities in Uganda to determine the total cost of a nationwide system rollout. Sensitivity analysis will be conducted to determine how sensitive the ICER is to varying effectiveness and system costs.

Ethical Considerations

The proposed research was minimal risk and did not present significant concerns regarding the ethical treatment of study participants. The protocol received institutional review board (IRB) approval by the Higher Degrees, Research and Ethics Committee at Makerere University, School of Public Health in Kampala, Uganda (HDREC 294), and was registered with the Uganda National Council of Science and Technology (SS 3924). The US Centers for Disease Control and Prevention relied on the Makerere University IRB (CDC Protocol #6721.0). The trial is registered with ClinicalTrials.gov (NCT04177485).

This research involved face-to-face interviews using questionnaires to determine vaccination status and assess knowledge, attitudes, beliefs, and perceptions of vaccination and text message reminders. There were no direct benefits for the participants. However, study results will be used to support evidence-based strategies to reduce vaccination dropout rates.

Written informed consent was obtained from the participants before data collection. Consent forms were available in both English and Lugbara. Study participants could include pregnant women (eg, an aunt caregiver with an eligible child may be pregnant with her own child) and emancipated minors (ie, mothers and fathers who are 14-17 years of age), but they were not the primary focus of this intervention. Study participants were provided details on how they could opt out of the study at any point and thus be removed from receiving text message reminders.

Results

Pretesting of the preintervention questionnaire and the text message reminders occurred in November 2015. Pretesting of the postintervention questionnaire occurred in February 2016. Enrollment began in February 2016 and concluded in August 2016. Of the 3485 screened participants, 1961 were enrolled from a sample size of 1962. The preintervention questionnaire was administered during enrollment. Text message reminders were sent to the intervention group between February 2016 and April 2017. Follow-up interviews of study participants, including data extraction from the children's vaccination cards and FGDs occurred between September 2016 and December 2017. A total of 8 FGDs were conducted and varied in size from 6 to 10 participants. Data extraction from the health facility immunization registers, completion of the health facility record review forms, and cost data collection occurred between January 2016 and September 2017. Data cleaning was completed. Logistic regression will test for differences between intervention and control groups; log-binomial regression and Cox proportional hazards regression will approximate the relative risk of vaccination and the hazard of timely vaccination, respectively, in the intervention group compared with the control group. The results are expected to be released in 2021.

Discussion

Despite recent improvements in Penta1 in Uganda, coverage of both Penta3 and MCV coverage are suboptimal and indicate that 17% of children are not returning for immunization services later in infancy [2]. As vaccination coverage continues to get closer to 100%, it is increasingly difficult and expensive to continue to make improvements in coverage. Prompting health-seeking behavior with reminders has been shown to improve health service uptake in many contexts, including through the use of mobile technology. However, most of the evidence surrounding the effectiveness of these interventions is from high-income countries where mobile phone technology usage is generally more prevalent [4]. According to Uganda's 2016 DHS, 46% of women and 66% of men aged 15 to 49 years owned a mobile phone in 2016 [2]. MOH-Uganda is interested in improving vaccination coverage, and Uganda has already been the site of many pilot projects that have attempted to use mobile technology to improve health. Faced with high rates of vaccination dropout, this research evaluates an intervention that uses text messages to remind mothers of upcoming vaccination visits, which is hypothesized to reduce vaccination dropout in children aged below 12 months and to eventually contribute to

a reduction in morbidity and mortality due to vaccine-preventable diseases. The study has several possible limitations, including contamination of the control group participants through their interactions with intervention group participants, attrition bias due to incomplete data from loss to follow-up, and a study population that excluded households that did not have a mobile phone. In addition, although logistic regression is appropriate to test the hypotheses of interest, the resulting odds ratios are inadequate approximations of the relative risks.

As mobile phone ownership continues to grow in Uganda, their use in health interventions is both logical and practical. However, the implementation of mobile technologies in immunization service delivery needs to occur alongside methodologically rigorous evaluations that assess their effects on both immunization uptake and caregiver acceptability.

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Conflicts of Interest

FB and PB work for the Health Information Systems Program, which developed and upgrades the DHIS2 products. The funding body was not involved in the planning and implementation of this study.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1634 KB - resprot_v10i2e17262_app1.pdf]

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Abbreviations

cRCT: cluster randomized controlled trial
DHIS: District Health Information System
DHS: Demographic and Health Survey
EIR: electronic immunization register
EPI: Expanded Program on Immunization
FGD: focus group discussion
HBR: home-based record
ICER: incremental cost-effectiveness ratio
IRB: institutional review board
LMIC: low- and middle-income country
MCV: measles-containing vaccine
mHealth: mobile health
MOH: Ministry of Health
OPV: oral polio vaccine
PCV: pneumococcal conjugate vaccine
Penta: pentavalent vaccine
RCT: randomized controlled trial

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Protocol

Smoking Cessation Using Wearable Sensors: Protocol for a Microrandomized Trial

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Abstract

Background: Cigarette smoking has numerous health consequences and is the leading cause of morbidity and mortality in the United States. Mindfulness has the ability to enhance resilience to stressors and can strengthen an individual's ability to deal with discomfort, which may be particularly useful when managing withdrawal and craving to smoke.

Objective: This study aims to evaluate feasibility results from an intervention that provides real-time, real-world mindfulness strategies to a sample of racially and ethnically diverse smokers making a quit attempt.

Methods: This study uses a microrandomized trial design to deliver mindfulness-based strategies in real time to individuals attempting to quit smoking. Data will be collected via wearable sensors, a study smartphone, and questionnaires filled out during the in-person study visits.

Results: Recruitment is complete, and data management is ongoing.

Conclusions: The data collected during this feasibility trial will provide preliminary findings about whether mindfulness strategies delivered in real time are a useful quit smoking aid that warrants additional investigation.

Trial Registration: Clinicaltrials.gov NCT03404596; https://clinicaltrials.gov/ct2/show/NCT03404596

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KEYWORDS

mHealth; microrandomized trial; smoking cessation; mindfulness; tobacco; mobile phone

Introduction

Tobacco Use and Stress

Cigarette smoking has numerous adverse health consequences and is the leading cause of morbidity and mortality in the United States [1]. Determining how to prevent relapse following a quit attempt is key to successful long-term tobacco abstinence. When considering predictors of relapse, the experience of stress, or negative affect, is strongly associated with the risk of relapse [2,3], and high stress is related to an increased likelihood of lapse during a smoking quit attempt [4]. Developing smoking cessation interventions that target stress are needed and may be particularly useful for individuals with low socioeconomic status (SES), given increased exposure to chronic stressors and other negative life events (eg, discrimination and violence) [5-8].

Mindfulness as a Quit Smoking Aid

One potential skill that could aid individuals in successful cessation, by enhancing resiliency to stressors, is the cultivation of mindfulness. Mindfulness is a multifaceted construct and is often described as the ability to pay attention to the present moment, with purpose and without judgment [9]. When applied to making a behavior change, such as quitting smoking,

mindfulness is hypothesized to decrease automaticity, such that an individual chooses how to respond in a given situation (vs automatically reaching for a cigarette, for instance) [10-13]. Mindfulness is also posited to enhance an individual's ability to be present with discomfort, which is particularly relevant when managing cravings and symptoms of withdrawal [14]. Mindfulness may be particularly useful for those experiencing high levels of stress, as it teaches skills that are applicable to a host of experiences (eg, managing physical and emotional distress) and is not specific to only changing the targeted behavior of smoking.

Mindfulness-based interventions have been effective in reducing smoking [15-18] and have results comparable with those of other empirically supported treatments (ie, cognitive behavioral therapy) [18]. Most importantly, mindfulness is linked to underlying mechanisms associated with abstinence, such as decreasing negative affect [19-23], increasing positive affect [20,23,24], increasing self-efficacy [25-28], and lowering craving [29-32]. Nonetheless, studies that have examined mindfulness for smoking cessation have typically used the traditional format of mindfulness interventions (8 weekly group sessions lasting 2-2.5 hours). Although the results have been promising, this format is time- and resource-intensive and may discourage engagement, particularly among low SES populations. It is very likely that aspects of mindfulness, when delivered at key moments during the quit smoking process, can also be beneficial.

Microrandomized Trials

This study uses a microrandomized trial (MRT) design to deliver mindfulness strategies (referred to as ecological momentary interventions [EMIs]) to participants on a smartphone at key moments during a quit attempt. Using MRTs is an innovative way to investigate whether certain intervention components, when delivered at certain times, impact hypothesized mechanisms and behavior [33]. We are specifically interested in the impact of these EMIs in relation to negative affect and lapse [4,6,34-37]. Thus, during a quit attempt, moments will be randomized to either receive a strategy or not, based on (1) times of low and high negative affect and (2) smoking status (lapse and no lapse). Negative affect and smoking status will be detected unobtrusively via wearable wireless sensors, and EMIs will be delivered via smartphones.

Study Aims

This feasibility study will evaluate the provision of real-time, real-world mindfulness intervention strategies among a sample of smokers making a quit attempt. Outcomes are consistent with those evaluated in other feasibility studies [38,39]. Our feasibility outcomes will include participant retention, adherence, and score on the System Usability Scale. We will also measure acceptability outcomes that will include response to the Client Satisfaction Questionnaire and mindfulness strategies. As an exploratory outcome due to the small sample size, we hypothesize that providing mindfulness strategies in real time will be associated with lower negative affect, greater self-regulatory capacity, and a reduced likelihood of lapsing.

Goal of the Paper

This paper will describe the protocol for Time2QuitMindfully, which is a study that will evaluate the feasibility of an MRT to deliver mindfulness strategies at key moments in the real world during a quit smoking attempt.

Methods

Recruitment

All recruitment and study procedures have been approved by Moffitt Cancer Center's institutional review board. This study aims to recruit 24 participants who are interested in quitting smoking. To be eligible, participants must be aged 18 years or older; smoke an average of at least three cigarettes per day over the past year; have a carbon monoxide (CO) reading of at least six parts per million (ppm); are motivated to quit within the next 30 days; have a valid home address; have a functioning telephone number; and can speak, read, and write in English. Individuals will be ineligible if they have a history of contraindications for using the nicotine patch unless a doctor's note is provided, endorse current psychosis, have a pacemaker or implanted device similar to a pacemaker, use smoking products other than cigarettes and e-cigarettes, are pregnant or trying to become pregnant or are breastfeeding, physically unable to wear the equipment and provide good readings of physiological measures, currently trying to quit smoking, involved in a quit smoking program, using tobacco cessation medications, have another household member enrolled in the study, or have no prior experience using a smartphone.

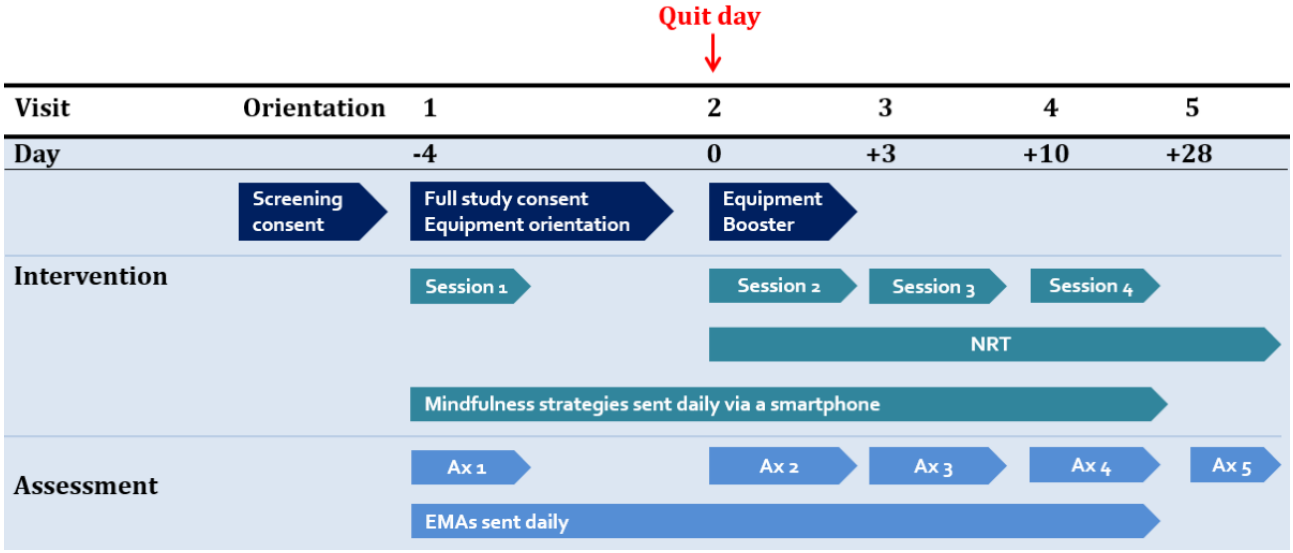
In-Person Procedures

Recruitment, Orientation, and Study Visits

Participants will be recruited from the community via a variety of methods: community flyers, web-based advertisements, and prior study databases containing the contact information of participants who agreed to be contacted about future research opportunities. Interested individuals will be screened over the phone to assess their eligibility. If eligible, individuals will be given more details about what the study entails and will be invited to schedule an in-person orientation session, which will take place either in a group or individually. At orientation, the informed consent process to collect eligibility data will be conducted. Next, individuals' CO will be measured to assess smoking status, a pregnancy test will be performed to rule out pregnancy, and the Mini International Neuropsychiatric Interview [40] will be conducted to rule out psychosis. If eligible, they will be shown a PowerPoint presentation to learn more about the study and to ask questions. After the PowerPoint presentation, participants who are interested in participating will be scheduled to attend the study visits.

The visit schedule is as follows: visit 1 is scheduled to occur 4 days before the quit day, visit 2 is on the quit day, visit 3 occurs 3 days after the quit day, and visit 4 occurs 7 days later. At 28 days after quit day, participants will return for a follow-up visit at visit 5. Figure 1 shows an overview of the timeline of the study sessions. Most sessions will last 1-3 hours, with visit 1 being the longest session at 3 hours.

Figure 1. Study timeline. Ax: assessment; EMA: ecological momentary assessment; NRT: nicotine replacement therapy.



At the beginning of visit 1, participants will complete the informed consent process for study participation, which involves the experimenter explaining the purpose of the study, why they are being asked to participate, that participation is voluntary, what will happen during the study period, benefits, risks, and confidentiality. All study information presented at orientation will be revisited at visit 1, before having participants sign the informed consent document. After consent is complete, participants will be asked how many cigarettes they currently smoke per day to determine the correct dosage for nicotine replacement therapy (NRT) administration (details of patch administration described further below). CO, height, and weight will be measured, and participants will complete a battery of baseline questionnaires. Questionnaires measure constructs such as mindfulness, stress, anxiety, tobacco history, financial strain, and previous use of technology. The full list of questionnaires for each visit is presented in Table 1.

In the second portion of visit 1, participants will be trained in detail on how to use the study equipment. First, all pieces of equipment (2 wrist sensors, 1 chest box, 1 chest band, 2 types of electrodes, and 1 study phone) will be laid out on a table, and each piece of equipment and their purpose is to be explained in detail by the experimenter. The experimenter will then assemble the equipment on a mannequin one by one to demonstrate how equipment should be worn and will answer any questions along the way. Participants will be presented with their own set of equipment and asked to put it on, and the experimenter will leave the room. The experimenter will then return and check for correctness. After this is completed, there will be a discussion with the participants to ensure they will be wearing the sensors every day (at least 8-12 hours), and to set up a start and end time for each day on the phone.

The experimenter will then go through a participant packet that explains how to put on the equipment and navigate the study apps' features, such as privacy mode (participants can choose if they do not want data collected for a period of time). The packet also details how to identify data quality, access the troubleshooting features, take off the equipment, end data collection if needed, and charge the equipment overnight. General information on how to use a smartphone and tackle common issues, such as poor data quality, will also be addressed. Before the session is over, the experimenter will ensure that all data quality collected on the phone is optimal and that the equipment is functioning as expected. Participants will also be provided phone numbers to contact if they experience any equipment issues. Equipment training will take approximately 1 hour to complete. At the end of the visit, participants will receive brief counseling and will be given instructions on wearing the patches for their quit day (visit 2). More details on the intervention are provided below.

During visits 2, 3, and 4, the following procedures will occur: assessment of cold or flu-like symptoms since the last visit (to account for if needed when analyzing physiological data), CO collection, administration of questionnaires, equipment check, presentation of technology boosters and provision of additional electrodes, brief counseling, and patch administration. Participants are to return their assigned equipment at visit 4, after 2 weeks of use. A follow-up visit will occur 28 days after quit day (visit 5), where tobacco use will be assessed, questionnaires completed, patches administered, and quit smoking resources provided.

Table 1. Study measures overview.

Measure	Visit 1, baseline (−4)	Visit 2, quit day (0)	Visit 3, (+3)	Visit 4, end of Tx[a] (+10)	Visit 5, follow-up (+28)
Demographics	X[b]	—[c]	—	—	—
Agency and acculturation					
Self-Efficacy Scale-Smoking [41]	X	X	X	X	X
Financial Strain Measure [42]	X	—	—	—	—
Subjective Social Status [43]	X	—	—	X	X
Affect, stress, alcohol, and mental health					
Positive and Negative Affect Scale [44]	X	X	X	X	X
Perceived Stress Scale [45]	X	X	X	X	X
Alcohol Use Disorders Identification Test [46]	X	—	—	X	X
Patient Health Questionnaire-Alcohol [47]	X	—	—	X	X
Center for Epidemiologic Studies Depression Scale [48]	X	—	—	X	X
Generalized Anxiety Disorder-7 [49]	X	—	—	X	X
Distress Tolerance Scale [50]	X	—	—	X	X
Difficulties in Emotion Regulation Scale-Short Form [51]	X	—	—	X	X
Mindfulness and personal resources					
Shift and Persist [52]	X	—	—	X	X
Five Facet Mindfulness Questionnaire [53]	X	—	—	X	X
Mindful Attention Awareness Scale [54]	X	—	—	X	X
Mindfulness Self-efficacy [28]	X	—	—	—	X
Toronto Mindfulness Scale [55]	X	X	X	X	X
Smoking					
Wisconsin Smoking Withdrawal Scale [56]	X	X	X	X	X
Brief Wisconsin Inventory of Smoking Dependence Motives [57]	X	—	—	X	X
Smoking status and biochemical verification					
Tobacco history	X	—	—	—	X
CO[d] reading	X	X	X	X	X
TLFB[e]	—	X	X	X	X
Tobacco Abstinence Questionnaire	—	X	X	X	X
Other					
Experience with technology survey	X	—	—	—	—
Experience with mindfulness survey	X	—	—	—	—
System Usability Scale [58]	—	—	—	X	—
Feasibility of technology survey	—	—	—	X	—
Mindfulness strategies feedback survey	—	—	—	X	X
Client Satisfaction Questionnaire [59]	—	—	—	X	—

[a]TX: treatment.

[b]Procedure occurred at the indicated visit.

[c]Procedure did not occur at indicated visit.

[d]CO: carbon monoxide.

[e]TLFB: timeline follow back.

Check-Ins and Troubleshooting With Study Staff

During the 2 weeks of participants wearing the data collection equipment (visits 1-4), the study staff will monitor equipment use via a dashboard. Staff members will be able to see the quality of participant data (eg, wrist sensors, electrocardiography, and respiration) as well as whether participants have been receiving and completing surveys and strategies on the study phone. To troubleshoot and resolve issues, participants will be contacted if poor or no data appear in the system. Participants will be given phone numbers to contact if they experience issues during business hours and weekends.

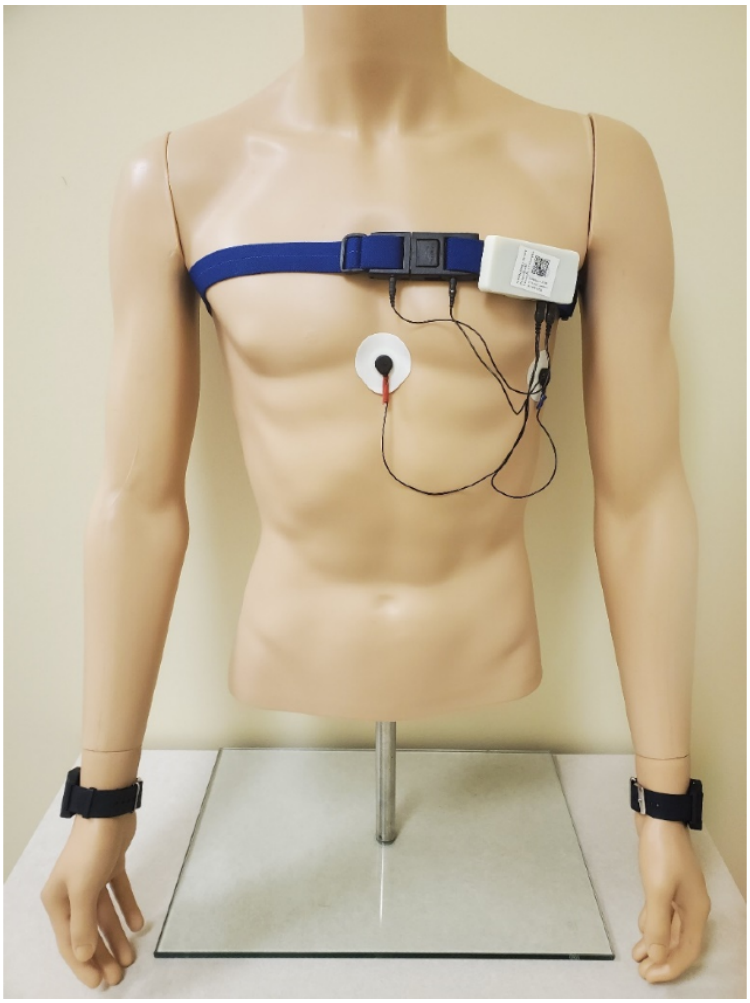
Compensation and Incentives

Participants will be compensated at the end of each visit for completing questionnaires and to cover the costs of transportation, childcare, etc. At orientation, the participants will be compensated with US $10 for attending. At visits 1-3, participants earn US $30 in each session and US $50 at visits 4 and 5. Participants can also earn bonuses throughout the study by answering survey questions administered daily via the study phone. Participants will be compensated with US $1.25 for completing each phone survey if they have worn the on-body sensors at least 60% of the time since the last phone survey or US $0.50 for completing each phone survey if they have not worn the sensors at least 60% of the time. This pay schedule was developed to encourage continuous use of the equipment [60]. Depending on how often participants wear the on-body sensors and complete the surveys over the 14 days, they can earn US $0-$11.25 per day, for a total of US $0-$157.50 over the entire study, in bonuses.

Equipment

At visit 1, participants will be given a set of equipment to wear for 2 weeks. The equipment suite is called AutoSense [61] and consists of a Samsung Galaxy S5, 2 wrist sensors that look and feel similar to watches or Fitbits, a chest box, and a chest band (Figure 2 shows an image of the equipment) [62,63]. The study phone will have the mCerebrum software [64] that restricts the participant to only accessing the study app when using the phone; this procedure is in place to reduce the use of the phone battery. When the participant turns on the phone, they will see a home page with the study's contact information and app icon that will lead them directly to the app. The phones will upload data automatically to the Cerebral Cortex cloud [65] and include battery packs that make all-day use possible.

Figure 2. Autosense equipment.



Participants will be given 2 wrist bands that are labeled with either an L or R on the straps, so that they can be placed on the appropriate wrist for data collection. The chest strap can be adjusted to accommodate a participant's size, and participants will be instructed to wear the band around their chest right under the armpits, under their clothes. The strap has 2 ports where the chest box can be connected. The chest box is a small white box with 2 sets of wires clipped onto the chest band. One set of wires will connect to ports located on the chest band. The other set of wires will connect to the electrodes that are to be placed in the middle of the chest, right below the sternum, and on the left-hand side of the ribcage. Participants will be given 2 types of electrodes and instructed to wear what they are most comfortable with. Participants will also be provided a charging station and a draw string bag to transport their set of equipment and other materials to and from the laboratory.

Ecological Momentary Assessments/Surveys on Phone

Ecological momentary assessments (EMAs) will be delivered randomly within prespecified time blocks as well as after a subset of EMIs during the 2-week period. All methodologies for randomly allocating EMAs were preprogrammed using a random number generator function. Randomization also considers what has already been sent historically during that day and is based on certain conditions, as described below. Random EMAs are delivered within 3- to 4-hour blocks throughout the day. Thus, participants will receive no more than 1 survey per 4-hour block to limit the participant burden (up to 3 random EMAs per day). The system is also configured to deploy EMAs after EMIs (described below), 50% of the time. For an EMA to be delivered, certain conditions must be met: time since the last delivered EMI followed by EMA must be more than 15 min, data quality must be classified as good (ie, sensors are attached correctly to the user and the sensors are communicating correctly with the smartphone; red, yellow, and green indicators will be visible to participants so they can fix the equipment if needed. This allows for the sensor data collected in the vicinity of the moment of EMA to be available for analysis), and the participant cannot be driving or engaging in physical activity (to increase the likelihood of responding) [66].

When it is time to take a survey, participants will receive a notification on their phone. Participants will have the option of completing it, delaying it for 5 min, or canceling it altogether. EMAs take an average of 3-5 minutes to complete and assess the following broad areas: mindfulness, affect, motivation, urge to smoke, expectancies, self-efficacy, smoking behaviors, patch use, social setting, alcohol use, discrimination, stressors, and general emotional support. An item assessing whether participants have been using the mindfulness strategies, without the aid of their smartphone, will also be presented.

Intervention Components

EMIs

The use of technology in this study allows participants to receive interventions in real time via the study smartphone in their natural environment. The study app on the phone has been configured to deploy specific interventions triggered by smoking status or the level of negative affect. Data are continuously collected via the sensors. Here, we describe the content of the EMIs, followed by the delivery procedure.

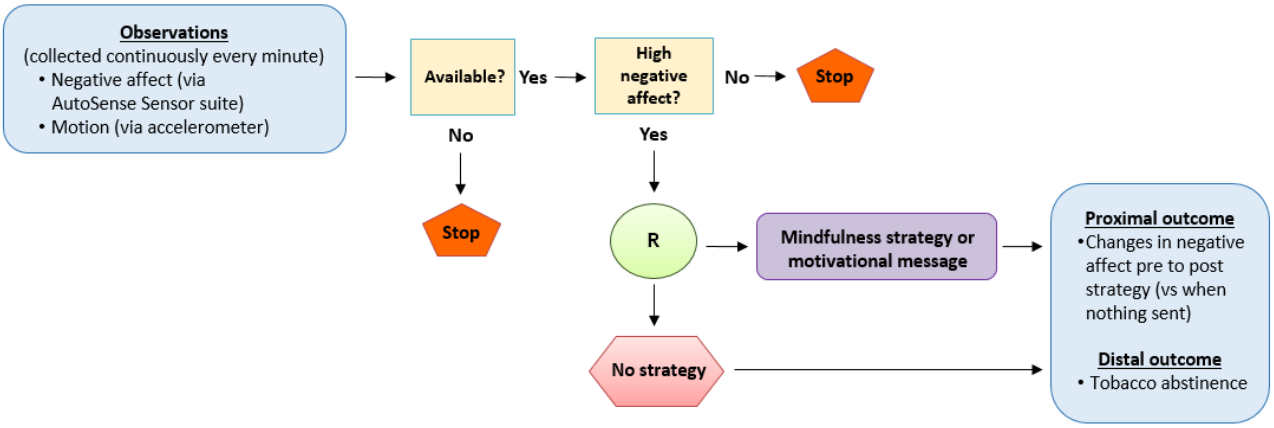
Active strategies include prompts to engage in mindfulness-based strategies and read motivational messages throughout the day. The majority of messages will be mindfulness strategies (n=76), which fall into the following topic areas: breath (eg, Turn your attention to your breathing. Notice where you feel your breathing most in your body), thoughts (eg, Observe any thoughts you are having right now. Watch them go by, just as leaves float down a stream of water—they just come and go), sensations (eg, Shift your attention to what you see around you. Be aware of the colors, shapes, textures, and shadows for the next several moments), acceptance/nonjudging (eg, Try to let go of labeling things as good or bad. Be present with what is happening and suspend judgment), and craving (eg, Whenever you have a craving to smoke, think of the craving like a wave in the ocean—it will come and go over time). Examples of motivational messages (n=40) are: "Quitting smoking may be uncomfortable at times, but it will get easier! Your cravings will become less frequent and less intense the longer you go without smoking. Don't give up!" Figure 3 provides screenshots of the example strategies shown to the participants.

Figure 3. Mindfulness strategies.

Strategy content is personalized in various ways to the participant. First, it is tailored to whether the participant is in the prequit or postquit portion of the study. For example, a prequit strategy would be “You’re doing a great job preparing to quit smoking!”, whereas a postquit strategy would be “Quitting is a process and takes time. Each hour you go without a cigarette is a step toward your freedom from nicotine. You’re doing great!” Second, strategies in the postquit phase are based on whether a participant has experienced a smoking lapse. An example of a lapse strategy is “Draw your attention to any thoughts you may be having about smoking. Remind yourself that you can get right back on track if you slipped off.” Third, participants rate how much they like a given strategy on a 5-point scale. If they rate it as one star (the lowest rating), they will not see that strategy again.

The day is separated into six 2-hour blocks for the delivery of EMIs. The decision point for randomization (ie, to send an active strategy or not) is based on smoking status and negative affect, both of which are being continuously monitored every minute while the equipment is being worn. For high negative affect, the decision to randomize is made as soon as a high negative affect event is detected within a 2-hour block and the participant is available. For lapse (ie, the detection of smoking), the decision to randomize is also made as soon as smoking is detected within the 2-hour block and the participant is available. Within a 2-hour block, this process is limited to one randomization occasion for high negative affect and one randomization occasion for lapse. For low negative affect, the decision point to randomize is randomly chosen at the start of the block, and if available when that time arrives, randomization occurs. If the participant is not available, another time is randomly chosen within that time block, and when that time arrives, assuming the participant is available, randomization occurs. This pattern is repeated until the end of the block. The process for randomization for no lapse is identical to the process of low negative affect, as previously described. Within a 2-hour block, randomization is limited to one occasion for low negative affect and one occasion for no lapse. In summary, up to 4 randomizations can occur within a 2-hour block (high negative affect, lapse, low negative affect, and no lapse). Moments will be randomized to receive a strategy or not in a 1:1 manner, and factors to ensure this 1:1 randomization will be included in the algorithm (ie, inclusion of historical data of what has already been triggered that day). Figure 4 shows the process of randomization based on the detection of high negative affect (low negative affect, lapse, and no lapse processes are not included in the figure for simplicity purposes, but their procedures mimic what is shown for high negative affect).

Figure 4. Randomization process based on the detection of high negative affect (low negative affect, lapse, and no lapse are not represented here for simplicity purposes). R: randomization.



When considering low/high negative affect and lapse/no-lapse occasions, participants can receive up to 2 active strategies within a block (ie, they receive a mindfulness strategy or motivational message). Thus, participants can receive up to 12 active strategies per day. Other conditions are also considered for the delivery of the strategies. These include time since last EMA being at least 15 min, time since last EMI being at least 30 min, good quality data detected via sensors, no driving, phone battery level at least 10%, and no engagement in physical activity. Given the above conditions for the delivery of EMIs, we do not anticipate individuals receiving more than 6 per day, and they may even receive fewer than 6. For instance, if someone does not lapse, then no strategies are sent for that purpose. AutoSense will not send messages when it detects driving, so no messages are sent during those times.

When active strategies are sent to participants, they will receive a notification on the phone, allowing them to know that a strategy is available. They will have the option of accepting it, delaying it for 5 min, or canceling it altogether. When participants agree, they will have the option of receiving a new strategy if they do not like the first one that appears on the phone. Participants will then let the app know whether they completed the strategy, and if they indicate *yes*, they will be asked to rate how much they liked the strategy on a scale of 1 to 5 stars. If they select 1 star, then this strategy will not be shown again to the participant.

On-Demand Mindfulness Content

In addition to the strategies and surveys that will be sent to a participant's phone, participants will also have the opportunity to practice strategies on their own (ie, user-initiated). There is a mindfulness strategy button within the app that can be clicked at any time by the participant to receive a strategy. Although participants will be choosing to engage in a strategy as opposed to being sent one, the process will be similar to that described above (eg, rating the strategy). Participants will be informed at visit 1 that they can click on this button at any time. The phone also has a Mindfulness Frequently Asked Questions (FAQ) button that participants can click at any time to learn more about mindfulness. This feature contains 13 common questions about mindfulness, such as *What is mindfulness?* and *How does being aware of my thoughts relate to me quitting smoking?*

In-Person Counseling

During visits 1-4, participants will receive brief counseling (20-30 min) at the end of their sessions. Counseling will be consistent with the Treating Tobacco Dependence Guidelines [67] and will also incorporate a brief mindfulness component. At visit 1, participants will be provided with the National Cancer Institute's Clearing the Air Booklet [68] as well as instructions on how to use the nicotine patch. They will also be given a single-page handout on mindfulness (eg, definition of mindfulness and why we suggest using mindfulness to help quit smoking). In visits 1-3, participants will listen to a 10-minute audio recording of a mindfulness meditation. At visits 1 (prequit) and 3 (postquit), participants will listen to a recording on urge surfing; at visit 2 (quit day), an audio recording of guided breath meditation will be used. Following these meditations, the counselor will ask questions such as *What did you notice while listening to the recording?* and *How do you think what you just heard is related to quitting smoking?*

NRT

Participants will receive 6 weeks' worth of 14 mg or 21 mg nicotine patches throughout the duration of the study. At visit 1, participants will receive patches and instructions on how to use them. Participants will be instructed to begin wearing the patch at the beginning of the day of their visit 2 (quit day). If a participant smokes 10 or less cigarettes per day, they will be given 14 mg patches. If the participant smokes more than 10 cigarettes per day, they will be given 21 mg patches. At visit 5 (follow-up), participants will receive 2 weeks' worth of the dosage that they have been using for the last 28 days (totaling 6 weeks of patches) and will be given additional guidance on how to continue the patch regimen. At the end of the last visit, participants will also be given recommendations on how to obtain nicotine patches from community sources as well as additional quit smoking and counseling referrals, if needed.

Analyses

Feasibility Outcomes

Our measures of feasibility and associated benchmarks of success include the following: retention (≥75% through follow-up), adherence (eg, expect ≥70% of participants to wear the equipment the majority of the 14 days; of those who wore

the equipment the majority of the 14 days, ≥70% completion of EMAs; ≥60% of strategies completed), and a score of 68 or higher on the System Usability Scale. Acceptability will be primarily driven by scores on the Client Satisfaction Questionnaire (≥3), followed by responses to the mindfulness strategies.

Exploratory Outcomes: Sensor-Based Collection of Negative Affect, Self-Regulatory Capacity, and Smoking Status

Wearable sensors are configured to detect negative affect, self-regulatory capacity, and smoking status, to deliver and ultimately collect outcome data on relevant intervention content to the study phone. The experience of negative affect is detected through a machine learning model applied to continuous sensor-based measurements based on electrocardiogram (ECG) and respiration data [62]. Respiration data are measured via inductive plethysmography (RIP), which is the contraction of the chest and abdominal wall, as collected by the chest band [62]. ECGs are measured via 2 electrodes connected to a chest box unit. Probability of experiencing negative affect is derived from these measures, which will be used as our indicator of negative affect; additional detail can be found in the study by Hovsepian et al [62]. Self-regulatory capacity will be captured via heart rate variability, which is also captured by the ECG data.

Smoking episodes are detected via the *puffMarker* model, a machine learning algorithm that uses respiration data to detect deep inhalation and long exhalation and wrist movement patterns to detect hand-to-mouth gestures [63]. Inhalation and exhalation data are collected via RIP sensors, whereas specific wrist movements indicative of smoking are collected by wrist bands with a 3-axis accelerometer and a 3-axis gyroscope [63]. All of the data collected by the sensors are continuously measured and wirelessly streamed to the study phones and then sent to the cloud for analysis [63].

Tobacco Abstinence

Tobacco abstinence will be defined as biochemically confirmed 7-day point prevalence, which is the self-report of no smoking in the past 7 days combined with a CO reading of <6 ppm. Self-reports of smoking status will be collected via the timeline follow back at visits 2-5.

Analytic Plan

Descriptive statistics (eg, means and percentages) will be derived for feasibility and acceptability outcomes. Given that this is a feasibility study, sensor-driven analyses will be exploratory with the goal of providing preliminary results. The unit of analysis is the pre/postengagement data pairs comparing the average negative affect, self-regulatory capacity, and lapse counts within a prespecified time frame (eg, negative affect and self-regulatory capacity in the 30 minutes before and after randomization and lapse status in the time period between randomization of EMIs). These data will be analyzed using a generalized linear mixed model with proper adjustment for the within-subject correlation. The model can also include indicators for the category of mindfulness strategy. Each variable pair (negative affect, self-regulatory capacity, and smoking) will be analyzed separately in a pre/postengagement comparison to determine whether the mindfulness intervention creates any changes in these variables when compared with receiving no strategy at all. Examples of potential time-invariant covariates that will be included in the model are gender, age, education level, baseline trait mindfulness, and nicotine dependence. Time-varying covariates to be considered in the models include smoking status and use of the *on-demand* mindfulness content. Given that MRTs require unique considerations regarding data analysis (eg, participant availability and changes in the use of the intervention over time), we will incorporate the most recent recommendations in the literature when examining the data [69,70].

Results

Recruitment is complete, and data management is ongoing. This study was funded in February 2017 and received IRB approval in February 2017; data collection occurred from January 2019 to November 2020 (note that some of recruitment occurred during COVID-19). As of the submission of this manuscript, 43 participants consented to participate in the full study.

Discussion

This manuscript describes a study that aims to recruit individuals who are motivated to quit smoking (N=24), with the overall goal of testing whether a 2-week mindfulness-based MRT is feasible as a quit smoking treatment. All participants will receive brief mindfulness-based strategies in real time, NRT, and 4 brief smoking cessation counseling sessions. Participants will be asked to wear AutoSense equipment that gathers physiological data and to carry a study smartphone that will deliver EMAs and EMIs to them during the initial weeks of their quit attempt. Participants will attend 1 follow-up visit after treatment.

Limitations of this study, along with the next steps, should be noted. First, this study will recruit a small sample size consistent with feasibility studies [38,71], which will limit any conclusions that can be made. Second, this study requires participants to wear equipment that could be burdensome or complicated to navigate, which may impact compliance with the intervention. Third, the inclusion of in-person brief counseling and NRT limits our ability to determine the impact of the mobile health (mHealth)-only aspects of the intervention. Nonetheless, we thought it is best to provide basic evidence-based cessation treatment to participants (pharmacotherapy plus brief counseling), given the novelty of the mHealth intervention component. Future research may choose to deliver and evaluate a remote-based treatment (ie, mail-out NRT and conduct phone counseling) or to provide an mHealth-only treatment with the entire smoking cessation intervention delivered via a smartphone and sensors. On the basis of the findings of this study, the next steps should include a large-scale randomized clinical trial to compare this treatment with a usual care/control condition to ultimately determine treatment efficacy.

This study will provide initial data on whether brief mindfulness strategies, delivered in real time at key moments during a quit smoking attempt, are a useful quit smoking aid. This project is

highly innovative because (1) to date, no studies have examined these constructs via real-world, real-time data among smokers and (2) findings can directly inform treatment development to specify how mindfulness impacts underlying mechanisms, leading to the reduction of tobacco-related health disparities.

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Conflicts of Interest

None declared.

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Abbreviations

CO: carbon monoxide
ECG: electrocardiogram
EMA: ecological momentary assessment
EMI: ecological momentary intervention
mHealth: mobile health
MRT: microrandomized trial
NRT: nicotine replacement therapy
ppm: parts per million
RIP: inductive plethysmography
SES: socioeconomic status

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Protocol

The Building Educators' Skills in Adolescent Mental Health Training Program for Secondary School Educators: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: In Australia, secondary school educators are well positioned to recognize mental illness among students and provide support. However, many report that they lack the knowledge and confidence to do so, and few mental health training programs available for educators are evidence based. To address this gap, the Black Dog Institute (BDI) developed a web-based training program (Building Educators' Skills in Adolescent Mental Health [BEAM]) that aims to improve mental health knowledge, confidence, and helping behaviors among secondary school educators in leadership positions. A pilot study of the training program found it to be positively associated with increased confidence and helping behaviors among educators and reduced personal psychological distress. An adequately powered randomized controlled trial (RCT) is needed.

Objective: The primary objective of this cluster RCT is to evaluate the effectiveness of the BEAM program for improving educators' confidence in managing student mental health. The trial will also evaluate the effect of the BEAM program in increasing educators' frequency of providing help to students and improving their mental health knowledge and reducing educators' psychological distress and stigma toward students with mental health issues.

Methods: The target sample size is 234 educators from 47 secondary schools across New South Wales, Australia. Four waves of recruitment and enrollment into the trial are planned. Schools will participate in one wave only and will be randomized to the intervention or waitlist control conditions. Participants from the same school will be assigned to the same condition. Assessments will be conducted at baseline, posttest (10 weeks after baseline), and follow-up (22 weeks after baseline) using the BDI eHealth research platform. Intervention participants will receive access to the BEAM program for 10 weeks upon completion of baseline, and the control condition will receive access for 10 weeks upon completion of the follow-up assessment.

Results: Recruitment for this trial began on July 21, 2020, with the first baseline assessments occurring on August 17, 2020. To date, 295 participants from 71 schools have completed baseline. Due to the unexpected success of recruitment in the first 3 waves, the final fourth wave has been abandoned. Intervention participants are currently receiving the program, with follow-up due for completion in March 2021.

Conclusions: This is one of the first RCTs to examine the effectiveness of a web-based adolescent mental health training program for Australian secondary school educators in leadership positions. If found to be effective, this training program will offer a sustainable and scalable delivery method for upskilling educators in caring for students' mental health.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12620000876998; https://covid-19.cochrane.org/studies/crs-14669208

International Registered Report Identifier (IRRID): DERR1-10.2196/25870

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KEYWORDS

mental health training; schools; teachers; educators; mental health; student mental health; secondary school

Introduction

Background

Over half of all mental illnesses experienced by adults begin before the age of 18 years [1], yet many young people have difficulty recognizing the early signs and symptoms [2,3]. Unfortunately, many of these young people do not actively seek professional help (eg, from school counselors or psychologists) [4-6]. As secondary schooling is compulsory in Australia, educators are well positioned to identify changes in students' mental health, offer support, and facilitate access to treatment services [7-9]. However, many report that they lack the confidence and knowledge to recognize and respond to mental health issues among their students [7,10,11]. Educators also report that the increased responsibilities and expectations of caring for students' mental health increases their levels of work-related stress and psychological distress [12,13]. Thus, there is a clear need for mental health training to improve mental health outcomes for students and to reduce personal stress for educators.

Despite the recommendation by government bodies for greater training in adolescent mental health [14,15], there are very few evidence-based training programs available to educators about student mental health. Recent systematic reviews have identified 6 training programs, only 1 of which was assessed in the Australian context (adult and youth versions of Mental Health First Aid [MHFA]) [16,17]. Of the remaining 5 programs, the Mental Health High School Curriculum Guide teacher training program [18,19], the Go-to Educator Training [20], and The Guide Pre-Service Professional Development Program [21] were all assessed in Canada; the Teachers As Accompagnateurs (TAPS) [22] in Haiti; and the African Guide: Malawi Version [23] in Malawi. All programs provided teachers with information about the common adolescent mental health issues, along with associated signs and symptoms, and directed teachers to additional resources and services. Only the MHFA and TAPS programs provided additional information for teachers on how to identify and support students experiencing a mental health crisis. Of the 6 identified programs, only 1 was assessed using a randomized controlled trial (RCT) methodology, with the remaining 5 employing noncontrolled pre-post designs.

Although all 6 programs were shown to be effective for improving mental health knowledge, none have yet been shown to be effective in increasing helping behaviors, for example, recommending or referring a student to seek professional help, or in reducing the distress experienced by educators [24,25]. In addition, these programs are typically delivered through face-to-face, didactic-style workshops, requiring educators to take leave to attend [24,25]. This may be a barrier to large-scale uptake and increase the financial burden for schools, as they are required to find replacement teachers. With the advancement of technology and effective digitally delivered mental health training programs being developed for workplace settings (eg, refer to the study by Gayed et al [26]), there is an opportunity to develop mental health training for educators that is delivered in new ways.

To fill this gap, the Black Dog Institute (BDI) developed the Building Educators' Skills in Adolescent Mental Health (BEAM) program. BEAM is a web-based training program on adolescent mental health for secondary school educators in leadership positions, such as year advisors, heads of well-being, and principals. To accurately identify educators' training needs, the BEAM program was initially developed in collaboration with an advisory group of teachers in general teaching and leadership roles. The group consisted of 12 school teachers from various secondary schools located in New South Wales (NSW), Australia. BEAM was originally designed for year advisors, given their role in maintaining student engagement and the well-being of an entire cohort of students. They also often act as case managers, linking students with services and resources when needed, and are usually the first point of contact for parents and teachers. However, there is no formal training for this role, and it is performed in addition to their regular teaching duties. Research on workplace mental health has indicated that training programs for managers can improve their mental health knowledge, thereby improving their confidence and increasing their helping behaviors toward their staff's mental health needs [26-28]. Furthermore, as nonstigmatizing attitudes have been shown to be associated with intentional or actual contact with individuals with known mental illnesses [28,29], improving stigma may also help increase the assistance provided to students. Therefore, the BEAM program aims to model this workplace mental health research [26-28] while also reducing educators' stigmatizing attitudes toward students with mental illness. BEAM consists of 5 self-paced and self-directed modules on adolescent mental health (Multimedia Appendix 1), including quizzes, blog style story sharing, and case studies. The program also includes informal, nonmandatory, peer coaching activities that encourage participants to meet with a colleague to discuss the program and apply the content to their own school context. By blending web-based content with face-to-face peer learning,

the program aims to foster professional relationships, consolidate learning, and facilitate new problem-solving skills [30]. This flexible model allows users to complete the program at a time that is convenient for both the educator and their school without the educator having to take leave to attend face-to-face workshops.

A recent pilot study examined the acceptability of the BEAM program among secondary school year advisors (N=71) from NSW, Australia. After using the program for 6 weeks, the year advisors reported significantly higher levels of self-reported confidence in their ability to care for students' mental health and lower levels of personal psychological distress. Year advisors also reported an increased frequency of helping behaviors at the 19-week follow-up. However, many of the year advisors did not complete the entire program (59/70, 84%) reporting that the 6-week duration was insufficient, and barriers such as forgetfulness hampered their completion. In preparation for this trial, several modifications were made to the program to increase engagement and completion: program access was extended to 10 weeks, SMS reminders in addition to email reminders were embedded, sequential module completion was removed so that participants can complete the modules in any order, a *module suggestion* function was embedded that encourages the participant to complete modules based on their interest, and the program was optimized for completion on both mobile and desktop devices to increase accessibility. The eligibility criteria for BEAM have also been extended to encompass other leadership roles within the school, including principals, heads of well-being, and directors of pastoral care, among others. This decision was made because these staff members also have responsibilities regarding student well-being in addition to their regular teaching duties and are well placed to influence schools' policies and possibly enact change. The program is now ready to be evaluated for its effectiveness using an RCT.

Objectives

The primary objective of this trial is to evaluate the effectiveness of the BEAM program in improving secondary school educators' confidence in recognizing and responding to their students' mental health needs. The secondary objective is to assess BEAM's effectiveness in increasing the frequency of help provided to students, improving educators' mental health knowledge, reducing educators' stigma toward others with mental illnesses, and reducing their own psychological distress.

Hypotheses

The primary hypothesis is that educators who are allocated to receive the BEAM program will report significantly higher levels of confidence at posttest (primary endpoint) when compared with the waitlist control condition and that these effects will be sustained at follow-up. It is also hypothesized that educators who receive the BEAM program will report greater improvements in mental health knowledge, stigma, and psychological distress at posttest and a greater frequency of helping behaviors at follow-up, when compared with those in the control condition.

Methods

Design

This study is a cluster randomized controlled effectiveness trial with 2 parallel conditions (the BEAM program and waitlist control), with measurements taken at baseline, posttest (10 weeks from baseline completion), and follow-up (22 weeks from baseline completion). This study protocol was approved by the primary ethics body of the University of New South Wales (UNSW) Human Research Ethics Committee (HREC; HC200257). Approval was also sought and obtained from the NSW Department of Education State Education Research Applications Process (SERAP2020222) to conduct research within government schools and from the Catholic Schools Office Dioceses of Maitland-Newcastle, Canberra-Goulburn (schools located in the Goulburn area only), and Wollongong to conduct research with schools located within their dioceses.

This research project is also guided by a trial management committee consisting of experts in research and trial design and service and program implementation to oversee and provide guidance on the study procedures. This committee meets bimonthly or more frequently on an as-needed basis.

Participants

Inclusion Criteria

To be eligible to participate, secondary school educators must be (1) employed in a school leadership position that includes responsibility for student well-being (eg, year advisors, directors or heads of student well-being, principals, directors of pastoral care, student coordinators, and heads of year); (2) currently working in this role at a government, Catholic, or independent secondary school in NSW, Australia, for the duration of the study; and (3) obtain their principal's consent for their involvement.

Exclusion Criteria

Secondary school educators who participated in the pilot study are not eligible to participate in this trial.

Sample Size

The target sample size for this trial is 234 participants from at least 47 schools. This calculation is conservatively based on the participation of an average of 5 educators per school and an intraclass correlation of 0.07, which yields a design effect of 1.28. To detect a standardized effect size of 0.50, (a minimum of a moderate effect size is required to warrant future value and benefit of the program) with 80% power and α=.05 (2-tailed), an individually randomized trial would require 64 participants per arm. This number is inflated by the design effect to 82 to allow for clustering, with the recruitment increased to conservatively allow for attrition of up to 30%. This yields a minimum of 117 participants per arm.

Randomization and Blinding

Cluster randomization at the school level is used to avoid potential contamination and bias effects from other participants, reduce administrative tasks for schools, and enable implementation of the peer-to-peer component of the program.

As such, all participants from the same school will be allocated to the same condition and complete the trial at the same time using randomly permuted block randomization with block sizes of 2 and 4. Schools will be assigned to either the intervention or control arm using a 1:1 allocation, stratified by school size (<400 or >400 students) and index of community socioeducational advantage (ICSEA) level (<1000 or >1000) as per a computer-generated randomization schedule. Randomization is conducted by a statistician not involved in the day-to-day running of the trial to avoid influence or bias. The research team will be aware of the allocation once registration is scheduled to begin because they are responsible for providing the link to participants for the intervention or control program study website. Participants will be unaware of which group they are allocated to during registration and baseline. Upon completion of baseline, they will be informed, via email, of their allocation. This is because the intervention participants will receive immediate instructions and access to the program, and the waitlist control participants will be asked to wait for their next survey.

Recruitment

Multimedia Appendix 2 outlines the recruitment, randomization, and procedure for this trial.

A passive approach to recruitment is being undertaken using study advertisements. The advertisements are being placed on the BDI's website and social media channels (Facebook, LinkedIn, and Twitter), within BDI newsletters, and circulated to BDI mailing lists and contacts. The study is also being advertised in the NSW Health School-Link e-newsletters (an NSW Health service that connects schools with local mental health services), Teacher Magazine, and Catholic Diocese bulletins. After viewing the study advertisements, interested educators are directed to a web-based expression of interest form on the BDI website, which collects their name, school, suburb, email, and role at their school. Once registered, prospective participants are encouraged to share the study information with their colleagues to increase cluster sizes and encourage peer-to-peer interaction. To promote a representative sample from metropolitan, regional, and rural locations, participation will be open to all government, Catholic, and independent schools within the Australian state of NSW for which we have ethical approval.

Consent

Principal Consent

After expressing interest, the educators are emailed the study information. Interested participants consult their principal to obtain a signed letter of support. The school and its educators are randomized after the letter of support is received by the research team. Only 1 signed letter of support is required per school.

Educator Consent

Educator consent is obtained online. Prospective participants provide consent by confirming the declaration statements in the web-based participant information sheet and consent form (PISCF). Participants can download the PISCF before providing consent, and they are emailed a copy for their records.

Withdrawal of Consent

Participants can withdraw consent at any time without providing a reason by contacting the research team, replying to any email communication with the word *withdraw*, or completing the withdrawal form located within the PISCF. When a participant withdraws, all study data are retained, but no further data are collected, and all study communication ceases.

Procedure

Registration

This trial will include 4 waves of registration and enrollment. A predetermined cut-off date indicates which wave a school participates in, as determined by the date on which the letter of support is received. Using waves ensures that data collection does not occur during summer school holidays, allows flexibility for when schools enroll in the trial based on their schedule, and ensures that participants from the same school commence the trial concurrently. Once all registered participants from a single school commence the baseline survey, no other prospective colleagues from that school can register. This prevents the influence that knowledge of group allocation might have on future participant enrollment. To avoid disappointment, educators are asked to tell their colleagues about the study at the time of recruitment.

Participants are sent an email directing them to the study registration website 1 week before the scheduled baseline start date. Here, they are asked to confirm their eligibility, register their personal details (including their name, school, and email), provide consent, and create a study account. They have the option to enter their mobile phone number to receive SMS notifications and reminders. Once completed, they await further instructions and access to the baseline survey.

Baseline, Posttest, and Follow-Up Assessments

On the day each wave is due to begin, participants receive an email (and optional SMS) inviting them to complete the baseline survey. The survey is accessible for 7 days, and participants who do not complete it are automatically withdrawn. This process is repeated for the 10-week and 22-week assessments. All participants receive 2 email reminders (and 2 optional SMS reminders) for the survey completions.

Intervention Condition

The BEAM program is a web-based training program accessible on any internet-enabled device. Each of the 5 modules consists of information, web-based interactive activities, and downloadable resources related to adolescent mental health. In this trial, participants can complete the 5 program modules in any order; however, an initial module is suggested to participants based on their response to the *module recommendation* question in the baseline survey. This question presents participants with a list of 10 topics (such as *signs and symptoms* and *about my role*) that are linked to the learning objectives of each module. Participants are then asked to rate the 3 they are most interested in learning about from 1 (*most interested*) to 3 (*least interested*). The program then recommends that they begin with the module

corresponding to their first choice. Each module includes an optional peer coaching activity that asks participants to meet with a colleague from their school to discuss focus questions, practice, and apply program learnings. Participants then submit their responses to the focus questions through the program. The research team then send standardized feedback via email within 3 business days. Participants who do not have another colleague from their school taking part in the trial can either complete the peer coaching themselves, talk to another colleague who is not taking part, or skip the activity, as it is not mandatory. No other program activities are reviewed by the research team. All participants receive access to the program at no cost for 10 weeks, and it is estimated that the full program takes approximately 6.5 hours to complete. Participants can complete the program at their own pace; however, they are recommended to undertake 1 module per fortnight. Given the current COVID-19–related school closures and physical distancing guidelines, participants are encouraged to complete the peer coaching activities via teleconference or phone. Participants will receive fortnightly email reminders to use BEAM and optional SMS reminders. All program use data are collected by the BDI web-based eHealth research platform hosted on the UNSW servers.

Control Condition

This study uses a waitlist control condition. Participants in the control condition will receive access to the intervention at no cost immediately after they complete the follow-up survey (22 weeks post baseline). If they do not complete the follow-up survey, they will receive access immediately after the survey has closed. They will receive access to the full program whether they have not completed the survey or not.

Reimbursements

Participants in both conditions will receive an Aus $15 (US $11.59) e-gift voucher to thank them for their time and completion of the posttest survey. They will also receive an Aus $15 (US $11.59) e-gift voucher after completing the follow-up survey. All e-gift cards will be emailed within 5 working days of a participant completing the survey and will be issued through GiftPay.

Outcome Measures

Table 1 shows the administration schedule of measures.

Table 1. Schedule of outcome measures.

Measure	Data collection timepoint		
	Baseline	Posttest (10 weeks)	Follow-up (22 weeks)
Demographics and background	✓[a]	—[b]	—
Experience of mental health	✓	—	—
Self-care	✓	✓	✓
Experience in mental health training	✓	—	—
School factors	✓	✓	✓
Impact of COVID-19 on helping behaviors	✓	✓	✓
Perceived mental health knowledge and awareness	✓	✓	✓
Mental health knowledge	✓	✓	✓
Stigma	✓	✓	✓
Confidence	✓	✓	✓
Helping behaviors	✓	✓	✓
Psychological distress	✓	✓	✓
Module recommendation question	✓	—	—
Barriers to use	—	✓	—
Program satisfaction	—	✓	—
Process evaluation	—	✓	—
Program impact on future behaviors	—	—	✓

[a]Indicates the timepoint measure is administered.

[b]Indicates the measure is not administered at that timepoint.

Primary Outcome Measure

The primary outcome for this trial is educators' confidence in recognizing and responding to students' mental health needs. This is measured using an adapted version of the confidence to recognize, refer, and support subscale from the study by Sebbens et al [31]. Participants are asked to rate how confident they feel about a set of 15 scenarios (eg, *recognizing a student with mental health problems*) using a 5-point Likert scale ranging from 1 (*not at all confident*) to 5 (*very confident*). Mean total scores are calculated to represent participants' self-reported confidence in managing their students' mental health needs.

Total scores can range from 15 to 75, with higher scores indicating greater levels of confidence. Scores will be compared over time and between the intervention and control arms at each time point.

Secondary Outcome Measures

Helping Behaviors for Mental Health

A modified version of the Help Provided to Students Questionnaire by Jorm et al [16] is used to assess the frequency of helping behaviors for mental health among educators. Participants indicate how often they have engaged in 13 helping behaviors (eg, *spent time calming a student down*) during the past 2 months. This is answered using a 4-point scale (*never*, *once*, *occasionally*, *frequently*). Items are then summed to create a total score (range: 15 to 60), with higher scores indicating a greater frequency of helping behaviors.

Perceived Mental Health Knowledge and Awareness

This is assessed using the Perceived Knowledge and the Perceived Awareness subscales from the Mental Health Literacy and Capacity Survey for Educators [32]. Participants are asked to rate their level of perceived knowledge on a set of 4 statements (eg, *how would you rate your knowledge of the signs and symptoms of student mental health issues*) from 0 (*not at all*) to 4 (*extremely*). Items are then summed to create a total score (range: 0-16), with higher scores indicating greater knowledge of mental health.

For the awareness subscale, participants are asked to rate their level of perceived awareness on a set of 5 statements (eg, *how would you rate your awareness of the risk factors and causes of student mental health issues*) from 0 (*not at all*) to 4 (*extremely*). Items are then summed to create a total score (range: 0-20), with higher scores indicating greater awareness of mental health issues.

Mental Health Knowledge

This consists of 2 constructs: mental health literacy and the recognition of common mental illnesses. These 2 constructs are measured using an adapted version of the 12-item Mental Health Knowledge Schedule (MAKS; [33]) and 2 vignettes adapted from the study by Jorm and Wright [34]. To measure mental health literacy, participants are asked to rate how much they agree with the first 6 items on the MAKS (eg, *Most students with mental health problems want to complete their schooling*) using a Likert scale ranging from 1 (*strongly disagree*) to 5 (*strongly agree*). Items are then summed to create a total score (range: 6-30), with higher scores indicating higher mental health literacy. Recognition of common mental illnesses is assessed using the remaining 6 items from the adapted MAKS (items 7-12), where participants are asked to rate whether they believe the conditions of depression, stress, grief, anxiety, self-harm, and substance misuse are mental illnesses using a Likert scale ranging from 1 (*strongly disagree*) to 5 (*strongly agree*). Participants are also asked to read 2 vignettes adapted from the study by Jorm and Wright [34]. These vignettes describe 2 adolescents with depression or anxiety, and the participants are asked to indicate which mental illness they believe the scenario depicts (free response).

Stigma

A modified version of the Personal Stigma subscale from the Depression Stigma Scale from Griffiths et al [35] is used to measure stigma toward mental health illnesses. Participants are asked to rate how much they agree with 9 statements (eg, *students with a mental illness could snap out of it if they wanted*) using a Likert scale ranging from 1 (*strongly disagree*) to 5 (*strongly agree*). Items are then summed to create a total score (range: 9-45), with higher scores indicating greater levels of stigma.

Psychological Distress

The Distress Questionnaire-5 (DQ-5) [36] is used to assess the personal psychological distress of educators. Participants are asked to rate how frequently, in the past 6 weeks, they have experienced 5 symptoms (eg, *Thinking back over the past 6 weeks, how often have you felt hopeless*). Answers are given using a 5-point scale ranging from 1 (*never*) to 5 (*always*). Items are then summed to create a total score (range: 5-25), with higher scores indicating greater levels of psychological distress. The DQ-5 has high internal consistency and convergent validity [36,37].

Supplementary Measures

Demographics and Background Factors

Participants are asked to provide their name, age, gender identity, whether they identify as Aboriginal or Torres Strait Islander, current role at their school, duration of employment at their current school (years), overall experience as an educator (years), and experience in their current role (years) at baseline.

Experience of Mental Illness

Participants are asked to indicate whether they have had a personal, family, or close friend experience a mental illness (answered *yes* or *no* or *prefer not to answer*).

Participants are also asked to rate how frequently they engage in self-care. This is to be answered on a 6-point scale (*never*, *less than once a month*, *once a month*, *a few times a month*, *weekly*, or *daily*).

Experience in Mental Health Training

Participants are asked to rate how important they believe mental health training is for educators (answered 0, *not at all important* to 4, *extremely important*), how they rate their level of mental health training (answered 0 *none to date* to 3 *extensive training*), the mental health training programs they have completed (free response), and how confident they are that an online program can meet their training needs (answered 0 *not at all confident* to 4 *extremely confident*).

School Factors

Participants are asked to indicate their school location (*metropolitan*, *regional*, or *rural*), school type (*government*, *Catholic*, or *independent*), and whether their school is same sex (answered *yes* or *no*). Participants are also asked to indicate whether their school has a student well-being policy (answered *yes* or *no*) and staffing roles to support students' mental health (answered *yes* or *no*). Participants are also asked to rate the degree to which mental health is their school's priority

(answered 0 *not a priority* to 4 *high priority*) and how responsible they feel for their students' mental health and well-being (answered 0 *not at all responsible* to 4 *completely responsible*). Participants are also asked to indicate, on average, the hours per week they spend supporting students' mental health needs and how supported they feel by their colleagues, supervisor or employer, workplace, friends, and family (answered 0 *not at all* to 4 *extremely*).

Impact of COVID-19 on Helping Behaviors

In response to COVID-19, participants in this trial are asked questions regarding helping behaviors that may have changed due to the pandemic. The first 3 questions, "Have you reached out to students in a way that is different than you have done so in the past because of COVID-19? (eg, connecting via technology)?", "Have you implemented a service, program, or educational information session about mental health?", and "Are there any other ways you have responded to your students' mental health that isn't covered here?" will require a *yes* or *no* response. If a participant answered *yes* to the latter 2 questions, they were asked to specify (free response). Participants are also asked how often then have contacted their students about mental health using technology (email or school e-learning platform); this is answered using a 4-point ordinal scale from 1 (*never*) to 4 (*frequently*).

Measures for Intervention Participants Only

The following measures will be obtained only from participants assigned to BEAM and will be used in subsequent research into factors that may moderate or mediate outcomes.

Program Use

Program use will be measured by the number of completed lessons (maximum of 27), collected automatically by the eHealth research platform.

Barriers to Use

Program barriers will be identified using a 13-item list at posttest.

Participants will be asked to report if they experienced any of the listed barriers throughout the trial (eg, *Forgot about it* and *Didn't have enough time*); this is answered as *yes* or *no*. If a participant answers *yes* to the 13th item *Other not listed above (Please specify)*, a mandatory free response textbox will appear for the participant to provide more detail.

Program Satisfaction

Participants are asked to rate the extent to which they agreed with a set of 14 statements about the BEAM program (such as *I enjoyed using BEAM* and *the content was easy to understand*). This is answered using a 5-point Likert scale ranging from 1 (*strongly disagree*) to 5 (*strongly agree*).

Process Evaluation

Participants are asked whether they completed the peer coaching activities with a colleague (answered *yes* or *no*), and if yes, how frequently they met (*more than once a week*, *about once a week*, *about once a fortnight*, and *about once a month*) and whether they found these activities to be valuable (answered *yes*, *no*, or *not appropriate*). Participants are also asked "What could we do to improve the program," "Is there any content or topics you would have liked to have been covered in the training?", and "Is there anything else you would like to say about the program and its value for you?" (all answered with free responses). Finally, participants are asked what device they completed the program on (eg, laptop, tablet, or mobile).

Program Impact on Future Behaviors

Participants are asked to indicate whether the program content or resources were shared with other school staff and if any well-being programs had been implemented during the trial period (answered *yes* or *no*). If they answer *yes*, participants are asked to provide more detail (free response).

Statistical Methods

The primary analysis will use a mixed model repeated measures analysis of variance (MMRM), accounting for repeated assessments within individuals and a random effect to account for clustering within schools. Models will include the factors time, condition (intervention vs control), and their interaction, with the critical test of effectiveness being planned contrasts of this interaction from baseline to postintervention (the trial primary endpoint) and follow-up (secondary endpoint). An unconstrained variance-covariance matrix will be used to accommodate within-participant effects. The method of Kenward and Roger [38] will be used to estimate the degrees of freedom for tests of all effects. Any baseline variables identified as substantially imbalanced between groups will be added to the models on an exploratory basis to confirm the robustness of the findings to this imbalance. Where distributional assumptions cannot be satisfied, bootstrapping methods or generalized mixed models (eg, binary MMRM) may be used to confirm the robustness of the findings. MMRM constitutes an intention-to-treat analysis, as it includes all available data under the missing-at-random assumption. Between-group effect sizes will be estimated using the estimated model means and variances.

Secondary and additional outcome analyses will involve contrasts comparing changes from baseline to follow-up analyses of secondary outcomes (mental health knowledge, stigma, helping behaviors, and psychological distress) from baseline to other occasions of measurement, using an MMRM approach, as described above. If the intervention is found to be effective, exploratory analyses will examine evidence for moderation effects, that is, whether the intervention was more effective for certain subgroups of the sample. This may include teacher attributes such as gender or age and school characteristics such as ICSEA status.

Results

Approval was obtained from the primary ethics body (UNSW HREC) on April 21, 2020, SERAP on July 21, 2020, Maitland-Newcastle Catholic Diocese on May 27, 2020, Canberra-Goulburn Catholic Diocese on June 12, 2020, and Wollongong Catholic Diocese on August 4, 2020. Recruitment of educators started on July 21, 2020, and the baseline for waves 1, 2, and 3 are complete. To date, 465 educators have expressed interest in participating in the trial. In total, 308 educators have

registered and 295 have completed baseline, representing 71 schools. Due to the unexpected success of recruitment in the first 3 waves, the decision has been made to not go ahead with the final fourth wave. Intervention participants are currently receiving the program with follow-up due for completion in March 2021. It is planned that the results will be presented at both national and international conferences and submitted to peer-reviewed journals. The results will also be disseminated to stakeholders through reports and presentations and on the BDI website.

Discussion

Principal Findings

This protocol describes the RCT of the BEAM program, a study that aims to evaluate the effectiveness of a new web-based mental health training program for secondary school educators in leadership positions. Through the provision of mental health information and interactive activities, the BEAM program aims to improve educators' knowledge of adolescent mental health. It is anticipated that their confidence in managing their students' needs and the frequency of help provided will thereby increase, whereas their stigma toward mental ill-health and their own levels of psychological distress will reduce.

There remains a significant lack of available evidence-based mental health training programs for educators [24,25] and few high-quality studies that have evaluated adolescent mental health education for educators. Of those identified in the study by Anderson et al [24], only 2 studies were conducted as RCTs, whereas the others used a pre-post design with no comparator. Furthermore, only 1 study identified in the study by Anderson et al [24] was conducted in Australia [16], which significantly limits the quality of training options for educators containing information relevant to their education system. It is recommended that educators are provided with professional development opportunities regarding adolescent mental health [14,15]; however, there are few good-quality and relevant programs available. The BEAM program may help fill this training gap if shown to be effective, providing more education options for Australian secondary school educators that have been formally evaluated. To our knowledge, this is the first RCT assessing a web-based training program for educators, which also measures changes in helping behaviors and psychological distress. This is important, given the ongoing impact of COVID-19 on education delivery and school closures, which has likely added to both student and teacher stress. Physical distancing guidelines have caused the cessation of most face-to-face training, meaning the options for educators are now further limited and other methods, such as web-based delivery, are ever more important if they are effective.

If the effectiveness of the BEAM program is demonstrated through this trial, there are significant implications for how mental health training can be delivered to educators. For example, traditional educator training is typically delivered through face-to-face didactic-style workshops that require participants to take leave and have their classroom duties covered by another staff member [24]. By delivering the training online, educators can access the standardized material in a flexible and personalized manner anywhere there is an internet connection. Web-based delivery potentially lowers organization and administration costs when compared with attending face-to-face training, including the financial cost of replacing staff to cover classroom duties or paying for extensive travel for training. Finally, by delivering the training online, educators can easily revise the relevant material at any time by simply logging back into the program. The drawbacks to web-based program delivery are, however, acknowledged, in particular, the full completion of the training and engagement with the content and possible ambiguity for workplaces to determine when it is reasonable for their staff to use work time to complete training. Therefore, it is worthwhile to explore methods to ensure completion and engagement with the content, such as professional accreditation with the NSW Education Standards Authority.

Limitations and Strengths

There are limitations to this trial that are acknowledged, including the reliance on self-report questionnaires, which may be susceptible to biases. Self-report outcomes, such as confidence, may not match actual educator behavior; however, we will use validated measures where possible and assess teacher reports of actual helping behavior.

Another limitation is that the trial is being conducted among educators who self-selected to participate from within NSW only. The results may not be generalizable to interstate educators or educators who chose not to participate. Although Australia has a national education curriculum, schools are governed by each of the States' and Territories' Department of Education, and Catholic schools are governed by the Diocese to which they belong. Each has their own set of frameworks, policies, and rules that guide staffing. For example, there are structural differences between the states of South Australia (SA) and NSW, such that secondary school begins in year 8 in SA and year 7 in NSW. It may also be the case that participating educators are employed at better-resourced schools and have the time to take part. Furthermore, participation is limited to educators from schools for which we have approval from their governing ethical body and could obtain support from their school principal. Not all Catholic Dioceses in NSW granted approval to conduct this research, and gaining principal support might not have been possible for all interested educators.

A further limitation is the use of waitlist control and trial length. The total amount of time a control participant is required to wait without any access to the intervention is 22 weeks, which may affect attrition. We have conservatively estimated a 30% attrition in our target sample size, and a monetary reimbursement will be used to motivate completion of the posttest and follow-up surveys. The waitlist control also only enables the assessment of whether the intervention is more effective than the passage of time. Future follow-up studies to compare the intervention with active controls are needed once effectiveness relative to waitlist control is established.

Despite these limitations, this trial has several strengths, including the RCT design to examine the effectiveness of BEAM and the clustering and randomization at the school level to reduce the risk of bias and contamination. Once a school begins

in the trial, no other educators from that school can enroll, ensuring that participants are not influenced by the participation of other staff members from their school. The standardized delivery of the intervention helps maximize the fidelity of the training being delivered to educators, ensuring that all participants receive the same standardized intervention. Other strengths include the suite of measures included to examine a range of outcomes; the long-term follow-up period; targeted recruiting approach to include educators from metropolitan, regional, and rural areas; exploration of possible moderators; and stratification of school variables to account for factors hypothesized to influence the results. If shown to be effective, the assessment of BEAM through an RCT will provide a novel method for delivering mental health training to secondary school educators.

Acknowledgments

BP and CC conceived the study and the trial design. BP prepared the protocol, and both BP and CC initiated and coordinated the trial. AM contributed to the randomization, and PB and AM contributed to the statistical analyses. All authors contributed to the refinement of the protocol, and all authors read and approved the final manuscript. This project is funded by the Balnaves Foundation. PB is supported by National Health and Medical Research Council Fellowship 1159707.

Conflicts of Interest

BO is a section editor for JMIR Mental Health. No other authors have any conflicts of interest to declare.

Multimedia Appendix 1
Overview of the Building Educators' Skills in Adolescent Mental Health Training program.
[PDF File (Adobe PDF File), 604 KB - resprot_v10i2e25870_app1.pdf]

Multimedia Appendix 2
CONSORT (Consolidated Standards of Reporting Trials) flow diagram that will be used to outline participation through the Building Educators' Skills in Adolescent Mental Health Training program for secondary school educators. NSW: New South Wales.
[DOCX File , 58 KB - resprot_v10i2e25870_app2.docx]

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Abbreviations

BDI: Black Dog Institute
BEAM: Building Educators' Skills in Adolescent Mental Health
DQ-5: Distress Questionnaire-5
HREC: Human Research Ethics Committee
ICSEA: index of community socioeducational advantage
MAKS: Mental Health Knowledge Schedule
MHFA: Mental Health First Aid
MMRM: mixed model repeated measures analysis of variance
NSW: New South Wales
PISCF: participant information sheet and consent form
RCT: randomized controlled trial
SA: South Australia
SERAP: State Education Research Applications Process
TAPS: Teachers As Accompagnateurs
UNSW: University of New South Wales

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Protocol

Comparison of Endoscopy First and Laparoscopic Cholecystectomy First Strategies for Patients With Gallstone Disease and Intermediate Risk of Choledocholithiasis: Protocol for a Clinical Randomized Controlled Trial

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Abstract

Background: The optimal approach for patients with gallbladder stones and intermediate risk of choledocholithiasis remains undetermined. The use of endoscopic retrograde cholangiopancreatography for diagnosis should be minimized as it carries considerable risk of postprocedural complications, and nowadays, less invasive and safer techniques are available.

Objective: This study compares the two management strategies of endoscopic ultrasound before laparoscopic cholecystectomy and intraoperative cholangiography for patients with symptomatic cholecystolithiasis and intermediate risk of choledocholithiasis.

Methods: This is a randomized, active-controlled, single-center clinical trial enrolling adult patients undergoing laparoscopic cholecystectomy for symptomatic gallbladder stones with intermediate risk of choledocholithiasis. The risk of choledocholithiasis is calculated using an original prognostic score (the Vilnius University Hospital Index). This index in a retrospective evaluation showed better prognostic performance than the score proposed by the American Society for Gastrointestinal Endoscopy in 2010. A total of 106 participants will be included and randomized into two groups. Evaluation of bile ducts using endoscopic ultrasound and endoscopic retrograde cholangiography on demand will be performed before laparoscopic cholecystectomy for one arm (“endoscopy first”). Intraoperative cholangiography during laparoscopic cholecystectomy and postoperative endoscopic retrograde cholangiopancreatography on demand will be performed in another arm (“cholecystectomy first”). Postoperative follow-up is 6 months. The primary endpoint is the length of hospital stay. The secondary endpoints are accuracy of the different management strategies, adverse events of the interventions, duct clearance and technical success of the interventions (intraoperative cholangiography, endoscopic ultrasound, and endoscopic retrograde cholangiography), and cost of treatment.

Results: The trial protocol was approved by the Vilnius Regional Biomedical Research Ethics Committee in December 2017. Enrollment of patients was started in January 2018. As of June 2020, 66 patients have been enrolled.

Conclusions: This trial is planned to determine the superior strategy for patients with intermediate risk of common bile duct stones and to define a simple and safe algorithm for managing choledocholithiasis.

Trial Registration: ClinicalTrials.gov NCT03658863; https://clinicaltrials.gov/ct2/show/NCT03658863.

International Registered Report Identifier (IRRID): DERR1-10.2196/18837

(JMIR Res Protoc 2021;10(2):e18837) doi:10.2196/18837

KEYWORDS

choledocholithiasis; endoscopic ultrasound; intraoperative cholangiography; common bile duct stone; endoscopic retrograde cholangiopancreatography; laparoscopic cholecystectomy

Introduction

Gallbladder stones can be silent or symptomatic. This statement is also valid when speaking about choledocholithiasis, which involves stones situated in the common bile duct (CBD). About 10% to 18% of people undergoing cholecystectomy for gallstones have concomitant CBD stones [1]. Untreated choledocholithiasis can lead to acute biliary pancreatitis, acute ascending cholangitis, and secondary sclerosing cholangitis; thus, it is essential to diagnose and treat it on time. Endoscopic retrograde cholangiopancreatography (ERCP) became a prominent diagnostic method for CBD stones since its introduction to clinical practice in the 1970s [2]. Later on, it was agreed that use of ERCP for diagnostic reasons should be minimized and that it should not be used for first-line diagnostics as it carries a considerable risk (5% to 10%) of postprocedural complications [3]. It has been noticed that adverse events occur more often in patients with low risk of choledocholithiasis [4]. The possibility to avoid using ERCP for diagnostic purposes came with the introduction of new less invasive diagnostic procedures, such as magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), and intraoperative cholangiography (IOC) during cholecystectomy. Therefore, in the 2000s, a discussion about more careful patient selection for ERCP began, as it should be considered only in those with high probability of demand for therapeutic interventions (ie, stone removal), and patients with intermediate risk for choledocholithiasis should undergo additional investigation.

The most frequently used system to evaluate the risk of choledocholithiasis was proposed in 2010 by the American Society for Gastrointestinal Endoscopy (ASGE) [5]. It already stratifies the probability of CBD stones into low, intermediate, and high risk groups, and it suggests noninvasive investigations for the intermediate risk group, although its predictive value is not completely satisfying [6-10]. These results encourage the development of more accurate prognostic systems.

At the Center of Abdominal Surgery of Vilnius University Hospital Santaros Klinikos, an original prognostic index (Vilnius University Hospital Index [VUHI]) is being used for the prediction of choledocholithiasis risk before laparoscopic cholecystectomy (LC). Recently, we evaluated its accuracy and determined new threshold values for low, intermediate, and high risk groups [11]. The intermediate risk group (risk for choledocholithiasis of 25%-75%) would benefit from additional examination before ERCP. EUS and IOC are less invasive procedures with high accuracy for identifying CBD stones. These procedures will be applied for patients with intermediate risk of CBD stones and will help to decide if ERCP is indicated.

We aim to compare EUS as the first diagnostic biliary intervention to LC with IOC in patients with intermediate risk of choledocholithiasis in order to evaluate the accuracy, technical success, and safety of these two management strategies.

The hypothesis is that LC with IOC (“cholecystectomy first” strategy) will decrease both the length of hospital stay and morbidity by lessening the number of endoscopic investigations (EUS and ERCP) and thus the number of possible complications of ERCP, as well as decreasing the complications related to delayed cholecystectomy.

Methods

Recruitment

This study is a single-center, randomized, active-controlled trial comparing EUS and IOC for finding CBD stones in patients with intermediate risk of choledocholithiasis. Participants will be enrolled and the trial will be carried out at Vilnius University Hospital Santaros Klinikos, a tertiary referral center. All patients with planned LC due to gallstone disease will be evaluated for trial eligibility.

Ethical approval has been obtained from the Vilnius Regional Biomedical Research Ethics Committee (approval protocol number 158200-17-978-473).

The eligibility criteria are listed in Textbox 1 [12-14]. The trial will enroll patients with cholecystolithiasis aged 18 to 80 years, for whom LC is indicated and who have intermediate risk of choledocholithiasis. We will not include patients who are pregnant, morbidly obese (BMI >40), or severely ill (IV-VI class of the American Society of Anesthesiologists physical status classification, contraindications for general anesthesia or surgery). Additionally, patients with anastomosis in the upper gastrointestinal tract, known or suspected hepatitis of another origin (viral, toxic, etc), and other known cholestatic hepatopancreatobiliary disease will be excluded. We will rule out patients with known complications of gallstone disease, such as biliary pancreatitis, acute cholangitis, and acute cholecystitis (degree II-III, as defined in the Tokyo guidelines) [12,13].

Textbox 1. Eligibility criteria.

Inclusion Criteria

- Age 18-80 years
- Symptomatic cholecystolithiasis (stones in the gallbladder seen on imaging studies and causing episodes of biliary colic)
- Intermediate risk of choledocholithiasis (Vilnius University Hospital Index 2.6-6.9 and one of the following predictors: dilated common bile duct >6 mm, elevated total bilirubin >21 μmol/L, or suspected stone in the common bile duct [CBD] on ultrasound)

Exclusion Criteria

- Acute cholangitis, as defined in the Tokyo guidelines 2013 [12]
- Moderately severe or severe biliary pancreatitis, as defined in the revised Atlanta classification [14]
- Acute cholecystitis (degree II-III), as defined in the Tokyo guidelines 2013 [13]
- Anastomosis in the upper gastrointestinal tract
- Known cholestatic hepatopancreatobiliary disease (primary biliary cholangitis, primary sclerosing cholangitis, secondary biliopathy, tumor of the head of the pancreas or major papilla, or benign or malignant CBD stricture)
- Known or suspected hepatitis (viral, toxic, alcoholic, etc) or liver cirrhosis
- Contraindications for general anesthesia or surgery
- IV-VI class of the American Society of Anesthesiologists physical status classification
- Morbid obesity (BMI > 40)
- Pregnancy
- Patient refusal to participate in the study

Elimination From the Trial

Patients will be omitted from the trial if the situation changes to incompatible with the trial protocol. This can happen because of the following reasons: a neoplastic condition is found at the time of management; the general status of the patient worsens owing to other health issues not related to cholelithiasis (eg, myocardial infarction) and the patient needs urgent interventions not included in the trial protocol; and LC is converted to open cholecystectomy before IOC in the "cholecystectomy first" arm. Additionally, if the patient refuses to further participate in the trial, all the patient's data are eliminated and further follow-up is not carried out. Informed consent will be obtained from all study participants.

Randomization and Data Protection

Eligible patients who provide informed consent will be assigned to the groups "endoscopy first" or "cholecystectomy first" randomly, according to a premade sequence. The sequence is generated by a randomization website [15]. The sequence is created using block randomization of two elements A and B ("endoscopy first" and "cholecystectomy first") in a ratio of 1:1. According to the sequence, sheets with group names are enclosed in opaque envelopes. Envelopes are numbered, and the envelope number is the patient number in the trial. When a new participant is enrolled, the topmost envelope is opened by one of the investigators and the participant is randomized into the specified group.

All collected data are coded, that is, every case receives an individual number. Only coded data will be employed for statistical analysis and publishing. Uncoded data are available only for researchers of the trial and, on special and reasonable request, for the coordination center for biomedical research of the institution and Biomedical Research Ethics Committee.

Data are processed and stored in an electronic database, and physical ("paper") copies are stored at the trial center in accordance with procedures established by law.

Procedure

The participants of the trial will undergo CBD evaluation depending on the group assignment. For the group "endoscopy first," EUS is used to evaluate bile ducts. If stones are seen in the extrahepatic bile ducts, ERCP and CBD stone removal are performed during the same general endotracheal anesthesia. LC is performed after endoscopic procedures as soon as possible. In the group "cholecystectomy first," LC with IOC is performed. If stones are found, postoperative ERCP with CBD stone removal is applied (during cholecystectomy if the CBD is completely blocked or as soon as possible).

EUS is performed with linear or radial Olympus ultrasound endoscopes. The CBD, pancreatic head, and adjacent structures are visualized from the duodenal bulb and descending duodenum. EUS is considered positive for a CBD stone when a constant hyperechogenic lesion with acoustic shadowing is seen in CBD projection.

ERCP procedures are performed by experienced endoscopists (each has more than 5 years of experience in ERCP and has done more than 500 procedures). Olympus side-viewing endoscopes (TJF-160VR) are used. Primary deep selective cannulation of the CBD is performed with a sphincterotome or cannula and guidewire technique. Diatrizoate (Urografin, Bayer) and iohexol (Omnipaque, GE Healthcare) are used as contrast media. Endoscopic sphincterotomy is performed over a

guidewire technique with an Olympus pull-type sphincterotome. Papillary balloon dilation using a through-the-scope balloon catheter is applied when a stricture is indicated. Stones are removed using a retrieval balloon catheter and/or a Dormia basket. Complete clearance of the CBD is documented with a balloon catheter cholangiogram at the end of the procedure. ERCP is considered positive when a filling defect is seen in the cholangiogram and/or a stone is evacuated from the CBD. ERCP is considered unsuccessful when cannulation of bile ducts is technically impossible.

All patients will undergo a standard four-port LC (a 10-mm port at the umbilicus, a 10-mm port at the subxyphoid, a 5-mm port at the bottom of the gallbladder, and a 5-mm port at the right epigastrium). A 30-degree laparoscope is used for intra-abdominal visualization. After exposure and identification of the elements of the hepatocystic triangle, a small transverse cut is made in the cystic duct close to the gallbladder infundibulum with laparoscopic scissors. A 4-French cholangiogram catheter is placed in a 5-mm cholangiography fixation clamp and then inserted into the cystic duct. After verifying the absence of leakage at the catheter insertion site, contrast medium (Urografin) diluted in NaCl 0.9% solution (1:1 ratio) in a 20-mL syringe is injected under fluoroscopic vision (C-arm, Siemens GmbH). Cholangiograms are assessed by the operating surgeon and radiologist. IOC is considered positive when there is a filling defect or lack of contrast evacuation to the duodenum.

Blinding

As both management strategies (endoscopic evaluation and intraoperative examination) differ in nature and postprocedure effect on the patient, complete blinding of participants is not possible. Before enrollment in the trial, the participant, treating clinician, and investigator will not know to which group the participant is assigned.

Follow-Up

Participants are followed as treated inpatients after LC (short-term surveillance) and for 6 months after hospitalization (long-term surveillance). In the short-term surveillance period, postprocedural adverse events, signs of cholestasis, and need for repeated procedures are recorded. In the long-term surveillance period, participants are encouraged to contact the investigators if any symptoms of recurrent cholelithiasis are suspected. Participants will be contacted via phone or email 6 to 12 months later. Their health status will be evaluated using a questionnaire on the possible symptoms of choledocholithiasis (Multimedia Appendix 1). If any symptoms of possible gallstone disease are observed, the participant is invited for additional investigation (biochemical blood tests, transabdominal ultrasound, and MRCP on demand). All the enrollment, intervention, and surveillance procedures are listed in Multimedia Appendix 2.

Statistical Analysis

The sample size was calculated in reference to collected data on the management of choledocholithiasis in the trial center Vilnius University Hospital Santaros Klinikos [11]. In our previous study, the mean treatment durations for different management strategy groups (LC-IOC first and ERCP first) were 5.37 and 7.13 days, with SDs of 2.5 and 2.8, respectively, and these findings were used to calculate the requested sample size. The program G*Power version 3.1.9.2 was used for calculations. It was calculated for a two-tailed *t* test for means of two independent groups. The significance level was selected to be .05, with a power of 0.8. The required sample size is 74 (37 valid participants in each of the two groups).

The endpoints in different management groups will be analyzed using the chi-square test or *t* test for independent means. Two-sided hypotheses are to be checked, and a *P* value <.05 will be considered statistically significant. If the distribution is nonnormal, a transformation, such as the logarithm or square root function, can be applied to obtain a normal distribution or nonparametric tests, such as the Mann-Whitney test, can be used. To evaluate the achieved power, a post-hoc power analysis calculation will be performed. As for the primary outcome, a difference of 2 days of hospital stay will be considered clinically meaningful.

Outcomes

The primary endpoint is the length of hospital stay (duration from enrollment into the trial to discharge, in days).

The secondary endpoints are as follows:

1. Diagnostic accuracy of the different management strategies (proportion of correctly diagnosed [true positive and true negative] cases in the entire sample; time frame: 6 to 12 months).

2. Technical success of diagnostic and therapeutic biliary procedures (IOC, EUS, ERCP) (during the active treatment period). For IOC, successful cannulation and contrast media injection into the CBD are considered. For EUS, successful visualization of the CBD is considered. For ERCP, successful cannulation and contrast media injection into the CBD are considered. Successful CBD clearance is also considered.

3. Postoperative course and possible complications of treatment (time frame: up to 1 month). With regard to adverse events of endoscopic interventions and IOC, we consider (1) bleeding, hematemesis and/or melena, or hemoglobin drop >20 g/L; (2) perforation, evidence of air or luminal contents outside the gastrointestinal tract; (3) post-ERCP pancreatitis, new or worsening abdominal pain persisting for at least 24 h and requiring analgesics after ERCP in conjunction with an elevation in serum amylase or lipase levels greater than three times the normal upper limit [16,17]. We also consider assessment of the postoperative course by the Clavien-Dindo classification of surgical complications [18].

4. Cost of treatment (charges for diagnostic procedures, invasive procedures, surgery, and antibacterial treatment, if needed, as well as hospital charges).

Results

The trial protocol was approved by the Vilnius Regional Biomedical Research Ethics Committee in December 2017.

Enrollment of patients was started in January 2018. As of June 2020, 66 patients have been enrolled.

Discussion

In the era of minimally invasive surgery and personalized medical care, the optimal cost-effective strategy for the management of patients with symptomatic gallstones and suspected choledocholithiasis has not been categorically defined yet.

The whole approach to patients with gallbladder stones consists of the following steps: evaluation of the probability of stones in the CBD, visualization, and evacuation of the stones when present along with treatment of cholecystolithiasis itself [19]. There are a few main clinical dilemmas in the management of choledocholithiasis, including which patients should be investigated for CBD stones and what is the optimal way to treat it (single-stage technique [LC with intraoperative CBD evaluation] or two-stage technique [preoperative ERCP followed by LC]).

First, it is essential to define the criteria for different risk groups. While the majority of recent trials evaluating the accuracy of choledocholithiasis prediction refer to ASGE guidelines, we performed an analysis of seven different studies on this prognostic system, and the predictive values of high-risk criteria were quite mediocre. The general sensitivity was 52.4%, specificity was 60.8%, positive-predictive value was 65.6%, negative-predictive value was 47.4%, and accuracy was 55.9% [11]. At the center of this trial, an original prognostic index (VUHI) has been used for the prediction of choledocholithiasis risk before LC since 1999. It is calculated by the following formula: VUHI = A / 30 + 0.4 × B, where A is the total bilirubin concentration (μmol/L) and B is the CBD diameter measured by ultrasound. The results of our previous study showed that the VUHI had comparable and, for some parameters, superior performance than the prognostic system of the ASGE guidelines [11]. The most modest measure was the specificity of VUHI (54%), while the sensitivity was 80.5%. This implied that earlier threshold of the index was kind of a weak spot in the evaluation system. The newly generated model for predicted probability of choledocholithiasis sets limits for the intermediate risk group, that is, it determines which patients should undergo additional noninterventional investigation. We chose thresholds for the intermediate risk group of 25% and 75% of the probability for CBD stones considering that the upper limit of 50% in the ASGE guidelines would still leave a certain number of patients for unnecessary ERCP. Latest European Association for the Study of the Liver (EASL) guidelines also state that patients with intermediate probability should undergo further evaluation with EUS or MRCP, but do not define what this intermediate probability is [20]. Meta-analyses showed that these two diagnostic procedures are quite comparable, but EUS has better diagnostic accuracy [21,22]. Just one trial comparing EUS and IOC was found in the PubMed database, and it showed better predictive values of IOC [23]. Considering that this study was performed 20 years ago and imaging technologies have advanced since then, it is worth comparing these two methods again. When comparing IOC with ERCP as a diagnostic procedure, a systematic review of 10 trials by Gurusamy et al showed slightly higher sensitivity for IOC with no difference in specificity [24].

All imaging methods are somehow operator dependent (or assessor dependent). EUS can have higher operator dependency as agreed by experts in the field because it requires not only evaluation of images but also proper positioning of the scope [25]. On the other hand, EUS is considered to be able to detect smaller CBD stones, which increases its value. Overall, this potentially is reflected in meta-analyses when evaluating not common specificity or sensitivity but the range in different studies. For example, Meeralam et al presented a pooled sensitivity and specificity of 0.97 (range 0.91-0.99) and 0.90 (range 0.83-0.94) for EUS and 0.87 (range 0.80-0.93) and 0.92 (range 0.87-0.96) for MRCP, respectively [21].

In terms of the level of "invasiveness" of these diagnostic methods, MRCP can be considered the least invasive; however, it has its own disadvantages, such as possible reaction to the contrast material and contraindications for the procedure (claustrophobia and ferromagnetic foreign objects). Additionally, EUS can be compared to conventional upper endoscopy, and the main possible complication is injury of the gastrointestinal tract wall with the scope, which is extremely rare. However, this procedure requires sedation or general anesthesia. IOC could seem to be the most invasive option because it is performed during operation, but it is just an additional step in an already ongoing surgery.

Determination of the best exploration method greatly depends on local expertise and availability of certain procedures. At our institution, availability of magnetic resonance imaging is limited because of the lack of equipment, so we decided to choose investigational procedures performed by surgeons and endoscopists themselves to compare.

The next step is to choose the optimal management strategy. In the aforementioned study, we assessed the effectiveness of different approaches (LC with IOC and ERCP "on demand" versus preoperative ERCP with sphincterotomy and necessary therapeutic interventions followed by LC). Some advantages in both strategies were found. There were less missed stones and false-positive cholangiographies in the ERCP first group. On the other hand, the LC-IOC group had less ERCP-related complications, and the mean length of hospital stay in this group was shorter, reflecting no need to wait for another procedure in most cases [11]. Barreras González et al also found these two strategies comparable in efficacy [26]. Moreover, meta-analyses of various different trials showed that there is no difference in the mortality, morbidity, retained stones, and failure rate between single-stage and two-stage choledocholithiasis management [1,27]. The main drawback of the preoperative ERCP plus LC strategy compared with various single-session approaches (intraoperative ERCP, LC with laparoscopic bile duct clearance, and open bile duct clearance) is higher time. Usually, there is a waiting period between the two procedures, which prolongs the duration of hospital stay and slightly increases the risk of developing recurrent biliary events and cholecystitis [20,28,29]. The reduced length of hospital stay (mean difference −3.01 days, 95% CI −3.51 to −2.50; I^2=12%)

was the only significant advantage of intraoperative ERCP found by a Cochrane systematic review when comparing single-stage and two-stage approaches in another way (laparoscopic endoscopic rendezvous versus preoperative endoscopic sphincterotomy) [30]. A recent meta-analysis by Ricci et al of four laparoscopic and endoscopic techniques for managing gallstone disease with biliary duct calculi showed that the safest and most successful approach is LC combined with intraoperative ERCP [31]. However, one of the biggest limitations of single-session ERCP and LC is difficult coordination of medical personnel, equipment, and location of the procedure [32,33]. Despite these restraints, a large survey of general surgeons in the United States showed that the majority of respondents preferred ERCP to laparoscopic CBD exploration for the management of choledocholithiasis if CBD stones were diagnosed preoperatively or intraoperatively [34]. IOC followed by laparoscopic CBD exploration is another possible single-stage strategy. This method appeared to be the safest for avoiding bleeding, took the shortest operative time, and was the least costly in the review by Ricci et al [31]. Unfortunately, this method is not usually applied in our institution, so we decided not to involve it in the trial owing to lack of local expertise.

CBD clearance was found to be alleviated by flushing saline after anterograde balloon dilatation of the Oddi sphincter or after glucagon injection, but these methods are described in singular trials and confirmatory studies are needed [35-37].

This trial is aimed to clarify which one of the two strategies (preoperative EUS or LC with IOC) is the optimal solution for patients with intermediate risk of CBD stones. We intend to compare various aspects of the two approaches of choledocholithiasis management, ranging from accuracy to cost and time efficiency. The thresholds of different risk groups according to the VUHI (original prognostic index) will also be verified prospectively. The index was designed to evaluate the risk for CBD stones in patients with gallbladder stones and an intact gallbladder [38]. Symptomatic cholelithiasis is the main inclusion criterion because it is a major indication for cholecystectomy. We will include adult subjects under 80 years of age as the CBD diameter tends to increase with age [39]. Individuals with other diseases that can cause cholestasis or abnormal liver function test results will be excluded. The diseases include parenchymal disease and mechanical obstruction (from primary sclerosing cholangitis to tumor of the pancreas), as well as biliary pancreatitis, which has been found to not be associated with the risk of choledocholithiasis [10,40,41]. Additionally, we chose to exclude patients with severe acute cholecystitis or cholangitis, as these cases must receive immediate intervention. Finally, patients with absolute or conditional contraindications or burdensome factors for surgery or ERCP (eg, morbid obesity, Billroth II type resection, and severe general condition) are ruled out. We presume that LC with IOC could be the preferred management strategy because of saved time compared with a two-stage strategy, so the study is planned as a superiority trial. We chose to designate hospital stay of 2 days as the minimal important difference between the two groups because it causes a considerable increase in management cost and is barely influenced by nonmedical reasons, which can happen when the difference is chosen to be 1 day. If the difference in inpatient treatment duration is not statistically significant, there are yet other outcomes to be evaluated to compare these two strategies. Overall, this trial is planned to define a simple and safe algorithm for managing choledocholithiasis.

Acknowledgments

This trial will be conducted with no external funding and will be performed with the resources of the hospital as it is a part of the PhD research of one of the investigators (AA) and the center of the trial is a university hospital. Approval to carry out the trial with the resources of the hospital has been obtained, and a contract has been signed between the hospital and the investigators.

Authors' Contributions

GS and AA conceived the project, designed the study, drafted the manuscript, and approved the final submission. GS, AA, JS, TJ, and MD created the inclusion criteria, and will participate in patient selection and enrollment. AA performed sample size calculation. KS and JV helped design the study, revised the manuscript, and approved the final submission. All authors read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Possible symptoms of choledocholithiasis.
[DOCX File , 13 KB - resprot_v10i2e18837_app1.docx]

Multimedia Appendix 2
Enrollment, intervention, and surveillance procedures.
[DOCX File , 14 KB - resprot_v10i2e18837_app2.docx]

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Abbreviations

ASGE: American Society for Gastrointestinal Endoscopy
CBD: common bile duct
ERCP: endoscopic retrograde cholangiopancreatography
EUS: endoscopic ultrasound
IOC: intraoperative cholangiography
LC: laparoscopic cholecystectomy
MRCP: magnetic resonance cholangiopancreatography
VUHI: Vilnius University Hospital Index

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Protocol

Tracking Demographic Movements and Immunization Status to Improve Children's Access to Immunization (TDM-IAI): Protocol for a Field-Based Randomized Controlled Trial

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Abstract

Background: In Cameroon, the coverage, completeness, and timeliness of the Expanded Programme on Immunization (EPI) vaccines administration in children have remained heterogeneous and below the national and districts targets in several districts. In an effort to solve this problem, many interventions have been tested but none has shown significant improvement of the situation.

Objective: This trial aims to test whether involving Community Volunteers to assess children vaccination status and demographic movements and using recorded data to plan catch-up immunization sessions can improve children vaccination timeliness, completeness and coverage.

Methods: Communities of the Foumban Health district, West region of Cameroon will be selected and assigned to either intervention or control groups using a restricted randomization of 2. In the intervention group, one Community Volunteer per community will be trained to visit households and record EPI-targeted children in a register, record their demographic movements, and assess their immunization status monthly for a year. The information recorded will be snapped and sent to the competent health center immunization team through WhatsApp. These will be used to plan and implement monthly community catch up immunization sessions in collaboration with the community volunteer. In the control group, the routine immunization sessions will be conducted with health centers organizing either weekly vaccination sessions for communities situated not farther than 5 kilometers away from the health facility or monthly vaccination sessions in communities situated more than 5 kilometers away from the health center. Baseline, mid-term and end-line surveys will be conducted to assess and compare immunization coverage, timeliness, and completeness.

Results: Funded in 2018, data collection started in 2018 and has been completed. Data analysis and reporting are ongoing.

Conclusions: This trial is expecting to test an innovative approach to improving children's immunization timeliness, completeness and coverage of immunization by tracking EPI targeted population vaccination status and denominator at household level and building collaboration between the community and health facilities vaccination teams to organize monthly community-based response vaccination sessions. This intervention is expected to improve children sustainable access to EPI vaccination as it offers assessing and responding to their immunization needs at monthly basis using low cost local human resources.

Trial Registration: Pan African Clinical Trials Registry ID PACTR201808527428720; tinyurl.com/u058qnse

International Registered Report Identifier (IRRID): DERR1-10.2196/21734

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KEYWORDS

immunization status; coverage: completeness; timeliness; EPI vaccines; children under five; Foumban; Cameroon; vaccines; infectious; immunization

Introduction

Vaccines save lives cheaply, and many countries have adopted a number of antigens to be administered to children and pregnant women under the Expanded Programme on Immunization (EPI). The program has been successfully implemented in many contexts but in many others, vaccination performance in terms of coverage, completeness, and timeliness remains low and is associated with outbreaks of vaccine preventable diseases [1-3].

In Cameroon, 11 vaccines are planned to be administered to children and pregnant women through the EPI [4]. These vaccines are routinely offered in health facilities on a scheduled day weekly and monthly in communities with limited access to health care. Community-based sessions are outreach activities organized by health facility staff in collaboration with community volunteers. Due to limited resources (human, financial, vaccine supply and cold chain, transportation, and power supply) on one hand and limited knowledge of caregivers and their demographic movements on the other, many children fail to receive their planned vaccine doses, be vaccinated on time, or complete their vaccination as required by the national EPI program [1,5].

In 2018, the Demographic Health Survey conducted at the household (HH) level reported 86.7%, 71.5%, and 65.3% rates of vaccination for bacille Calmette-Guérin (BCG), Diphtheria-Pertussis-Tetanus and Hepatitis B + Hemophilus Influenzae type b (DPT-Hi+Hb3), and measles, respectively, with a zero-dose proportion of 9.7% [6]. Many other studies and reports highlighted heterogeneous immunization coverages and high dropout rates in the child vaccination cascade [7,8]. The association between missing planned vaccination doses and the incidence of EPI-preventable diseases is yet to be investigated in Cameroon. In other settings, low vaccination coverage, timeliness, and completeness rates have been consistently reported to be associated with a high incidence of EPI vaccine–preventable diseases (EPI-PD) [9]. Most cited factors associated with low immunization coverage and incomplete vaccination status of children include maternal socioeconomic status, forgetting the vaccination schedule, limited access to health care services, population health care–seeking behaviors, perception of vaccination, misestimating the targeted population, migration, and demographic movement [10].

Strategies have been tested in many countries to reduce missed opportunities of vaccination and improve access to vaccines. Those frequently reported to have shown some positive impact include providing information on immunization to parents and community members, offering memory cards specifically designed for immunization, offering vaccines through proximity vaccination sessions with or without incentives, identifying unvaccinated children in home visits and referrals to health facilities, and integration of immunization services with other services [11,12].

From previous experience with EPI activity supervision, we noticed that many children and pregnant women miss vaccinations during the scheduled periods because of short- or long-term travel. In the national immunization guidelines, no procedure has been planned to catch-up and reduce the time gaps between the recommended vaccination date and the date of vaccine administration. In about one-third of 191 currently functional health districts, most deliveries occur in communities, and newborns are not brought to health facilities to be vaccinated and thus not considered when planning outreach vaccination sessions. In the same line, immigrants and emigrants are not taken into account when planning or monitoring health facility or outreach immunization sessions. Nomads move permanently from one village to another and are not targeted by immunization sessions. In some cases, nomads' children receive several doses of the same vaccine at any time on their way, but none is recorded. This often leads to delaying or not vaccinating about 30%-70% of the targeted EPI population depending on the district. In 2004, we were able to improve the rates of timely immunizations of the third dose of the combined DPT-Hi+Hb vaccine in the Mada Health District in Far North-Cameroon. This was done in a year, using community volunteers to record the following information at the community level: births, travel of the EPI-targeted population, and immunization status of immigrant children. The resulting information was communicated to the vaccinating health facility to plan immunization sessions and organize the catch-up of those who missed the sessions. There was neither a control group nor sufficient power to draw a conclusion from this experience. To the best of our knowledge, this has not yet been tested. This project aims to test if using community volunteers to record vaccination status and demographic movement of children at the HH level and using the recorded data to plan immunization

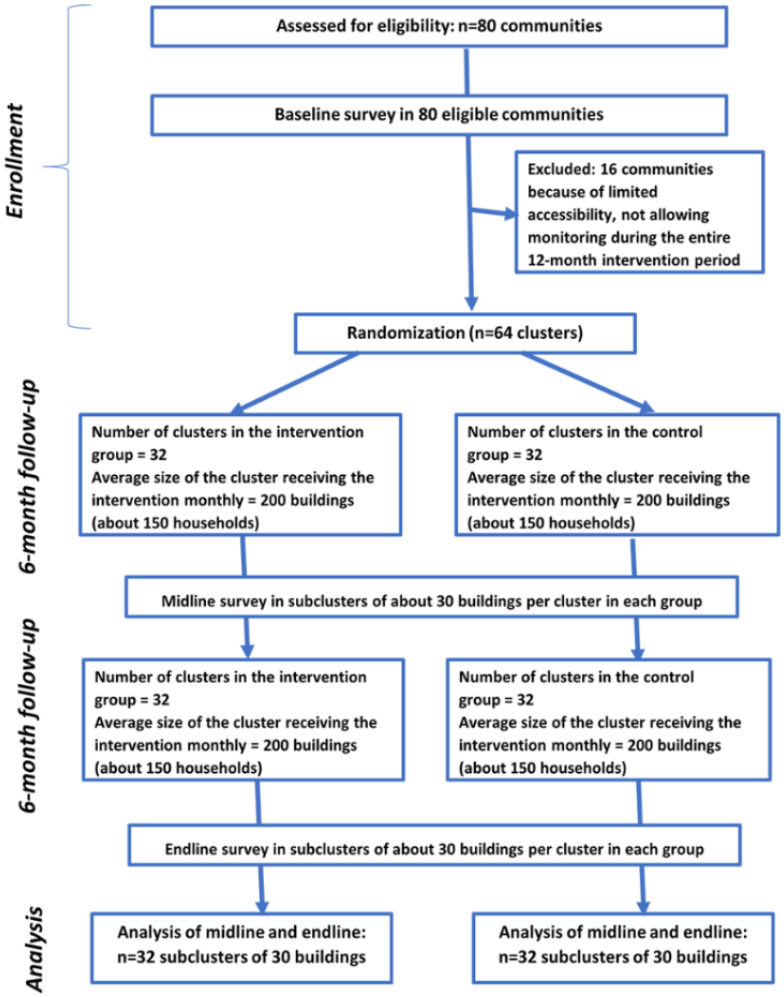
sessions and organize catch-up of missing children can improve EPI immunization timeliness, completeness, and coverage.

Methods

Trial Status

The process of the field phase of the trial, which is ongoing, is described in Figure 1. The unique version of the protocol is registered in the Pan African Clinical Trials Registry with the number PACTR201808527428720. This protocol was also submitted to the Cameroon National Ethics committee for Human Health Research for ethical review, and after evaluation, ethical clearance (2018/07/1058/CE/CNERSH/SP) was obtained.

Figure 1. CONSORT diagram of the study.



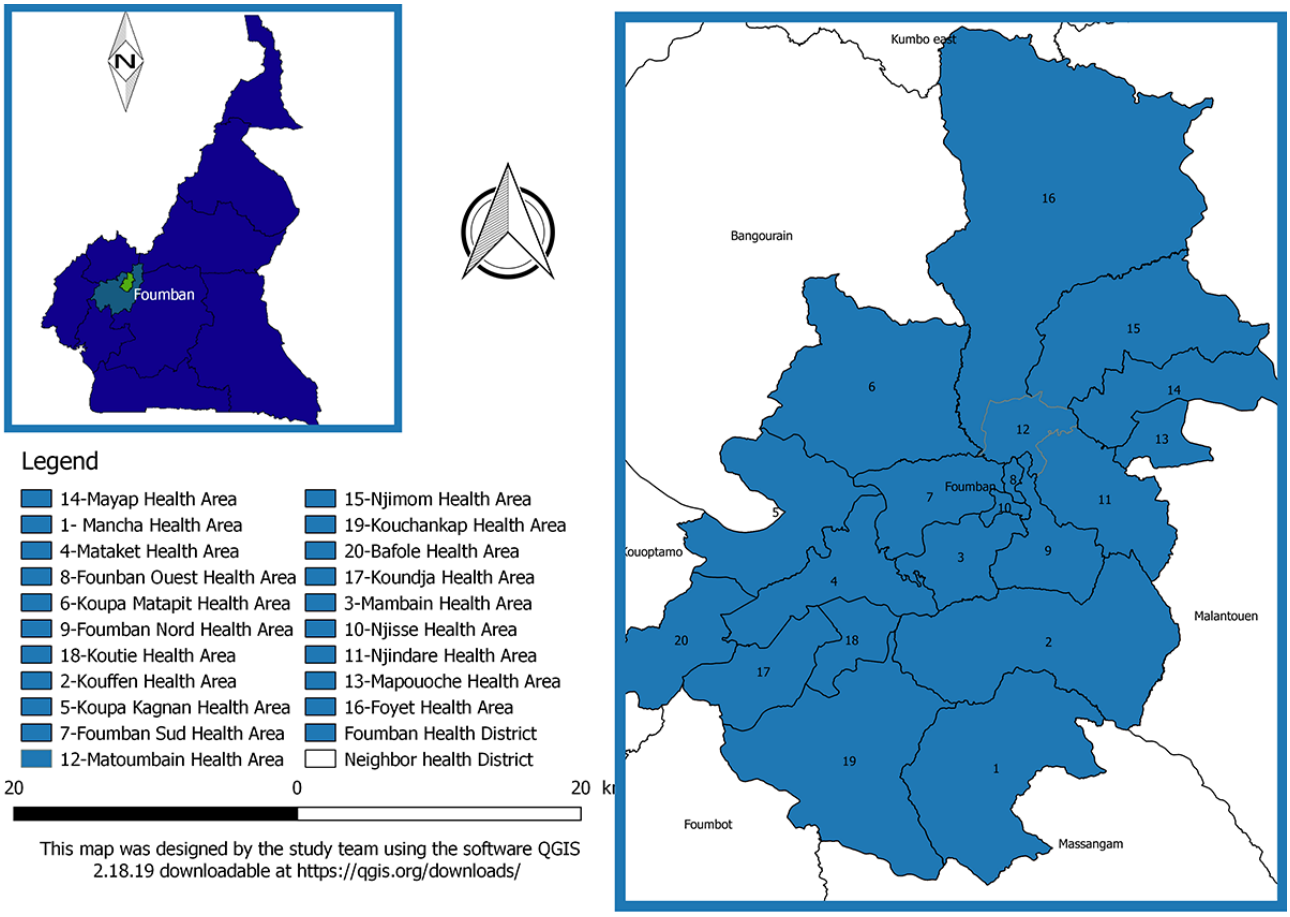
Trial Design

This is a cluster randomized controlled trial in which communities of the targeted health district were randomly assigned to either the intervention or the control group. In the intervention group, community volunteers were trained to visit HHs monthly to record children's immunization status and demographic movement in a community register, and the page of the register was scanned and sent to the health facility in charge of vaccination. The health facility vaccination team used the scanned page to plan where an outreach vaccination session was needed in the community. For the control group, EPI vaccination was organized as per routine, meaning on a weekly basis at health facilities for children living <5 km from the health facility or on a monthly basis during an outreach activity in the community for children situated ≥5 km away from the health facility.

Study Site

The study was conducted in the Foumban Health District, West region of Cameroon, as shown in Figure 2. From the 2018 health population denominators of Cameroon, the total population of the district in 2018 was estimated at 235,828 inhabitants distributed in 311 communities [13]. This district is inhabited by a seminomadic population moving periodically each year with part or all their HH and cattle in search of pasture for farming activities. From weekly reports of the Epidemiological Surveillance Unit of the Department of Diseases Control, Cameroon Ministry of Public Health, it is one of the health districts that have been affected with at least one outbreak of EPI-PD during each of the previous 5 years.

Figure 2. Map of the Foumban Health District.



Study Period

This study was planned for a period of 18 months (from May 2018 to October 2019).

Sampling

Sampling and Randomization of Clusters

To be eligible, communities had to have limited access to a vaccinating health facility and either have recorded a case of EPI-PD in the previous 12 months or belong to a health area with administrative DPT-Hi+Hb3 vaccine coverage <70% in the routinely EPI-targeted population. Communities with limited seasonal accessibility limiting the monitoring of the intervention in some period of the implementation of the intervention were excluded.

In this study, we considered a "community" to be the smallest geographic area (quarter) with a traditional leader (commonly called head of quarter) gathering 100-300 HHs in rural areas or 200-500 HHs in urban areas.

Selected communities were stratified according to their setting (urban/rural), the importance of yearly population movement, the distance to the vaccinating health facility, and the occurrence of EPI-PD in the previous year. In each stratum, communities were ranked in alphabetic order from A to Z and in blocks of 2. All combinations of blocks were listed, and a 1-digit number was assigned to each combination. Numbers were generated from Table XXXIII of Wishart [14], as follows: An arbitrary point was chosen in the table, and numbers were read in a single digit row by row across the page. Each number read and corresponding to a pair of communities dictated the distribution of these communities by study group. Randomized communities were divided into subunits of up to 200 buildings (ranging 100-150 HHs) called clusters using the Google Maps app installed on a smartphone. From previous experience, this is the number of buildings that can be visited in a week by a community volunteer to implement planned activities. One of these clusters per village was randomly chosen per village in each study group. To be able to compare immunization coverage and other indicators between baseline, midline, and endline surveys, eligible but not selected communities were similarly and independently randomized but did not receive the intervention.

Participants

All children aged 0-59 months living in HHs of the selected communities were eligible. This includes the age group targeted by the Cameroon national EPI for routine immunization (0-11 months) and the catch-up vaccination group program (12-59 months) [4]. Children arriving in a HH to stay for less than a month were excluded, and those leaving or planning to stay out of the HH for more than a month were not included. Those leaving the HH for less than a month were not excluded. Parents of children leaving the HH to stay for more than a month were followed up on phone when possible to sensitize them on the necessity of completing the child vaccination program.

Intervention

One community volunteer per community was selected with the help of the head nurse of the competent health center (CHC) and trained to visit HHs of the community cluster monthly, record in a register all children aged 0-59 months and their demographic movements for the last month and next month, and assess their immunization status from the vaccination card or using a tracking grid if the child did not have a vaccination card. The recorded information page was snapped and sent through WhatsApp to the immunization team of the CHC. The information was used by the vaccination team that had received standardized training on reading and using WhatsApp images to plan and implement monthly community immunization sessions. This community vaccination session was conducted in collaboration with the community volunteers who chose an accessible vaccination site in the community and informed parents with children needing vaccination about the session. Health centers and communities were visited monthly to be supervised on their activities.

Control

In the control group, immunization sessions were conducted as per routine. This meant the vaccination team organized weekly vaccination sessions at health facilities for villages situated <5 km away from the health center and when possible, monthly vaccination sessions in communities situated ≥5 km away.

Outcomes Assessment

Data to assess effects of the interventions were collected from baseline, midline, and endline surveys. The baseline survey also provided data on population characteristics and child access to EPI vaccination prior to the intervention. Each village was mapped using the "my position" function of the Google Earth smartphone app and divided into clusters of about 30 buildings, assuming that each cluster would have at least 20 children aged 0-59 months (based on a pretest conducted in the area). One cluster was randomly selected per village and all its HHs visited for data collection. Data were collected by trained and supervised surveyors from the immunization card, community immunization register, and questionnaire administered to parents of children living in the village. Main data collected included the immunization status and timing regarding BCG, polio zero, DPT-Hi+Hb1, DPT-Hi+Hb2, and DPT-Hi+Hb3 and sociodemographic characteristics. The sampling and implementation process of the surveys were similar but independent [1]. The surveys were conducted by independent survey teams different from the team in charge of implementation of the intervention under investigation.

The primary outcome is the timeliness of documented immunization of children, defined as the proportion of children aged <5 years with documented BCG vaccination status administered within the first month of life.

Secondary outcomes include the documented completeness of general EPI vaccination of children, defined as the proportion of children who started vaccination with BCG and who completed it by receiving the measles-rubella vaccine, as documented on the immunization card, and documented completeness of specific immunization of children, defined as the proportion of children who received DPT-Hi+Hb1 and who completed pentavalent vaccination doses by receiving the DPT-Hi+Hb3 vaccine, as documented on the immunization card. In addition, we will assess the timeliness of overall immunization of children, defined as the proportion of children completing all their EPI-recommended vaccines within the first year of life, as documented on the immunization card or not documented but tracked from caregiver memory, and completeness of overall immunization of children, defined as the proportion of children who started vaccination with BCG and completed it by receiving the measles-rubella vaccine, as documented on the immunization card or not documented but tracked from caregiver memory. Documented coverage of child immunization is defined as the proportion of children who will have received DPT-Hi+Hb3, as documented on the immunization card, and overall coverage of child immunization is defined as the proportion of children who have received DPT-Hi+Hb3, as documented on the immunization card or tracked from caregiver memory. We will also assess the documented recruitment rate, defined as the proportion of children starting vaccination with BCG, as documented on the immunization card, and the overall recruitment rate, defined as the proportion of children starting vaccination with BCG, as documented on the immunization card or tracked from their mother's memory.

The effects of the intervention will be assessed by comparing completeness, timeliness, and coverage estimated from the intervention and control groups.

Sample Size Estimate

Using Stata software version 16.1 IC (StataCorp LLC, College Station, TX), the minimum required number of children to test the intervention was estimated at 20 children aged <5 years per cluster in at least 23 clusters of the control group and 20 in the intervention group. The estimate assumes between-cluster coefficients of variation of 0.38 and 0.19 in the control and intervention groups, respectively (estimated from baseline surveys in clusters assigned to each group), to reach 20 children who were <5 years old per cluster in each group, with assumptions that the proportion of children <5 years old vaccinated in the first month of life will remain at 20.5% (293/1430) based on a survey conducted in the targeted area prior to the intervention [1] and that an α error of .05 and 90% power will detect a 10% increase with the intervention in the proportion of children <5 years old vaccinated with BCG in the first month of their life. The estimate was guided by the method of estimating randomized controlled cluster trials proposed by Batistatou et al [15]. We adjusted to 32 clusters of at least 20 children per study group assuming 10% of the targeted children could not be reached (nonresponse and absence during the survey week) and in order to secure sufficient power to prevent cluster variation of estimated outcomes.

Data Analysis

The effect of the intervention will be assessed by estimating per study group and comparing (1) yearly immunization timeliness rates for BCG vaccine (proportion of children aged 0-59 months with evidence of vaccination in the first month of life) and measles-rubella vaccine (proportion of children aged

12-23 months with evidence of vaccination while 9-11 months old); (2) coverage of BCG (proportion of children aged 0-59 months who were vaccinated) and DPT-Hi+Hb1, DPT-Hi+Hb3, and measles-rubella (proportion of children aged 12-59 months who were vaccinated) vaccines; and (3) specific completeness (proportion of children who received DPT-Hi+Hb1 and DPT-Hi+Hb3 vaccines) and general completeness (proportion of children who received BCG and measles-rubella vaccines) while aged 12-59 months. Odds ratios for children being vaccinated, being vaccinated on time, and completing vaccination will be estimated and adjusted for the child's guardians' level of education and profession, type of population (seminomadic or sedentary), distance to the vaccinating health facility, and religion. The odds ratios will be controlled for variability using logistic regression random effects. The fixed parameters will include the outcome, study groups, child's guardians' level of education, type of population (seminomadic or sedentary), child's guardians' profession, distance to the vaccinating health facility, and religion, and the random effect will be controlled on the participants' cluster. The analysis will be done based on the intention to treat principle [16]. Data will be collected using Open Data Kit (ODK)–designed forms on smartphones, verified in the field, and submitted to a secure server. Data will be monitored and cleaned in Microsoft Excel 2013 and analyzed using Stata version 16.1 IC.

Implementation Procedures

Procedures of Survey Implementation

GPS coordinates were collected at the limits of each selected cluster to map and retrieve the map on Google Earth. With the help of community volunteers, the cluster was divided into multiple subclusters of approximately 30 buildings each. One of the subclusters was randomly selected, and all the buildings and inhabited HH of these buildings were visited. All heads of HH were informed by the survey team about the project, and only consenting HHs were enrolled. In these HHs, data were collected from the caregiver for all children aged 0-59 months and from their immunization card about their immunization status as well as any demographic movement in the recent 6 months. The survey lasted for a week in each subcluster. Closed HH that were visited up to 3 times either on the same day or on 3 different days in this period were classified as closed. The study team arranged appointments with the head of HH and children's guardian(s) if any were busy on the first day of the visit. Heads of HH and guardians who could not be met after 3 appointments on 3 different days were considered as nonrespondents. Children with caregivers refusing to respond to the questionnaire were not included, nor were children normally living in the HH but absent during the data collection period.

The study questionnaires were pretested and developed into electronic forms by the data management team. Skip patterns and required and formatted fields were used to ensure data accuracy and completeness. Data were collected with smartphones using the ODK Collect application by trained surveyor teams. Each team of 3 surveyors was trained on the study procedures and supervised daily for participant sampling, informed consent, and data collection processes. A protected online server was deployed by the data management team to compile the survey data. During the survey, completed forms were uploaded to the server daily by the supervisor after reviewing and correcting discrepancies. The data management team ensured daily data cleaning, sharing of reports with field supervisors, and monitoring of corrections, updates, and backups. These procedures were the same in both study groups for the baseline, midline, and endline surveys.

Procedures for the Interventions

In the intervention group, one community volunteer living in selected communities was selected with the help of the head of the CHC and trained to collect data monthly per HH in the same periodicity over 12 months: demographic movements of children aged 0-59 months (births, deaths, immigration, emigration, travel, and short-term visits) and immunization status regarding each of the EPI vaccines. They assessed immunization status of all children aged 0-59 months staying in the visited HH or visiting for a stay of at least one week, or who stayed there in the previous month and had left definitely or for less than a week. Data were recorded in a designated register. The filled pages of the register were snapped and sent to the CHC through WhatsApp to the team in charge of vaccination. From a rapid analysis of received data, the nurse communicated by SMS to the community volunteer the list of children eligible for the monthly immunization session. The community volunteers informed the parents of these children about the place and time of the immunization session and why they should not miss the immunization session. The community volunteers educated all pregnant women on the importance of delivering in a health facility to increase the chance of the newborn being vaccinated. For births occurring in a community on a date far from the planned community immunization session, the community volunteer encouraged the mother to carry the newborn to the closest vaccinating health facility to be vaccinated. The community volunteer of this group had to contact any nomadic group crossing his community to list all children aged 0-59 months and collect data on their vaccination status. If there were children that needed to be vaccinated, the community volunteer completed the register and sent the page to the nurse in charge of vaccination in the community. A vaccination session was organized to vaccinate these children in case the nomad group had to leave the village before the monthly immunization session. The community volunteer was asked to collect telephone contacts from all parents who planned to travel from his community with the child. The child's parent was called by phone to be reminded to have his or her child vaccinated by the competent team.

During this period, EPI vaccination was delivered in the control group as per routine (ie, health facilities organized either the weekly vaccination session in health facilities for communities situated <5 km away from the health facility and monthly vaccination sessions in communities or monthly as an outreach activity in the communities). In each group, vaccination was recorded on a vaccination card and given to the children's parents or guardians. Each community volunteer and one representative from each nomadic group had a register on which the immunization status of each child was recorded and updated after each immunization session and used to trace the

immunization status in case the vaccination card was lost. A copy of the register was kept in the health facility, updated from the community register, and used to draft monthly immunization reports.

Health facilities in charge of vaccination in each of the communities organized routine vaccine supply to cover the vaccine needs in all study groups. Cold chain monitoring was also conducted as per routine. All health facilities were supervised regarding vaccine supply and cold chain monitoring. The community volunteers were supervised on a monthly basis to make sure they implemented the intervention as planned.

Ethical Considerations

The present study is proposed to test an intervention that is expected to improve timely access to EPI vaccines by children in areas with frequent outbreaks of EPI-PD. It will involve interacting with communities, heads of HH, and caregivers to collect data on child vaccination status and demographic movements as well as organizing vaccination catch-ups. All local health, administrative, and traditional authorities with competency over the targeted study area were given information on the study, and they provided permission for study implementation. All caregivers were informed and provided consent for their participation and that of their children before being included in the study. For adults (≥21 years old), they were informed, and their consent required. For children (12-20 years old), their assent was required as well as parental consent for children aged <12 years. Surveillance of adverse events will be conducted routinely by the health facilities in charge. Data collected in registers for the monitoring of child vaccination will be shared between community volunteers and the health facility vaccination team but data extracted from these registers for the study purpose will be anonymous and stored in a secure database with access limited only to members of the study team. The protocol was evaluated and approved by the Cameroon National ethics committee (2018/07/1058/CE/CNERSH/SP), authorized by the Cameroon Ministry of Public Health (631-19-18), and registered in the Pan African Clinical Trials Registry (PACTR201808527428720; August 22, 2018). Relevant national and international regulations will be respected during the implementation of the protocol. Results of the study will be presented to representatives of targeted communities, community volunteers, local and ministerial health authorities, and scientists, hoping it will be used to improve children's access to immunization.

Results

This study is funded by the Bill and Melinda Gates Foundation under the 2018 Grand Challenges Opportunities round 20. As of January 2020, data collection was completed. Data cleaning and reporting are ongoing.

Discussion

This project aims to assess the effect of community-based tracking and recording of child vaccination status and demographic movements and using these to plan immunization sessions and organize catch-up vaccination and to assess the effect on EPI immunization timeliness, completeness, and coverage. To the best of our knowledge, this is an innovative approach that has not yet been tested.

The EPI is proposed in almost all countries of the world to reduce the burden of EPI-PD in children [16]. Despite the fact that this program is supported by international and national organizations and institutions to be delivered free of charge to the targeted population, access to vaccines is still limited [17]. Many studies have described and documented the distribution, characteristics, and consequences of low EPI vaccine coverage and resulting EPI-PD [9]. Many interventions including organization of supplementary immunization campaigns, facility-based education, redesigned immunization reminder cards, health education in HHs and communities, regular immunization outreach, or integration of immunization with other services have improved children's access to immunization but more is still required to achieve the objectives of EPI [11,12,18]. None of these studies assessed the effect of the interventions tested in this study on child vaccination timeliness, completeness, and coverage.

The intervention proposed in this study is expected to improve timely access by children to immunization since it includes collecting data from the community and making those data available to vaccination teams: reliable and documented data on children in need of vaccination on a monthly basis. Each HH was visited, and each child living in the HH, new birth, or impending child was recorded. In addition, each child's immunization status was assessed. Each death or departing child was also recorded for better monitoring of vaccination. The study also provided an opportunity for children aged 12-59 months to complete missed EPI vaccine doses. Improving the timeliness and completeness of EPI vaccination will improve the coverage of children aged 0-11 months and 12-59 months with EPI-recommended doses of vaccines. The use of 2 vaccination registers, one of which is community-based and the other kept in the health facility, that are both simultaneously updated from HH visits and community vaccination sessions will help monitor the administration of subsequent immunization doses, thus improving documented vaccination timeliness, completeness, and coverage.

The tested intervention has some limitations, as its implementation will need additional resources. It requires that the involved health facilities have available health personnel in charge of vaccination and its supervision as well as transportation facilities for community immunization sessions. It also requires incentive and transportation costs for monthly HH visits by community volunteers. In low- and middle-income countries, which are expected to benefit the most from the intervention, these resources are not always sufficient to cover resources needed for the intervention. Since these resources can be acquired through funding, the study will assess the costs of an administered vaccination dose and compare it to the costs of other proposed interventions as immunization campaigns implemented to catch-up with missed vaccination doses. This will be used to inform decision makers and funders of immunization activities to guide the decision-making process in choosing better, cost-effective vaccination interventions.

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Authors' Contributions

JA designed the project and drafted the manuscript. JA and NY developed and insured the development of the protocol and supervised its implementation. JA, FK, AG, and NY developed the data collection tools and monitored the data collection. AG drafted the manuscript. NY, AG, EG, BL, LA, NI, FK, NC, DB, and KB revised the protocol and the manuscript. All authors read and approved the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BCG: bacille Calmette-Guérin
CHC: competent health center
DPT-Hi+Hb: Diphtheria-Pertussis-Tetanus and Hepatitis B + Hemophilus Influenzae type b
EPI: Expanded Programme on Immunization
EPI-PD: EPI vaccine–preventable diseases
HH: household
ODK: Open Data Kit

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Protocol

Effects of the Active Choices Program on Self-Managed Physical Activity and Social Connectedness in Australian Defence Force Veterans: Protocol for a Cluster-Randomized Trial

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Abstract

Background: A stepped-down program is one in which clients transition from the care of a health professional to self-managed care. Very little is known about the effectiveness of stepped-down physical activity (PA) programs for military service veterans.

Objective: This study will test Active Choices, a stepped-down behavioral support program designed to help Australian Defence Force veterans and their dependents who are clients of the Department of Veterans' Affairs, transition from treatment by an exercise physiologist or physiotherapist to self-managed PA.

Methods: The study is a parallel-group, randomized trial, with city-based exercise physiology or physiotherapy practices that recruit eligible Department of Veterans' Affairs clients assigned to Active Choices or a comparison program. The study aims to recruit 52 participants (26 in each group). The Active Choices program will consist of 2 face-to-face (Weeks 1, 12) and 2 telephone (Weeks 4 and 8) consultations. During these sessions, the participant and Active Choices consultant will utilize an evidence-based resource booklet to review the key benefits of an active lifestyle, build an action plan for PA preferences, set and review goals, self-monitor progress relative to set goals, and discuss strategies to overcome PA barriers. Linking participants to local PA communities to overcome social isolation will be a program priority. The comparison program will consist of 2 consultations (Weeks 1 and 12) and use fewer behavioral support strategies (education, self-monitoring, and action planning only) than Active Choices. Outcome measures will be administered at baseline, end-intervention (12 weeks), and follow-up (24 weeks) to assess changes in moderate intensity self-managed PA, psychological well-being, and social connectedness. We will also measure health service utilization and costs as well as PA choices across the intervention period. End-intervention interviews will capture participant experiences.

Results: Due to the impacts of the COVID-19 pandemic on human research activities in Australia, participant recruitment will commence when it is safe and feasible to do so.

Conclusions: Findings will provide valuable pilot data to support up-scaling of the program and larger effectiveness trials with regional and rural as well as city-based Australian Defence Force veterans and their dependents.

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KEYWORDS

military service veterans; self-managed physical activity; behavioral support program; psychological well-being; social connectedness; health service utilization; health service costs; physical activity; well-being; health professional; veterans; behavioral; support program

Introduction

The numerous health and psychosocial benefits that accrue through regular participation in physical activity (PA) are well established [1]. PA is particularly beneficial for older people (≥65 years) and plays an important role in retaining independence and life quality through promoting functional fitness, cognitive function, psychological health and well-being, and social connectivity [2].

While active aging can help maintain holistic health and prevent disease, general practitioners are increasingly referring older patients to PA specialists for the treatment and management of existing health conditions, such as high blood pressure, diabetes, or musculoskeletal issues [3]. In Australia, for example, where referrals to exercise physiologists (EP) and physiotherapists may be government-funded, there has been significant growth in the provision of allied health services to older people. Data from the Department of Veterans' Affairs (DVA), the Australian Government department that provides support to Australian Defence Force (ADF) veterans and their dependents, many of whom are older adults, indicate that from the period of 2011/2012 to 2016/2017, there was a 51% increase in the number of funded services accessed by DVA clients. This was despite a 19% reduction in the number of DVA clients who were eligible to access allied health services [4]. Service uptake was significantly underpinned by large increases in the number of DVA clients who saw an EP or physiotherapist for treatments involving PA.

The benefits of referral to a PA specialist include receipt of expert care and tailored PA guidance during treatment. However, it has been argued that PA referral programs lack behavior change components that promote longer-term adherence [5]. Consequently, such programs do not enable or create channels for patients to "step-down" to self-managed PA after a course of allied health treatment. A stepped-down program is one in which patients transition from allied health care to self-managed behavior [6]. Thus, individuals take responsibility for initiating and maintaining their own PA regimes, instead of being dependent on supervision from a PA specialist.

Given the significant range of health disparities between military service veterans and the general population, stepped-down programs that promote self-management offer a means to support ongoing engagement in PA [7]. It is also the case that self-management is challenging and greater support for sustainability is obtained through engagement in PA with others [8]. This may have the added benefit of helping veterans deal with challenges of social disconnection that can come from losing long-standing connections to peers and support networks that enable positive health behaviors [9]. Engaging veterans in health promotion programs that emphasize social connectivity through PA may be an effective strategy not only for sustainability of PA but also for re-establishing social support networks that can help counter feelings of isolation and ill-health [10].

Recognizing the need to develop, implement, and evaluate scalable interventions that can empower healthy lifestyle choices and social connectivity for military service veterans, the aim of this study is to test "Active Choices," a stepped-down behavioral support program for ADF veterans and their dependents. The 12-week program seeks to connect and engage participants with their local active communities as they transition from DVA-supported treatment by an EP or physiotherapist to self-managed PA. This proof-of-concept study will determine the impacts of the Active Choices program on clients' moderate intensity self-managed PA, psychological well-being, and social connectedness and explore the potential effects on health service utilization and costs. The acceptability and feasibility of the program will also be examined.

Methods

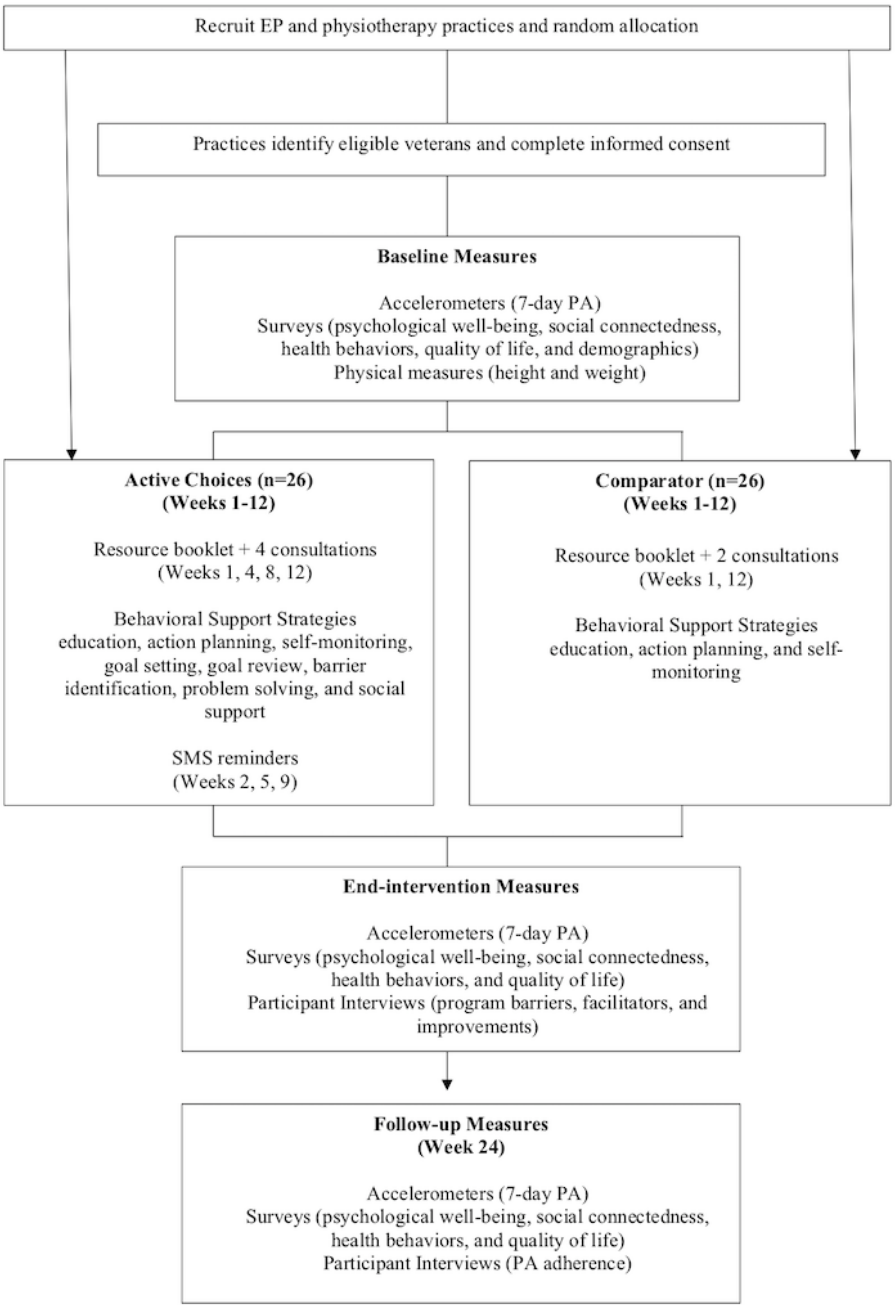
Study Design and Setting

The study is a 24-week, parallel-group, randomized trial for DVA clients (ADF veterans and their dependents) who have been cleared by their treating EP or physiotherapist as able to safely transition to self-managed PA. EP or physiotherapist practices that we engage to recruit eligible participants will be randomly assigned to the Active Choices or comparison program, using an allocation ratio of 1:1.

Randomization will be performed using a simple randomization procedure, based on a computer-generated sequence. Allocation of practices will be concealed at the time of assignment, and members of the research team who will analyze the study data will be blinded to allocation. However, blinding of participants and those who will administer the interventions and outcome assessments will not be possible due to the nature of the program.

Data will be collected from participants at 3 timepoints: baseline, end-intervention (Week 12), and follow-up (Week 24). The trial will be conducted in Brisbane, Australia. Intervention delivery and data collection will take place at the allied health practice the participant attends. A flow chart of the trial is shown in Figure 1.

Figure 1. Participant flow through the trial. EP: exercise physiology; PA: physical activity.



Sample Size

The reference parameters used to calculate the sample size were based on a recent large-scale survey conducted by our team, which examined accelerometer-measured PA in nearly 700 adults living in Brisbane, Australia. This study found participants accumulated an average of 10 minutes/day (70 minutes/week) of at least moderate intensity PA [11]. For our study, sample size was calculated based on change in accelerometer-measured PA, from baseline to 24 weeks, between the 2 groups, in order to detect a minimum average increase of 11 minutes/day (77 minutes/week) of moderate intensity PA. In addition to the PA observed in our reference study [11], this is equivalent to the minimum amount required to achieve standard Australian PA recommendations of 150 minutes/week of moderate intensity PA [12]. Assuming an average of 10 minutes/day (standard deviation of 12.7 minutes/day) at baseline, power of 80%, and significance level of 5%, our power analysis determined that a minimum sample size of 42 (21 in each group) is needed to detect a minimum average increase of 11 minutes/day in moderate intensity PA. To allow for 20% loss to follow-up and 10% noncompliance with PA device use, 52 participants will be recruited to the study (26 in each group).

Recruitment and Eligibility Criteria

Following ethics approval, we will contact EP and physiotherapy practices in the Greater Brisbane region through Federal Government (DVA) and professional organization (Exercise and Sports Science Australia and Australian Physiotherapy Association) communication networks (eg, newsletters and social media) to inform them of the trial. EPs and physiotherapists interested in offering the program to their

clients will act as "gatekeepers" for study recruitment. They will apply study inclusion criteria to DVA-funded clients and link eligible and interested clients with the study team for provision of informed consent. Eligibility criteria will be assessed a second time when obtaining informed consent from participants.

To be included in the study, participants must be ADF veterans and their dependents who are eligible to receive DVA-funded allied health treatment from an EP or physiotherapist, ≥50 years of age (this is based on recent data showing that 80% of the DVA treatment population are over 50 years old, with an average age of 67.25 years) [4], and identified by their treating EP or physiotherapist as able to safely transition from supervised treatment to self-managed PA. The DVA client population includes both ADF veterans and other eligible recipients of DVA-funded healthcare, mostly widow/ers of ADF veterans whose death was determined to be related to their military service.

Participants will be excluded if they are (1) under medical management for complex or chronic conditions that require supervised treatment from a health professional (inclusive of spinal cord injury, brain injury, severe mental health problems, chronic pain, stroke, amputations, and complicated orthopedic injury), (2) currently participating in another DVA-funded PA program, and (3) current serving ADF personnel.

Interventions

Active Choices Program

Participants attending EP or physiotherapy practices allocated to the Active Choices intervention group will receive a 12-week program consisting of two 1-hour face-to-face consultations (held in Weeks 1 and 12) and two 30-minute telephone consultations (held in Weeks 4 and 8), which participants will complete individually with an Active Choices consultant.

The program is based on the COM-B Framework [13] and incorporates evidence-based behavior change strategies to support participants' transition to self-managed PA. These strategies comprise education, goal setting, goal review, self-monitoring, social support, action planning, barrier identification, and problem solving. Strategy selection was also informed by the findings of a systematic review completed by the research team, which identified those utilized in previous intervention studies associated with increased self-managed PA among military service veterans [14].

During consultations held in Weeks 1, 4, and 8, participants will create their individualized Active Choices program, with the support of a consultant, for the proceeding 4 weeks; consistent with our sample size calculations and main outcome measure, focus will be on encouraging weekly activities that elicit self-managed moderate intensity PA equivalent to the recommended guidelines of 150 minutes/week [12], although lighter and more vigorous intensity activities will also be options clients can include in their program where appropriate. This will involve identifying PA preferences and linking participants to preferred activities in their local community, setting PA goals, developing a PA action plan, identifying barriers to PA, and problem-solving solutions to overcome these. Participants will also be actively linked to other participants in their area to facilitate the formation of PA social groups. In addition to these program elements, education about PA will be delivered to participants in Week 1, and a review of previously set PA goals will be conducted in Weeks 4 and 8. At the final consultation in Week 12, participants will review their progress throughout the program and develop a plan for continuing to self-manage PA.

Consultations will be guided by a resource booklet that contains educational and behavioral support materials that map to the behavior change strategies. This booklet will also be used by participants throughout the 12-week program as an educational resource and to self-monitor their PA. A sample of this booklet is provided in Multimedia Appendix 1. SMS reminders will be sent to participants the day before their PA choices in Weeks 2, 5, and 9 as a behavioral prompt.

Comparison Program

As Figure 1 describes, participants attending EP or physiotherapy practices allocated to the comparison group will receive a 12-week program that is more self-directed, has fewer consultation sessions, and incorporates fewer behavioral support strategies than the Active Choices program (ie, education, self-monitoring, and action planning only). The comparison program consists of two 1-hour face-to-face consultations (held in Weeks 1 and 12) that participants will complete individually with an Active Choices consultant. During the consultation in Week 1, participants will receive education about PA and identify their PA preferences. They will also be given materials to help them identify local opportunities for their PA choices and to develop their PA action plan independently at home. At the consultation in Week 12, participants will reflect on their progress during the past 12 weeks and identify their PA action plan for continuing to self-manage PA. Consultations will be guided by a resource booklet, and participants will use this booklet to self-monitor their PA across the 12-week program.

Concomitant Care

Involvement in the research will not replace existing treatment plans but seek to "value-add" scaffolding for behavioral support that can benefit clients and the PA specialist. Therefore, participants in practices allocated to both programs will continue to have the option of accessing allied health treatment from their EP or physiotherapist during the 24-week study period.

Outcome Measures

Overview

The primary outcome of self-managed moderate intensity PA and secondary outcomes of psychological well-being and social connectedness will be assessed at baseline, end-intervention (Week 12), and follow-up (Week 24; see Figure 1). In addition, physical measurements of height and weight and a lifestyle survey assessing quality of life and health behaviors (nutrition, smoking, and alcohol use) will be completed at these time points. Standard demographic items assessing age, gender, education, employment, and household status will be administered at baseline.

Measures will be administered by trained researchers and standardized with calibration of devices and equipment prior to measurement sessions. An Aus $50 (US $38.71) grocery voucher will be offered to incentivize participants to complete follow-up measures at 24 weeks.

Primary Outcome Measure

The primary outcome measure of Active Choices is moderate intensity self-managed PA (equivalent to recommended guidelines of 150 minutes/week [12]) assessed by accelerometer devices. Accelerometers are now widely recognized as an affordable, practical, and highly accurate means of assessing PA [15]. We will use a triaxial accelerometer (wGT3X+, ActiGraph, Pensacola, FL) to assess PA using the same protocol at the 3 measurement time points. Participants will wear the device on their nondominant wrist for 7 consecutive days (24 hours) and keep a diary to record times when they attended treatment with their EP or physiotherapist, when the device was removed, and sleep hours. Upon return, the raw data from the device will be downloaded and processed. The 24-hour wear-time protocol will record raw acceleration and will be used to quantify overall time in moderate PA (inclusive of land and water-based activities), as well as time spent in light and vigorous intensity activities, sedentary behavior, and sleep. Moderate intensity self-managed PA will be calculated as the difference between total moderate intensity PA minus supervised PA performed during treatment (recorded in the diary).

Secondary Outcome Measures

Psychological well-being will be assessed using the Satisfaction with Life Scale [16]. This is a widely used, validated instrument that is comprised of 5 items. Responses to each item are made using a 7-point Likert scale (1 = strongly disagree; 7 = strongly agree).

Social connectedness will be assessed using the New Group Membership Scale (NGMS), Social Identity Mapping, and Three-Item Loneliness Scale. The NGMS is comprised of 4 items that assess the extent to which people have joined new social groups and has strong internal reliability [17]. Responses are rated using a 7-point Likert scale (1 = strongly disagree; 7 = strongly agree). The NGMS will be used to determine whether engagement in PA provides a platform to extend people's social networks to impact on inclusivity. Social Identity Mapping is a validated online tool of social connectedness assessing the multidimensional and connected nature of people's social group networks (eg, family, work, arts-based, sports) and associated social identities (eg, as a veteran, member of a cycling club, or yoga class). Its elements—that comprise group importance, support, positivity, representativeness, and compatibility—are recognized predictors of a range of health and well-being outcomes. This project will use the latest online version validated in 5 studies [18]. The Three-Item Loneliness Scale is a validated and reliable measure of loneliness and social isolation. It is comprised of 3 items, with responses made using a 3-point scale (1 = hardly ever; 2 = some of the time; 3 = often) [19].

Process and Qualitative Measures

Self-report data logged by participants in the resource booklet will capture the frequency, quantity, and types of PA participants in both groups engaged with during the 12-week intervention. We will also conduct interviews with participants in both groups at end-intervention and follow-up to explore the extent to which program experiences promoted social connectedness and veteran social networks, aspects of the program that clients found beneficial and enjoyed, and aspects that could be further developed to improve program efficacy.

Health Service Data

In addition to the measures that will be administered through the trial, we will also seek DVA data custodian approval to access participants' deidentified health service data. We will use these data to assess treatment history prior to recruitment and health service utilization and costs to the DVA for providing these services during the intervention and follow-up period. This will enable us to determine the cost consequences of the program.

Data Analyses

Baseline descriptive statistics will be used to summarize the demographic, physical, and lifestyle behavior characteristics of participants, and data will be checked for parametric assumptions. Intention-to-treat analyses will be conducted using linear mixed effects models. This approach will be used to account for the repeated outcome measures over time and the clustered design of the study and will provide estimates on the within-group and between-group changes in accelerometer-measured moderate intensity PA, psychological well-being, and social connectedness. Sensitivity analyses will be conducted to assess the robustness of findings, and for exploratory purposes, subgroup analyses will be performed by gender, age group, and treatment history. The results of all comparative analyses will be presented with 95% confidence intervals, and statistical significance for main effects will be assessed at the 5% level. Statistical analyses will be conducted using Stata (v15; StataCorp LLC, College Station, TX).

To analyze cost consequences, we will determine the costs of Active Choices and of normal treatment alone, inclusive of both the direct costs of implementing the intervention and the implied cost to the DVA (such as the higher or lower utilization of EP or physiotherapist services relative to group allocation). Difference-in-difference analysis will be used to determine whether Active Choices contributes to cost savings, due to a possible reduction in service utilization.

Consistent with recognized guidelines for qualitative data analyses [20], members of our research team will thematically analyze and independently review interview data and discuss the range of responses to agree on key themes. We will use this qualitative approach to triangulate our findings from the statistical analyses (eg, the impacts of the program on self-managed PA) and determine the factors that encouraged or discouraged engagement with the Active Choices program.

Accelerometer Data Processing

Raw data will be processed in R using the most up-to-date GGIR package, a widely used open-source code [21]. This will involve a calibration to local gravity [22], adjustment for nonwear time, and a filter for abnormally high values. Nonwear time will be defined as periods of at least 60 consecutive minutes with low acceleration variability [23]. The vector magnitude of the 3 axes will be used to calculate activity-related acceleration using Euclidian Norm minus 1g [ENMO=√(x2+y2+z2)-1]. For segments with invalid data, the average of similar time-of-day data points from other days of measurement in the same individual will be imputed. Data will be included if wear time is at least 600 minutes/day on 4 or more days. Data will be used to quantify overall PA expressed as acceleration in milligravity units (mg), as well as time spent in activities at different intensities using the intensity thresholds proposed by Hildebrand et al [24]: light intensity, acceleration 30-100 mg; moderate intensity, acceleration 100-400 mg; vigorous intensity, acceleration higher than 400 mg.

Ethics Approval

The study has received approval from The Departments of Defence and Veterans' Affairs Human Research Ethics Committee (DDVAHREC/OUT/2019/BN11979933; December 13, 2019) and The University of Queensland Human Research Ethics Committee (#2020000034; January 31, 2020).

Results

The study was funded by the DVA in April 2019. Liaison with EP and physiotherapy practices began in February 2020. However, the study was suspended on March 20, 2020 due to the COVID-19 pandemic and restrictions to face-to-face research activities. Our aim is to commence participant recruitment when it is feasible and safe to do so. In our project timeline, the target duration for participant recruitment is 3 months, with study implementation planned to run for 9 months. We expect that results will be available 6 months after data collection is completed.

Discussion

The purpose of this study is to test Active Choices, a stepped-down behavioral support program to help DVA clients (ADF veterans and their dependents) self-manage PA as they transition from treatment by an EP or physiotherapist. Findings from the systematic review recently conducted by our research group suggest that such programs have the potential to promote short-term PA changes in US military service veterans with high-risk comorbidities (eg, diabetes, posttraumatic stress disorder, musculoskeletal disorders). Among those selected studies that compared a stepped-down intervention to a "usual care" group (n=14), 79% of studies (11/14) observed a positive between-group intervention effect, with the mean magnitude of change being 53 minutes/week of self-reported moderate intensity PA [14].

While this evidence is promising, our review identified no studies with ADF veterans. Similarities may well exist with US military service veterans; however, there is no direct evidence of generalizability to the Australian context or indeed outside of the United States to military service veterans in other countries. The proposed study will therefore contribute important evidence to an identified research need, and the findings provide valuable pilot data to inform larger effectiveness trials at the national level. Beyond this, our study will also address other limitations in the veteran evidence base. These include the use of self-report rather than objective measures of PA change and importantly, lack of data concerning the extent to which self-managed PA programs can benefit the psychological well-being and social connectedness of veterans or their dependents.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Sample from Active Choices Resource Booklet.
[PDF File (Adobe PDF File), 4062 KB - resprot_v10i2e21911_app1.pdf]

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Abbreviations

ADF: Australian Defence Force
DVA: Department of Veterans' Affairs
EP: exercise physiologist
NGMS: New Group Membership Scale
PA: physical activity

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Protocol

Valproic Acid as an Adjuvant Treatment for Generalized Convulsive Status Epilepticus in Adults Admitted to Intensive Care Units: Protocol for a Double-Blind, Multicenter Randomized Controlled Trial

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Abstract

Background: Generalized convulsive status epilepticus (GCSE) is a frequent medical emergency. GCSE treatment focuses on the administration of benzodiazepines followed by a second-line antiepileptic drug (AED). Despite this stepwise strategy, GCSE is not controlled in one-quarter of patients and is associated with protracted hospitalization, high mortality, and long-term disability. Valproic acid (VPA) is an AED with good tolerability and neuroprotective properties.

Objective: This study aims to demonstrate that administration of VPA as an adjuvant for first- and second-line treatment in GCSE can improve outcomes.

Methods: A multicenter, double-blind, randomized controlled trial was conducted, comparing VPA with a placebo in adults admitted to intensive care units (ICUs) for GCSE in France. GCSE was diagnosed by specifically trained ICU physicians according to standard criteria. All patients received standard of care, including a benzodiazepine and a second-line AED (not VPA), at the discretion of the treating medical team. In the intervention arm, VPA was administered intravenously at a loading dose of 30 mg/kg over 15 minutes, followed by a continuous infusion of 1 mg/kg/hour over the next 12 hours. In the placebo group, an identical intravenous administration of 0.9% saline was used. The primary outcome was the proportion of patients discharged alive from the hospital by day 15. Secondary outcomes were frequency of refractory and super refractory GCSE, ICU-related morbidity, adverse events related to VPA, and cognitive dysfunction at 3 months. Statistical analyses will be performed according to the intent-to-treat principle.

Results: The first patient was randomized on February 18, 2013, and the last patient was randomized on July 7, 2018. Of 248 planned patients, 98.7% (245/248) were enrolled across 20 ICUs. At present, data management is still ongoing, and all parties involved in the trial remain blinded.

Conclusions: The Valproic Acid as an Adjuvant Treatment for Generalized Convulsive Status Epilepticus (VALSE) trial will evaluate whether the use of VPA as an adjuvant for first- and second-line treatment in GCSE improves outcomes.

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KEYWORDS

generalized convulsive status epilepticus; intensive care unit; seizure; valproic acid

Introduction

Background and Rationale

Generalized convulsive status epilepticus (GCSE) is a diagnostic and therapeutic emergency. Mortality or long-term neurological deterioration increases with time to successful seizure termination [1]. In-hospital mortality reaches 20% to 40% in refractory GCSE, and 23% of patients with GCSE have permanent disability [2]. Underlying etiology, older age, and duration of seizure are the main predictors of unfavorable outcomes [2]. Guidelines have been established to improve the detection, management, and outcome of GCSE [3]. GCSE is defined as a convulsive seizure lasting more than 5 minutes or as consecutive seizures without recovery of consciousness between seizures [4]. Stepwise antiepileptic therapy is recommended. Emergent initial therapy consists of the administration of benzodiazepine (ie, lorazepam, clonazepam, diazepam, or midazolam). If GCSE is not controlled, current guidelines recommend second-line antiepileptic drugs (AEDs), including phenytoin or fosphenytoin, valproic acid (VPA), phenobarbital, or levetiracetam, administered intravenously [3]. Despite the proven efficiency of this stepwise strategy, cessation of seizures is still not obtained in about a quarter of patients [5,6], and GCSE remains associated with prolonged hospitalization and long-term disability. To improve seizure control and long-term outcomes, randomized clinical trials (RCTs) were therefore undertaken to determine the most efficient second-line AEDs [5-8].

Another approach consists of combining first- and second-line AED therapy with adjuvant treatment [5]. The addition of hypothermia did not improve neurological outcome in GCSE [9]. We reasoned that a strategy based on the administration at the time of intensive care unit (ICU) admission of a treatment exhibiting antiepileptic and neuroprotective properties as well as being well tolerated (ie, not inducing or requiring sedation) might be beneficial. At the time of the design of our RCT (ie, 2012), VPA seemed to be one of the best options [10]. Indeed, at that time, French guidelines did not recommend VPA as a second-line AED, except for GCSE, obviously related to its withdrawal [11]. Until recently, only six randomized trials compared VPA with either phenytoin, phenobarbital, or diazepam [12]. Their meta-analysis indicated a similar rate (77%) of seizure cessation with VPA compared with other AEDS [13]. However, these studies had major limitations, including single-center designs or their small size [13-15]. Interestingly, a very recent multicenter trial *Established Status Epilepticus Treatment Trial* (ESETT) showed on a large cohort that VPA was equivalent to fosphenytoin and levetiracetam as second-line AEDs in adult patients for the early control of seizures [16]. It must be noted that VPA is only prescribed during GCSE by 16% of neurologists, mostly when GCSE is refractory [17]. A French survey reported that VPA was used as a second-line AED in approximately 9% of cases [18]. Therefore, we think that addressing the effect of VPA as a complementary treatment to the recommended stepwise antiepileptic strategy remains relevant, notably because of its antiepileptic efficacy [14,15], potential neuroprotective effect [10], good tolerance, and compatibility with other AEDs [19].

We hypothesized that 1 mg/kg over 12 hours of VPA intravenously after a loading dose of 30 mg/kg over 15 minutes in patients admitted to the ICU for GCSE, in addition to the recommended stepwise antiepileptic strategy would increase the number of patients discharged alive from the hospital by day 15 after GCSE onset.

Objectives

Primary Objective

The primary objective is to assess whether VPA increases the proportion of patients with GCSE discharged alive from the hospital on day 15 following ICU admission after adjustment for age and existence of primary brain insult. The effectiveness of AED in GCSE is commonly assessed in terms of their ability to rapidly control seizures. However, measuring the effect of VPA on a longer-term outcome such as hospital discharge is clinically relevant and easily assessable. Indeed, prompt hospital discharge indicates that the global management of GCSE was appropriate with early control of epilepsy, prompt treatment of the underlying cause, low mortality, and a short hospital stay. Furthermore, this end point has previously been reported, facilitating sample size calculation. [9]. In the Veterans Administrations Cooperative study comparing different first-line treatments of status epilepticus, only 50% of patients enrolled in the placebo arm had been discharged from the hospital on day 30 [8].

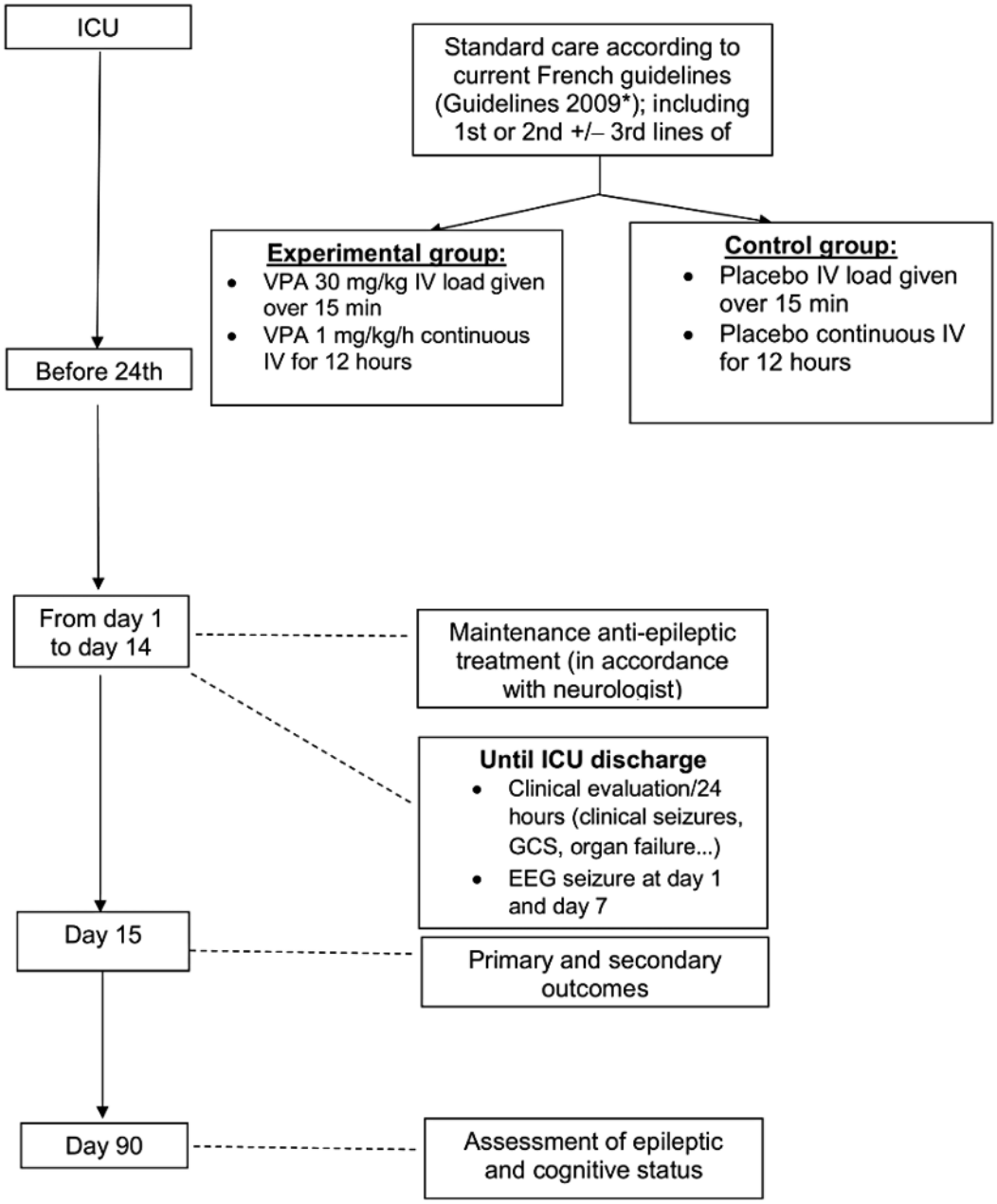
Secondary Objective

The secondary objective is to determine whether VPA decreases the rates of seizures, refractory and superrefractory GCSE, ICU-related morbidity, and poor neurological outcome at 3 months. We will control for the underlying cause of GCSE and monitor the side effects of VPA.

Trial Design

The Valproic Acid as an Adjuvant Treatment for Generalized Convulsive Status Epilepticus (VALSE) trial is a multicenter, parallel-group, double-blind RCT comparing the adjunction of intravenous VPA against placebo in patients admitted to the ICU for GCSE, in addition to firstand second-line AEDs and standard ICU care (Figure 1).

Figure 1. Study design. AED: antiepileptic drug; EEG: electroencephalogram; GCS: Glasgow Coma Scale; ICU: intensive care unit; IV: intravenous. *Guidelines from the French Intensive Care Society [11].



Methods

Study Setting

A total of 20 centers, including 10 general hospitals and 10 university hospitals, participated in this study. Factors determining which centers were selected to participate were capacity to include patients, knowledge, and adherence to current guidelines on the management of GCSE. Several participating physicians were involved in drafting the recommendations for management of GCSE issued by the French Intensive Care Society [11]. All participating centers had previously participated in clinical trials. Finally, training on the study procedures was provided to all participating staff members. Documents required for the study, including the study protocol and management guidelines, were available in each participating ICU.

Eligibility Criteria

Adult patients were eligible if admitted to the ICU for GCSE, defined as 5 minutes or more of continuous generalized clinical seizure activity or recurrent generalized seizure without recovery of consciousness between seizures [11] provided that antiepileptic treatment had been initiated before inclusion either within 6 hours if GCSE was controlled by the time of inclusion (ie, absence of seizure irrespective of the level of consciousness) or within 24 hours if GCSE persisted or reoccurred. The former criteria aimed to include patients during the early stage of GCSE; the latter subcriteria aimed at enrolling patients with superrefractory GCSE, as we reasoned that VPA could be beneficial for both types of population. The reported proportion of patients with superrefractory GCSE is approximately 15% [20]. The patient' s informed consent or next of kin assent was

obtained before inclusion. Alternately, deferred patient consent was obtained.

The exclusion criteria were as follows: (1) nonconvulsive status epilepticus; (2) postanoxic status epilepticus; (3) the primary clinical team decided to treat the patient with VPA before randomization; (4) GCSE occurred during hospitalization for a disease with an expected length of stay >15 days; (5) expected ICU length of stay <12 hours; (6) life expectancy <3 months; (7) women of childbearing age (>17 and <50 years), pregnant women, or women with eclampsia; (8) VPA contraindications, including liver disease (preexisting chronic or acute hepatitis, cirrhosis, hepatitis B or C virus or family history of acute hepatitis), porphyria, hypersensitivity to VPA or derivatives, treatment with mefloquine or hypericum-containing drugs; (9) included in any treatment trial; (10) previously been included in this trial; and (11) no health insurance coverage; and (12) being under guardianship. To reduce recruitment bias, we did not discourage the primary medical or ICU team to use VPA as a secondary AED.

All patients admitted for GCSE in one of the participating ICUs were screened for eligibility by the ICU physicians round the clock and reasons for nonrandomization were collected. In each participating center, GCSE diagnosis was made by ICU physicians specifically trained for.

Who Will Take Informed Consent?

Written informed consent of the patient had to be obtained by the investigator of the participating center. In case of impaired consciousness, the investigator sought written consent from the next of kin. If the latter was not present, the patient could be included, as deferred consent was approved by the Ethics Committee, according to the French law (Art L1122-1-2 du Code de la Santé Publique). As soon as the patient's status allowed, written informed consent for the continuation of the research and analyses of the data had to be obtained. A copy of the consent form was given to every patient. The investigator had to keep the original copy in his archives for a minimum of 15 years. A third copy was archived by the promoter.

Interventions

Explanation for the Choice of Comparators

As VPA was tested as an adjuvant therapy, patients were treated with AED according to local guidelines [11], which recommended clonazepam (or diazepam) as a first-line AED and phenobarbital or fosphenytoin as second-line drugs. Therefore, belonging to the comparator or the experimental group did not change the recommended treatment administration. Saline 0.9% administration was used as a placebo to control the intervention.

Intervention Description

In the intervention group, VPA treatment consisted of intravenous administration of a loading dose of 30 mg/kg over 15 minutes followed by a continuous intravenous dose of 1 mg/kg/hour over the next 12 hours. Given that the half-life of VPA is approximately 16 hours, this protocol aims to rapidly reach and maintain therapeutic plasma levels of VPA. In the control group, an identical intravenous administration of 0.9% saline as a bolus and continuous infusion was used as a placebo for VPA.

Criteria for Discontinuing or Modifying Allocated Interventions

A centralized phone and email center answered participating centers' questions regarding patient eligibility or management and declaration of any adverse event during the trial period. Reasons for any experimental treatment being discontinued before full-dose administration were recorded.

Strategies to Improve Adherence to Interventions

The participating teams were informed of the course of the study and reminded of the main elements of the trial on a monthly basis. Blood samples for VPA dosage were drawn before (T0), 15 minutes, and 12 hours after VPA administration to assess whether VPA has been appropriately administered in the intervention group and not mistakenly administered in the control group.

Relevant Concomitant Care Permitted or Prohibited During the Trial

In both groups, patients benefited from standardized care, including antiepileptic therapy, control of secondary brain injuries, etiological investigations, and neurological monitoring. As VPA was tested as an adjuvant therapy, patients were treated with AED according to local guidelines [11], which recommended clonazepam (or diazepam) as a first-line AED and phenobarbital or fosphenytoin as second-line drugs. Recommended anticonvulsant therapy for refractory and superrefractory GCSE includes the infusion of sedative agents (ie, propofol or midazolam) and thiopental, respectively [11]. Maintenance antiepileptic treatment was started between the 12th and 24th hours and was decided by the local physician independent of the trial protocol. In patients with a history of epilepsy, recommendations dictated the resumption of antiepileptic medications that controlled seizures in the patient before GCSE onset.

Prevention of secondary brain injuries was based on temperature, mean blood pressure, blood glucose, sodium levels, PaO_2, and $PaCO_2$ control. Etiological investigations were conducted by the physicians in charge of the patient. Patients were assessed neurologically every 4 hours using the Glasgow Coma Scale (GCS) or the Richmond Assessment Sedation Scale. When the GCS was ≤8, pupillary light reflex, and corneal and cough reflexes were assessed. In the absence of coma or sedation, delirium was detected using the Confusion Assessment Method in the ICU every 12 hours. The presence of focal neurologic signs and abnormal movements were systematically collected every 4 hours. This standardized neurological examination helped assess the duration of seizures, relapse of GCSE, progression to refractory and superrefractory GCSE, neurological deterioration, delay for arousal, and post-GCSE delirium. These standardized regular and frequent neurological assessments are used to potentially trigger complementary investigations such as imaging or electrophysiological tests. In every patient, at least one 30-minute electroencephalogram (EEG) was performed within 24 hours of admission and another one between days 2 and 7. EEGs were interpreted by the referent

neurophysiological team of the participating center. All EEGs were stored to be sent for a posteriori adjudication by a group of experts blinded to the randomization arm.

In both intervention groups, serum samples were obtained before and 15 minutes and 12 hours after the administration of the VPA load to measure serum VPA concentrations. Samples were stored at −20°C in the participating centers before being sent to the Department of Pharmacology and Toxicology of the Raymond Poincaré Teaching Hospital (Garches, France) for centralized VPA measurements.

Provisions for Posttrial Care

In France, research promoter insurance offers a subsequent period of 10 years from the end of the research. Consequently, in the event of poststudy damage to a subject related to their participation in research, the complaint would be admissible as soon as it occurs during this period.

Outcomes

The *primary outcome* was the proportion of patients discharged alive from hospital to their home or to a long-term care facility on day 15. Therefore, death within the first 15 days or a medical reason to keep the patient hospitalized beyond day 15 was considered a poor outcome. Conversely, hospitalization lasting more than 15 days was not considered a failure if the patient was declared fit for discharge from hospital but remained hospitalized because of social issues or a lack of bed availability in recovery facilities. The primary end point (ie, hospital status at day 15) will be collected by a blinded investigator.

Secondary outcomes were (1) frequency of refractory and superrefractory GCSE [20], (2) morbidity related to the ICU stay, (3) rates and types of VPA adverse effects, and (4) cognitive dysfunction at 3 months.

We aimed to determine whether intravenous VPA as an adjuvant AED prevented the recurrence of refractory GCSE within 3 months, reduced ICU-related complications, and improved cognitive status at 3 months, irrespective of the cause of GCSE.

Participant Timeline

For any patient admitted for GCSE into one of the participating ICUs, investigators checked the patient's eligibility criteria for the VALSE study. If a patient was eligible but unable to provide free and informed consent, the investigator attempted to obtain signed consent from the patient's next of kin or included the patient according to the deferred consent procedure. The investigator notified the patient or his next of kin of enrollment as early as possible and sought the patient's consent to continue whenever possible. The patient was then randomized through a centralized, secured website to receive either placebo or VPA.

Within 24 hours of inclusion, a 30-minute standard EEG was performed. Antiepileptic relay therapy was started 12 hours after completion of the treatment infusion or later in case of progression to refractory GCSE. Blood samples for VPA dosage were drawn before (T0), 15 minutes, and 12 hours after VPA administration (Table 1).

Table 1. Trial visits summary.

Time point	Enrollment	Allocation	Postallocation			Close-out				
	$-t_1$	0	*t0*	*15 min*	*12 h*	Day 1	Days 2,3,4,7	Day 15	Days 15-90	Day 90
Enrollment										
Eligibility screen	✓[a]	—[b]	—	—	—	—	—	—	—	—
Informed consent	✓	—	—	—	—	—	—	—	—	—
Allocation	—	✓	—	—	—	—	—	—	—	—
Interventions										
Valproate dosage	—	—	✓	✓	✓	—	—	—	—	—
Assessments										
Clinical assessment	✓	✓	✓	✓	✓	✓	✓	✓	—	—
CAM-ICU[c], GCS[d], and RASS[e]	—	—	✓	✓	✓	✓	✓	✓	—	—
Etiological investigation	—	—	✓	✓	✓	✓	✓	✓	—	—
Standard EEG[f]	—	—	—	—	—	✓	✓	✓	—	—
SOFA[g]	—	—	✓	—	✓	✓	✓	✓	—	—
SAPS-II[h]	—	—	—	—	—	✓	—	—	—	—
FAB[i], MMSE[j], GOSE[k], and SF-36[l]	—	—	—	—	—	—	—	—	—	✓
Valproate adverse effects reporting	—	—	✓	—	✓	✓	✓	✓	—	—
Primary outcome	—	—	—	—	—	—	—	✓	—	—
Secondary outcome	—	—	✓	—	✓	—	—	—	—	—
End of trial criteria	—	—	—	—	—	—	—	—	—	—

[a]✓: visit is scheduled.

[b]Absence of visits.

[c]CAM-ICU: Confusion Assessment Method for the Intensive Care Unit.

[d]GCS: Glasgow Coma Scale.

[e]RASS: Richmond Agitation-Sedation Scale.

[f]EEG: electroencephalogram.

[g]SOFA: sepsis-related organ failure assessment.

[h]SAPS-II: Simplified Acute Physiology Score.

[i]FAB: Frontal Assessment Battery.

[j]MMSE: Mini-Mental State Examination.

[k]GOSE: Glasgow Outcome Scale-Extended.

[l]SF-36: Short Form-36.

From the day of inclusion to day 7, a second 30-minute standard EEG was performed. From inclusion to day 15, patient monitoring was standardized to assess the evolution of GCSE, study drug side effects, and ICU-related complications (Table 1).

The primary end point was collected on day 15. ICU-related secondary end points were collected at the time of ICU discharge. From ICU to hospital discharge, the recurrence of seizures and changes in antiepileptic therapy were recorded. At the time of discharge, the patient was given a prescription for his antiepileptic treatment, its biological monitoring, and an appointment with a referral neurologist 3 months later. At day 90, vital, cognitive, and functional statuses were assessed by the referral neurologist or intensivist either by phone or through a medical examination (Table 1).

Sample Size

The study was powered to detect an absolute increase of 20% in the rate of patients discharged alive at day 15 with a power of 90% and a two-sided 5% alpha risk, assuming this rate would be 50% in the control arm. Accordingly, the sample size was 124 patients per group. To account for the decrease in power owing to potential errors in the administration of the allocated treatment, this number was increased to 150 per arm. Therefore, the study initially planned to enroll a maximal sample size of 300 patients.

In fact, following the inclusion of the 245th patient, the RCT was discontinued owing to difficulties in recruiting. The decision was made because 98.8% (245/248) of the calculated sample size (n=248) had been enrolled and the associated decrease in power would be less than 1%. In addition, no treatment allocation error was noted, so there was no reason to target 300 patients.

Recruitment

The study took place in 20 ICUs, which had been selected based on the interest expressed by local physicians, expertise in managing status epilepticus, their capacity to recruit eligible patients (ie, at least one patient per month), and RCT constraints as well as their easy access to a neurological department. A research assistant was available daily at every participating center to screen patients for inclusion. The steering committee met each month. A centralized phone and email center answered participating centers' questions regarding patient eligibility or management and declaration of any adverse event during the trial period. A newsletter was sent monthly, informing the participating centers on the number of patients included, main study constraints, and any protocol modifications.

Assignment of Interventions: Allocation

Sequence Generation

The randomization list was balanced between arms generated by the study statistician using permutation blocks of varying size (block of 2 or 4 patients, each with probability 0.5). Randomization was stratified by age group (≤65 or >65 years), center, and presence of *acute primary brain injury*. Stratification by age was performed, as it is a well-established prognostic factor for outcome of patients with GCSE.

Concealment Mechanism

Randomization and concealment were ensured using a web-based system accessible at each study center and managed by the clinical research unit, which had no role in patient recruitment.

Implementation

The allocation sequence was generated by the study statistician. Patient enrollment was ensured by the participating center investigator.

Assignment of Interventions: Blinding

Who Will Be Blinded

The promoter provided the centers with sequentially numbered and sealed treatment boxes of identical appearance for either VPA or placebo. Boxes were prepared, coded, and shipped to participating sites by the Agence Générale des Equipements et Produits de Santé—Assistance Publique-des Hôpitaux de Paris (AP-HP, Paris France). These boxes contained all the elements needed to prepare the allocated treatment. The number of a given box related to the treatment unit number provided at the end of the randomization procedure. Reconstitution of the treatment was carried out (1) either in the pharmacy of the participating site, provided that reconstitution could be performed rapidly at any time of the day, or (2) in the ICU by an out-of-protocol nurse, who was not involved in patient management, monitoring, or follow-up. This procedure ensured a double-blind design, as the investigator and the rest of the ICU team remained unaware of treatment allocation.

The randomization sequence was concealed from patients, staff members, investigators, members of the independent Data Safety Monitoring Board (DSMB), and the sponsor.

Procedure for Unblinding if Needed

Unblinding was permissible but had to be explained by the investigator to either the antipoison center (Paris, France) or to the promoter.

Data Collection and Management

Plans for Assessment and Collection of Outcomes

Baseline characteristics on admission were systematically collected by the center investigator: demographic and anthropometric data, location before ICU admission (community, hospital, or long-term facility); date and time of ICU admission, preexisting comorbidities using Knaus and McCabe scores, history of epilepsy and preexisting antiepileptic treatment, and other preexisting neurological diseases.

GCSE characteristics were recorded: circumstance of onset; focal or generalized onset; and time, type, and dosage of the AED administered. Neurological assessment included the GCS and occurrence of focal neurological deficit at any time. Paraclinical assessment of GCSE included the date and time of EEG, EEG features, brain imaging, and cerebrospinal fluid analysis when available. Finally, the etiology of GCSE was recorded and classified as acute, remote, progressive, or unknown [21].

Severity of critical illness was determined using the Simplified Acute Physiology Score II and Sequential Organ Failure Assessment score. Over the first 24 hours, vital signs including core temperature as well as hematologic and biochemical data, plasma level of creatine kinase, ammonia, and plasma level—human chorionic gonadotropin for women of childbearing age were recorded.

Patients were followed up for 90 days. From randomization to day 15, we recorded vital signs, Sequential Organ Failure Assessment score, need for mechanical ventilation or renal replacement therapy, and results of standard laboratory tests. GCSE assessment included date and time of cessation of clinical seizures, recurrence of seizure if any, evolution to refractory and superrefractory GCSE, as well as the date and results of EEG. The type and dose of the maintenance AED was also recorded. Neurological status was assessed daily by recording the GCS, Richmond Assessment Sedation Scale and Confusion Assessment Method in the ICU, type of sedation, and existence of focal neurological signs. At the time of ICU discharge, we collected information on the duration of sedation and mechanical ventilation, time for arousal, length of ICU stay, and antiepileptic treatment. At the time of hospital discharge, we collected the date of recurrence of seizure and GCSE, length of hospital stay, and destination (home, hospital, or long-term facility). In each participating center, the final diagnosis of GCSE and its cause were routinely confirmed by a neurologist. This evaluation will enable the identification of psychogenic

GCSE, which can amount up to 10% of the cohort. No adjudicators were provided in our study to confirm the GCSE.

At day 90, we assessed the epileptic status by recording the recurrence of seizures or of GCSE, modification of antiepileptic therapy, vital status by collecting the date of death when appropriate, and the cognitive status by assessing the Extended Glasgow Outcome Scale, Mini-Mental State Examination, Frontal Assessment Battery, and quality of life using the Short Form-36. Day 90 assessment was performed by the referral neurologist or intensivist during the consultation or through a phone interview.

At the end of the trial, plasma VPA levels before, 15 minutes, and 12 hours after inclusion as well as the centralized interpretation of EEGs will be collected.

Plans to Promote Participant Retention and Complete Follow-Up

The participating teams were monthly informed of the course of the study and reminded of the main elements of the trial, notably concerning the follow-up.

Data Management

Data management and statistical analysis were performed independently of the sponsor and investigators by the clinical research unit (*Unité de Recherche Clinique, Hôpital Ambroise Paré, Boulogne, France*) and by the Center of Clinical Epidemiology (*Centre d'épidémiologie clinique, Hotel-Dieu, Paris, France*), respectively. Data entry occurred at enrolling sites by the investigator using a web-based data entry system.

An e-CRF (electronic Clinical Report Form) was developed by the clinical research unit using dedicated software (CleanWeb) to facilitate data control and monitoring. Each patient was assigned a unique ID that was used to index the e-CRF and related study documents.

All information required by the protocol had to be entered into the e-CRF. Data were recorded in the e-CRF as and when they were obtained. Any missing data had to be coded. In addition, the coherence of the entered data was immediately verified, because of inbuilt consistency checks.

Data monitoring was performed by the sponsor (*AP-HP; Délégation de la Recherche Clinique d'Ile de France, DRRC*). This project was classified as a C risk based on the AP-HP risk level classification, meaning that a high level of monitoring occurred, aimed at determining whether centers adhere to the protocol and the various circuits put in place to check the completeness of the e-CRF, to ensure patient safety (adverse events or serious adverse events), and follow-up in accordance with the applicable regulations. A clinical research associate (CRA) appointed by the sponsor is responsible for the good completion of the study and for collecting, documenting, recording, and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the Clinical Research and Innovation Department and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements. During these visits, the following elements are reviewed:

- Written consent
- Safety and rights of subjects are being protected
- Compliance with the study protocol and with the procedures defined therein
- Quality of data collected in the CRF: accuracy, missing data, consistency of the data with the *source* documents (medical files, appointment books, original copies of laboratory results, etc). Data are authentic, accurate, and complete
- Management of the treatments used

Visits to pharmacies were also carried out in a way that verified compliance with the pharmaceutical circuit.

Baseline characteristics, eligibility criteria, primary outcome, and serious adverse events reported in the CRF were systematically checked against the original chart for all research participants by the CRA. In addition, for one-third of the study population, all data reported in the CRF were validated against the patient's original chart. Serious adverse events and major protocol violations were reported to the DRRC, Agence Nationale de la Sécurité du Médicament (ANSM), and Comité de protection des personnes (CPP).

At the end of the study, after clarification of discrepancies (data cleaning) and data validation, the database was frozen and transmitted to the statistician following procedures established by the promoter.

Each patient participated in the trial for 90 days. Premature study withdrawal occurred on request of the patient or next of kin, and their reasons were recorded in the CRF and patient's medical file. Withdrawn patients were not replaced. Conversely, patients who were lost to follow-up or did not receive the randomly assigned treatment were not considered to be prematurely withdrawn from the trial.

Confidentiality

As for any clinical research supported by the AP-HP, processing of personal data complied with the methodological recommendations of the MR001 reference established by the French Data Protection Authority (*Commission Nationale de l'Informatique et des libertés*) in January 2006 for biomedical research. During and after the clinical research, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialized collaborators) are rendered nonidentifying. Under no circumstances shall the names and addresses of the participants involved be shown. Only the participant's initials are recorded, accompanied by an encoded number specific to the study indicating the order of enrollment. Moreover, all nominal data were erased on the copies of the source files that were used for documentation of the research.

Plans for Collection and Laboratory Evaluation and Storage of Biological Specimens for Genetic or Molecular Analysis in This Trial and Future Use

There were no genetic or molecular analyses planned.

Statistical Methods

Statistical Methods for Primary and Secondary Outcomes

The comparison between arms will be adjusted for stratification variables (ie, age group and center) as recommended [22] as well as the presence of acute brain injury at inclusion, which is a major prognostic variable. The center will be considered as a random effect. In addition, two analyses will be performed according to age category (cutoff at 65 years) and acute brain injury.

Finally, unadjusted analyses will be performed for sensitivity analyses. Binary outcomes will be analyzed using logistic regression. Absolute risk reductions will be obtained using a binomial model with an identity link [23]. For time-to-event outcomes, Kaplan-Meier survival curves or cumulative incidence curves will be estimated, and the treatment effect will be analyzed using Cox proportional hazards regression. For continuous outcomes, mixed linear regression will be used, possibly after variance stabilizing transformation.

All tests will be two-sided, at a 0.05 significance level.

Interim Analyses

We neither planned nor performed an interim analysis.

Methods for Additional Analyses (eg, Subgroup Analyses)

Adherence to national guidelines on anticonvulsant therapy, control of secondary brain insult, etiological investigations, and neurological monitoring was strongly recommended to minimize heterogeneity in GCSE management. Moreover, randomization was stratified by center to limit any center effect. Finally, both randomization and statistical adjustments are likely to minimize discrepancies between therapeutic groups.

Methods in Analysis to Handle Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

Statistical analysis will be performed according to the intent-to-treat principle, after all patients have completed the 90-day follow-up. Accordingly, all patients will be analyzed in the arm they were allocated to, regardless of the protocol deviations. In addition, missing outcome data will be imputed. Before data analysis, a detailed statistical analysis plan will be issued by the study statistician. A comprehensive report of the statistical analysis will be issued, following the Consolidated Standards of Reporting Trials (CONSORT) statement recommendations. Any change in the analysis plan will be justified in this final report.

Although no missing data are expected for the primary outcome, the maximum bias method will be used for the analysis of the primary outcome, replacing missing data with a success in the control arm and by a failure in the experimental arm. For secondary outcomes, missing data will be handled by multiple imputations by chained equations. A sensitivity analysis will be performed by analyzing only complete cases.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code

Persons with direct access in accordance with the laws and regulations in force, in particular, articles L.1121-3 and R.5121-13 of the public health code (eg, investigators, persons responsible for quality control, monitors, clinical research assistants, auditors, and others involved in collaborating on trials), take all necessary precautions to ensure the confidentiality of information relating to the tested drugs, the trial, the persons involved, especially with regard to their identity and the results obtained. The data collected by these people during quality controls or audits are then made anonymous.

Oversight and Monitoring

Composition of the Coordinating Centre and Trial Steering Committee

The steering committee includes Dr Hervé Outin, Dr Bernard Clair, and Professor Tarek Sharshar, who were the initiators of the project. The steering committee, with the biostatistician and the promoter's representatives (Direction de la recherché Clinique et du développement—DRCD-headquarters and DRCD—Unité de Recherche Clinique) appointed for this research, may decide during the trial the procedures to be followed, taking note of the recommendations of the independent supervisory committee. They will define the general organization and conduct of the research and coordinate the information. The steering committee has decided the methodology and will decide during the course of the trial the conduct to be followed in case of unforeseen matters and will monitor the progress of the research, particularly in terms of tolerance and adverse events.

Composition of the Data Monitoring Committee, Its Role, and Reporting Structure

The DSMB was established by the sponsor. Its primary mission was to monitor safety data. It was composed of experts in Critical Care Medicine, Neurology and Statistics, who were not involved in the trial but had full access to the raw data. The DSMB was composed of Dr Nicolas Melé (Neurology-Sainte-Anne Teaching Hospital, Paris), Dr Olivier Lesieur (Intensive Care Medicine- General Hospital—La Rochelle), and Dr Cédric Laouenan (biostatistics Bichat Teaching Hospital, Paris). The DSMB was operated in accordance with the sponsor's procedures. The DSMB worked in an advisory capacity only, and the sponsor retained all decision-making authority. This committee met once a year.

Adverse Event Reporting and Harms

A centralized phone and email center answered participating centers questions regarding patient eligibility or management and declaration of any adverse event during the trial period. A newsletter was sent monthly, informing participating centers on the number of patients included, main study constraints, and any protocol modifications.

Baseline characteristics, eligibility criteria, primary outcome, and serious adverse events reported in the CRF were systematically checked against the original chart for all research participants. In addition, for one-third of the study population,

all data reported in the CRF were validated against the patient's original chart. Serious adverse events and major protocol violations were reported for DRRC, ANSM, and CPP.

Frequency and Plans for Auditing Trial Conduct

All data, documents, and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audits is to ensure the quality of the study, the validity of the results, and compliance with the legislation and regulations in force.

The individuals in charge of managing and monitoring the study agreed to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

An audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study. For this study, we did not conduct an audit in any of the participating centers.

Plans for Communicating Important Protocol Amendments to Relevant Parties (eg, Trial Participants, Ethical Committees)

All substantial modifications to the protocol by the coordinating investigator were sent to the sponsor for approval. After approval, the sponsor obtained approval from the CPP (Research Ethics Committee) and authorization from the ANSM within the scope of their respective authorities before the amendment can be implemented.

The information note and the consent form have been revised, particularly in the case of a substantial amendment to the study.

Dissemination Plans

Neither the study sponsor nor the study funder had any role in designing the trial; managing, analyzing, or interpreting the data; writing the report; or deciding to submit the report for publication.

Patient and Public Involvement

No patient involved.

Availability of Data and Materials

In accordance with Good Clinical Practices (1) the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents, and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority; and (2) the investigators allow individuals in charge of monitoring quality control to have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code).

The AP-HP had full access to patients' charts and checked all data recorded in the electronic CRF against the original charts. All information required by the protocol had to be provided in the electronic logbook and an explanation provided by the investigator for each missing data.

Ethics Approval and Consent to Participate

The protocol was approved by all investigators on January 25, 2012. The scientific and financial aspects were independently approved by the national jury of the Clinical Research Hospital Program in 2010, and the Ministry of Health confirmed funding under contract number AOM10268. The protocol and qualification of all investigators were approved by the Ethics Committee (CPP) of Saint-Germain-en-Laye, France, on May 14, 2012. CPP allowed for the waiver of consent and deferred consent. The trial was registered at ClinicalTrials.gov (identifier NCT01791868; registered on May 2012).

Written informed consent had to be obtained from all participants. Written informed consent of the patient was obtained by the investigator of the participating center. In case of impaired consciousness, the investigator sought written consent from the next of kin. If the latter was not present, the patient could be included as deferred consent was approved by the Ethics Committee, according to the French law (Article L1122-1-2 du Code de la Santé Publique). As soon as the patient's status allowed, written informed consent for the continuation of the research and analyses of the data was obtained. A copy of the consent form was provided to every patient. The investigator had to keep the original copy in his archives for a minimum of 15 years. A third copy was archived by the promoter. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Results

Inclusion Status

The first patient was recruited on February 18, 2013, and the last patient on July 7, 2018. The study was never suspended. The study sponsor, steering committee, investigators, pharmacists, and study statisticians remained blinded to study treatments throughout the trial. Data management is ongoing. Release of the results is planned for the end of 2021.

Amendments

There were 10 amendments to the study protocol (Table 2). All amendments were approved by the investigators, the study statistician, AP-HP, CPP, and ANSM.

Table 2. Study amendments.

Amendment number	Description	Date (CPP[a]-ANSM[b])

1	• Withdrawal of center 13 Bordeaux
	• Modification of exclusion criteria
	  • Addition of sodium valproate derivatives
	  • Precision on the Prothrombin time and Factor V assay algorithm
	• Suppression of the ATICE[c] score
	• Changes made to the balance sheets:
	  • Adding a balance sheet module before inclusion
	  • Suppression of SAPS-II[d] at H0 at inclusion
	  • Modification of bilirubin at inclusion, in the first 24 hours, from the 2nd to the 15th day of inclusion
	  • Modification of the SAPS-II in the first 24 hours
	  • CPK[e] change in the first 24 hours
	  • Add GCS[f], RASS[g] score and CAM-ICU[h] score to the resuscitation output
	• Numbering changes
	• Amended Protocol v2.0 of 20/10/2012
		ANSM: 11/27/2012; CPP: 11/12/2012

2	• Modification of the principal investigators:
	  • Center 006 Beaujon, Dr Catherine Paugam-Burtz
	  • Center 009 Strasbourg, Dr Marie-Line Harlay
	  • Center 015 Pontoise, Dr Pascal Blanc
		CPP: 05/12/2013

3	• Possible randomization of patients even if the biological results were not obtained within the deadlines • Amended Protocol v3.0 of 24/06/2013	ANSM: 07/29/2013; CPP: 09/16/2013

4	• Modification of the inclusion criteria:
	  • Admission to resuscitation for GCSE[i], that is, persistent or recurrent generalized convulsions without regaining consciousness for more than 5 minutes, and antiepileptic management <6 hours (if the GCSE is controlled at the time of inclusion) or <24 hours (if the GCSE has persisted or recurs)
	  • Age≥18 years
	• Deletion of the SAPS-II at H12 calculation
	• Dosage of depakinemia at T0, T15 minutes, and T12 hours 15 minutes. The sampling and shipping procedures are being finalized; we will come back to each center to discuss how to put them into practice
	• Addition of two centers (Reunion Island and Montpellier)
	• Amended Protocol v4.0 of 26/02/2014
		ANSM: 05/02/2014; CPP: 07/01/2014

5	• Modification of the inclusion criterion on admission to intensive care
	• Modification of the criteria for noninclusion:
	  • Forms of states of epilepsy
	  • Liver test
	  • The prior taking of VPA
	• Sampling procedure
	• Amended Protocol v5.0 of 04/12/2014
		ANSM: 02/03/2015; CPP: 02/13/2014

6	• Changes to the emergency and prosecution ICFs (version 2)
	• Changes to the criteria for noninclusion
	  • No. 5: pregnancy, especially eclampsia - check by a systematic pregnancy test
	  • No. 11: patient under guardianship
	  • No. 12: patient who has already been included in this protocol and who has completed the clinical trial
	• During the 3-month checkup, it will be asked if a pregnancy was initiated between the inclusion and the visit at 3 months, and if so, the date of the beginning of the pregnancy will be collected
	• Amended Protocol v6.0 of 01/02/2016
	• ICF v2.0 of 01/02/2016
		ANSM: 03/18/2016; CPP: 05/24/2016

Amendment number	Description	Date (CPP[a]-ANSM[b])
7	• Modification of the principal investigator of the Lariboisière center, Pr Bruno Megarbane • Modification of blood sampling roadmaps • Amended Protocol v7.0 of 22/06/2016	CPP: 11/04/2016
8	• Extension of the 12-month inclusion period • Amended Protocol v8.0 of 02/01/2017	CPP: 04/29/2017
9	• Extension of the inclusion period by 6 months • Amended Protocol v9.0 of 19/02/2018	ANSM: 03/26/2018; CPP: 05/07/2018
10	• The addition of an exclusion criterion (patients of childbearing age between 18 and 50 years), following an ANSM alert	ANSM: 07/19/2018; CPP: 10/18/2018

[a]CPP: Comité de protection des personnes (institutional review board).

[b]ANSM: Agence Nationale de Sécurité du Medicament (French National Agency for Drugs Safety).

[c]ATICE: adaptation to the intensive care environment.

[d]SAPS-II: Simplified Acute Physiology Score II.

[e]CPK: creatine phosphokinase.

[f]GCS: Glasgow Coma Scale.

[g]RASS: Richmond Agitation-Sedation Scale.

[h]CAM-ICU: Confusion Assessment Method for the Intensive Care Unit.

[i]GCSE: generalized convulsive status epilepticus.

Study Follow-Up

The DSMB met five times. The DRRC organized data monitoring and quality audits. Baseline characteristics, eligibility criteria, primary outcome, and serious adverse events reported in the CRF were systematically checked against the original chart for all research participants. In addition, for one-third of the study population, all data reported in the CRF were validated against the patient's original chart. Serious adverse events and major protocol violations were reported for DRRC, ANSM, and CPP. The study coordinator had quarterly face-to-face meetings with the DRRC, AP-HP, and independent pharmacists to monitor trial conduct according to the highest standard for protection of research participants. All randomized patients completed follow-up for the primary outcome and 180-day mortality data.

Discussion

Novelty of the Study

This multicenter, parallel-group, double-blind RCT was designed to determine whether VPA improves the outcome of patients admitted to the ICU for GCSE as an adjuvant therapy to recommended first- and second-line AEDs. This hypothesis was based on the antiepileptic and potential neuroprotective properties of VPA, which could improve seizure control and minimize GCSE-related additional brain injury. The amendments made to the protocol were aimed at improving patient recruitment.

One may argue that another AED could have been proposed instead of VPA. We opted for VPA mainly because it was not recommended by the national guidelines at the time of study design as second-line AED for GCSE, enabling us to avoid the risk of overdose and to undertake a stepwise strategy. In addition, we did not choose to assess levetiracetam, as it was being tested as adjuvant therapy to the first-line AED [5]. Adjuvant levetiracetam was not beneficial. Moreover, VPA is well tolerated and is not contraindicated with recommended second-line and most maintenance AEDs. The ESETT trial does not undermine the relevance of our RCT, as it showed that VPA is as efficient as levetiracetam and fosphenytoin as a second-line AED [16]. Therefore, it is likely that VPA will not be the second-line AED administered in many patients with GCSE, who could then be treated with VPA, if our RCT shows a benefit of VPA. Finally, if our RCT is positive, it would be necessary to test another AED as adjuvant treatment.

Randomization Procedure

Selection biases were minimized and homogeneity between the two groups was ensured by the double-blind design. First, the random list for allocating interventions was computer-generated by an independent statistician. Randomization was centralized through a secured website using permutation blocks, the size of which was unknown to research participants. Second, a centralized procedure for masking VPA and placebo was used; pharmacists received sealed boxes containing either treatment in identical forms. Reconstitution of the treatment was done by an *out-of-protocol* pharmacist or nurse. Therefore, research participants were unable to anticipate or identify patients' allocation. Third, hospital staff, investigators, pharmacists, and outcome assessors remained blinded for short- and long-term outcomes until public release of trial findings, to prevent any detection biases. Finally, there were no obvious attrition biases. No patient was lost to follow-up for the primary end point. Although reporting the study design and statistical analysis plan after completion of patient recruitment might be a potential source of bias, this was necessary to detail the way the trial was conducted and amended. We neither planned nor performed an interim analysis.

End Points

The primary end point (ie, discharge from hospital at day 15) might not be sufficiently specific but also liable to various biases. Indeed, hospital discharge depends on factors related to the patient's social and economic condition, as well as on hospital organization and health care facilities. However, randomization theoretically limits the risk of differential bias between the VPA and placebo groups. Therefore, we assumed that hospital status at day 15 would reflect the control of the epileptic process, its neurotoxic consequences, and underlying cause. Finally, an improvement in hospital status at day 15 is medically, socially, and economically relevant. A recent French clinical trial in a comparable population found length of hospital stay of about 19 days [9]. Although the median length of hospital stay was 3 days in a recent trial comparing VPA to levetiracetam and fosphenytoin, the included population is not comparable to our cohort in terms of age, course, and severity of GCSE [16]. Indeed, the included patients were 2 years old or more, and only half of the included patients were admitted to the ICU [16].

Our secondary end points are conventional, including information on the GCSE course such as duration, progress to refractory GCSE, EEG characteristics, and long-term control of epilepsy. We acknowledge that the duration of seizure would have been better assessed using a continuous EEG;, however, this was not available in most participating centers. It is likely that the clinical assessment at 3 months will be missing for a large number of patients. Indeed, in recent trials, less than 30% of the included patients were assessed at 3 months for epileptic and cognitive status, indicating the difficulty of follow-up of these patients [9].

GCSE

One may argue that the studied population could be heterogeneous in terms of severity, underlying cause, and pre-ICU management of GCSE. Indeed, both mechanically ventilated and nonmechanically ventilated patients were included, despite the fact that the need for mechanical ventilation mainly reflects the depth of consciousness impairment, likely to be related to the early severity of GCSE or its etiology. As age and acute brain injury are the two main prognostic factors in GCSE, we planned to adjust statistical analysis on these demographic and etiological predictors. Adherence to national guidelines on anticonvulsant therapy, control of secondary brain insult, etiological investigations, and neurological monitoring was strongly recommended to minimize heterogeneity in GCSE management. Moreover, randomization was stratified by center to limit any center effect. Finally, both randomization and statistical adjustments are likely to minimize discrepancies between therapeutic groups.

Therefore, the VALSE multicenter RCT is appropriately designed to address an original issue: the role of VPA as an adjuvant neuroprotective therapy in GCSE. VALSE aims to include a representative population of patients admitted to the ICU for GCSE, who will go on to receive standardized GCSE management. The objective of obtaining a 20% increase in the rate of patients with GCSE discharged alive from hospital at day 15 is clinically relevant and is also easily achievable and assessable. The trial is designed to integrate adjustments on the main outcome predictors and to collect potential confounding factors. Therefore, VALSE will provide reliable and relevant data that might improve ICU management of GCSE. At present, data analysis is still pending, and all parties involved in the trial remain blinded.

Strengths and Limitations of the Study Summary

This is the first multicenter randomized double-blind controlled trial that assesses whether VPA can be useful as an adjuvant therapy to recommend first- and second-line AED to improve the outcome of GCSE. This RCT has been designed and powered to address this major issue, as GCSE is still associated with high mortality and morbidity. The trial is based on a clinically relevant primary end point, that is, hospital status at day 15, as it reflects the control of the epileptic process, its neurotoxic consequences, and underlying cause. This trial concerns only adult patients admitted to the ICU for GCSE.

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Authors' Contributions

TS, BC, and HO conceived the study. TS, OB, NH, EA, AM, BC, BR, and HO each made substantial contributions to study design, have been involved in drafting the manuscript and revising it critically for intellectual content, and have given final approval of the version to be published. RP and LG provided statistical input and contributed to the study design. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT Checklist (2010).
[PDF File (Adobe PDF File), 100 KB - resprot_v10i2e22511_app1.pdf]

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Abbreviations

AED: antiepileptic drug
ANSM: Agence Nationale de la Sécurité du Médicament (National Agency for Drugs Safety)
AP-HP: Assistance Publique-Hôpitaux de Paris
CPP: Comité de protection des personnes (Institutional Review Board)
CRA: clinical research associate
DRCD: Direction de la recherché Clinique et du développement
DRRC: Direction Régionale de la Recherche Clinique (Regional Clinical Research Agency)
DSMB: Data Safety Monitoring Board
EEG: electroencephalogram
ESETT: Established Status Epilepticus Treatment Trial
GCS: Glasgow Coma Scale
GCSE: generalized convulsive status epilepticus
ICU: intensive care unit
RCT: randomized clinical trial
VALSE: valproic acid as an adjuvant treatment for generalized convulsive status epilepticus
VPA: valproic acid

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Protocol

Mobile Health–Supported HIV Self-Testing Strategy Among Urban Refugee and Displaced Youth in Kampala, Uganda: Protocol for a Cluster Randomized Trial (Tushirikiane, Supporting Each Other)

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Abstract

Background: HIV is the leading cause of mortality among youth in sub-Saharan Africa. Uganda hosts over 1.43 million refugees, and more than 83,000 live in Kampala, largely in informal settlements. There is limited information about HIV testing uptake and preferences among urban refugee and displaced youth. HIV self-testing is a promising method for increasing testing uptake. Further, mobile health (mHealth) interventions have been effective in increasing HIV testing uptake and could be particularly useful among youth.

Objective: This study aims to evaluate the feasibility and effectiveness of two HIV self-testing implementation strategies (HIV self-testing intervention alone and HIV self-testing combined with an mHealth intervention) in comparison with the HIV testing standard of care in terms of HIV testing outcomes among refugee/displaced youth aged 16 to 24 years in Kampala, Uganda.

Methods: A three-arm cluster randomized controlled trial will be implemented across five informal settlements grouped into three sites, based on proximity, and randomization will be performed with a 1:1:1 method. Approximately 450 adolescents (150 per cluster) will be enrolled and followed for 12 months. Data will be collected at the following three time points: baseline enrollment, 8 months after enrollment, and 12 months after enrollment. Primary outcomes (HIV testing frequency, HIV status knowledge, linkage to confirmatory testing, and linkage to HIV care) and secondary outcomes (depression, condom use efficacy, consistent condom use, sexual relationship power, HIV stigma, and adolescent sexual and reproductive health stigma) will be evaluated.

Results: The study has been conducted in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines. The study has received ethical approval from the University of Toronto (June 14, 2019), Mildmay Uganda (November 11, 2019), and the Uganda National Council for Science and Technology (August 3, 2020). The Tushirikiane trial launched in February 2020, recruiting a total of 452 participants. Data collection was paused for 8 months due to COVID-19. Data collection for wave 2 resumed in November 2020, and as of December 10, 2020, a total of 295 participants have been followed-up. The third, and final, wave of data collection will be conducted between February and March 2021.

Conclusions: This study will contribute to the knowledge of differentiated HIV testing implementation strategies for urban refugee and displaced youth living in informal settlements. We will share the findings in peer-reviewed manuscripts and conference presentations.

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KEYWORDS

adolescents and youth; implementation research; HIV testing; mobile health; refugee; Uganda

Introduction

HIV is the leading cause of death among young people globally and the main cause of death among adolescents and young people in sub-Saharan Africa [1]. In sub-Saharan Africa, half of newly infected adolescents and young people are girls [2,3]. Uganda's 2018 HIV prevalence among adolescent girls was over double that of adolescent boys, with 14,000 young women aged 15 to 24 reporting new HIV infections compared with 5000 young men [4]. Only 53.6% of adolescent girls in Uganda know their HIV status, and this is far below the Joint United Nations Program on HIV/AIDS (UNAIDS) goal of 90% of persons living with HIV knowing their status by 2020 to achieve an AIDS-free generation [5,6]. HIV testing is a critical entry point for access to HIV prevention and control solutions, specifically access to antiretroviral therapy, which is vital for preventing onward HIV transmission [7,8].

There are more than 79.5 million forcibly displaced persons worldwide [9], and refugee and displaced persons are largely underserved by current HIV prevention strategies [10]. HIV vulnerabilities among displaced/refugee adolescents are shaped by a complex interplay of factors, including poverty, violence, host community HIV prevalence, urbanization, HIV testing and care access, and living conditions [10-12]. Uganda hosts more than 1.4 million refugees [13], with 62% aged below 18 years [14]. Kampala, Uganda's capital city, hosts over 83,000 refugees [13], and 27% are aged 15 to 24 years [15]. It is important to explore HIV testing needs among urban refugees. There is a global trend of refugee urbanization, with refugees increasingly moving from refugee settlements to urban areas for employment and education opportunities [16-19]. Urban refugees and displaced adolescents and young people are at the nexus of HIV disparities among adolescents, displaced persons, and slum dwellers, and yet, there are knowledge gaps in the optimal HIV prevention for these groups [20,21].

HIV self-testing is a promising strategy to engage marginalized populations [20]. HIV self-testing can represent a convenient and private option, and may reduce stigma compared with clinic-based testing [21]. HIV self-testing has demonstrated acceptability, feasibility, and usability, with minimal harm, and is associated with increased HIV testing among individuals, including adolescents across Southern Africa and Malawi [20,22,23]. Mobile health (mHealth) strategies (digital media on mobile devices) have been efficacious in improving antiretroviral therapy adherence and HIV and sexually transmitted infection testing, and are relevant for the way youth learn and socialize [24-26]. In particular, two-way SMS-based mHealth interventions that are interactive and supportive have been found to be more efficacious in increasing adherence than one-way messages/reminders [27,28]. However, few studies have integrated mHealth into HIV self-testing delivery with adolescents or focused on optimal HIV self-testing delivery strategies with displaced/refugee youth.

Global HIV self-testing knowledge gaps include strategies to facilitate linkage to confirmatory testing and HIV care for persons testing positive [29]. Identifying strategies to promote linkage to HIV care is essential to realize the public health impact of HIV self-testing [30]. A recent systematic review reported a dearth of evidence-based strategies for linkage to HIV care following positive HIV self-testing results among adolescents [31]. This is an urgent knowledge gap that we aim to address with bidirectional text messaging strategies. We also aim to address the lack of evidence regarding the acceptability and feasibility of HIV self-testing among refugee and displaced persons [32]. In Uganda, HIV self-testing was feasible and acceptable; demonstrated the ability to identify new HIV diagnoses among men who have sex with men [33]; and was associated with increased recent and frequent testing among sex workers [34].

Tushirikiane, roughly translating to supporting each other in Swahili, aims to address these knowledge gaps among displaced and refugee adolescent youth in Uganda by testing a mHealth support strategy alongside HIV self-testing delivery to increase routine HIV testing uptake. The findings can be used to inform the implementation and scale-up of HIV self-testing programs with displaced and refugee adolescents across Uganda, sub-Saharan Africa, and other humanitarian contexts.

Methods

Study Aim and Objectives

This study aims to evaluate the feasibility and clinical effectiveness of two HIV self-testing delivery approaches (HIV self-testing intervention alone and HIV self-testing combined with a two-way supportive SMS mHealth intervention) in comparison with the standard of care in terms of HIV testing uptake among refugee and displaced youth aged 16 to 24 years in Kampala, Uganda. The specific objectives of this study are to determine the effectiveness of the interventions on the following criteria: (1) increased frequency of HIV testing; (2) increased knowledge of HIV status; (3) increased linkage to confirmatory testing (for those with an HIV positive self-test); and (4) increased linkage to HIV care (for persons testing positive for HIV in HIV self-testing and confirmatory testing). Secondary outcomes include (1) depression, (2) condom use self-efficacy, (3) consistent condom use, (4) sexual relationship power, (5) HIV stigma, and (6) adolescent sexual and reproductive health (SRH) stigma.

Study Design

To evaluate the intervention effectiveness, we will conduct a cluster randomized controlled trial (cRCT), where informal settlements are randomized. The clusters include five informal settlements grouped into three sites that are randomized in a 1:1:1 method to one of three study arms. Although outcome data will be collected at the level of the individual, we selected cluster randomization over individual randomization because the intervention is implemented at the settlement level. A cluster randomized design addresses threats of internal validity. It reduces the possibility of experimental contamination due to the shared social and physical environments between youth in the same or nearby informal settlements [35]. Data will be collected at the following three time points: baseline enrollment into the intervention, 8 months after enrollment, and 12 months after enrollment.

Study Setting

This trial is being conducted in Kampala, which is the capital of Uganda. Uganda's progressive refugee policies provide refugees and displaced persons in refugee settlements a plot of land. Yet, with the 2006 Uganda Refugee Law, refugees forgo rights to humanitarian assistance if they leave these refugee settlements [16,17]. The convergence of this law with refugee urbanization contributes to extreme poverty among Kampala's urban refugees, creating slum environments [16,36,37]. Among Ugandan youth aged 15 to 19 years, the HIV prevalence is estimated at 4% [38]. However, among vulnerable youth living in Kampala's informal settlements, this is estimated at 37.2% [39]. The five informal settlements selected for this study are grouped into three sites based on their proximity to one another (Kabalagala/Kansanga, Katwe/Nsambya, and Rubaga) and have been purposively chosen because these communities host many displaced/refugee persons in Kampala [16,18,36,37]. We focused on these refugee communities, largely from the Democratic Republic of Congo, Rwanda, and Burundi [13], where refugees continue to arrive, owing to similarities in socioeconomic status and living conditions, health care access, and shared languages (French and Swahili).

Study Population and Eligibility Criteria

A minimum of 432 youth (144 per cluster) between the ages of 16 and 24 years will be enrolled into this study and followed for 12 months. Individuals are eligible for inclusion if they meet the following criteria: (1) currently live in one of the following five informal settlements in Kampala: Kabalagala, Kansanga, Katwe, Nsambya, and Rubaga; (2) identify as a refugee/displaced person or have refugee/displaced parents; (3) are aged 16 to 24 years; (4) speak English, Swahili, Luganda, French, Kinyarwanda, or Kirundi; and (5) own a mobile phone. A brief eligibility screening (via phone, in person, or via WhatsApp) with interested participants will be conducted, asking self-reported HIV serostatus. Only participants reporting an HIV-negative status (baseline serostatus) will be eligible to participate.

Participant Recruitment and Retention

The project team includes a refugee youth-focused community-based nongovernment organization that implements economic empowerment programs for refugee youth and holds expertise on youth engagement. The team also involves academics and practitioners from the Ministry of Health and HIV clinics. Additionally, this project engages peer navigators who identify as refugees or displaced persons (aged 18-24 years) to help with participant recruitment and to provide feedback on the study design and survey. Twelve peer navigators (six young women and six young men) recruited for this study have been identified by community-based collaborators, have experience working in the various study communities as health or peer educators, and are deeply respected and connected in their communities.

Participants will be recruited within each settlement using purposive methods, including word-of-mouth and venue-based sampling at refugee agencies and community events. Peer navigators will conduct peer-driven recruitment at each site, sharing youth-designed flyers for potential participants to contact (via email and mobile number) peer navigators to join the study. Community collaborators and peer navigators will facilitate participant retention. Specifically, peer navigators will use multiple study reminder strategies (eg, social media and texts) to maintain engagement. We will utilize existing outreach and services by local refugee agencies and community partners.

Patient and Public Involvement in Research

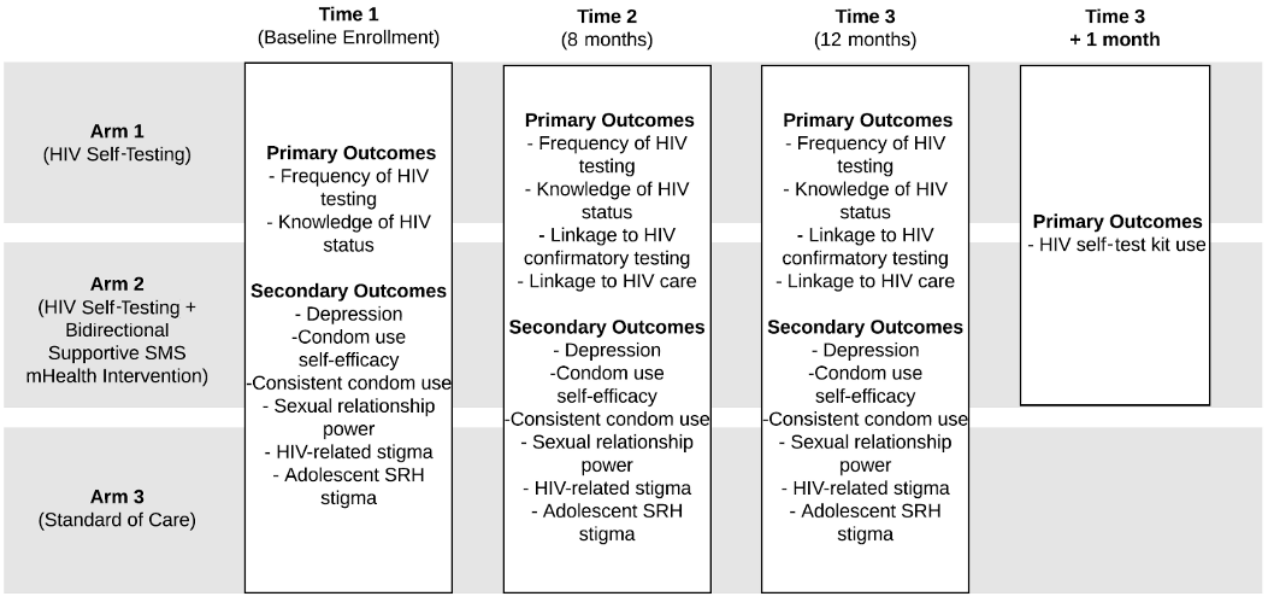
Study collaborators at Young African Refugees for Integral Development (YARID) have been involved in the research from the initial stage of developing the research question and focus. We conducted a preliminary exploration of the needs and priorities of refugees and youth with YARID prior to developing this study, and those findings indicated a low prevalence of lifetime HIV testing, which reinforced the importance of this study. Peer navigators, who themselves are urban refugee youth living in Kampala's informal settlements, provided feedback for the study design and outcomes; conducted recruitment and active engagement with study participants for retention; supported study implementation by facilitating linkages between

participants and data collectors; pilot tested the survey to assess the time required to participate in the research; and will engage in multiple dissemination strategies for community members (eg, providing input for infographic design and sharing community reports with community stakeholders including the Ministry of Health).

Intervention Description

The study has been designed as a three-arm cRCT consisting of two treatment arms and one control arm. Clusters will be randomized to one of the following three arms: (1) HIV self-testing, (2) HIV self-testing plus mHealth strategies (supportive text messages), and (3) standard of care (clinic-based HIV testing). The trial arms and interventions are described below and summarized in Figure 1.

Figure 1. Study design for Tushirikiane, a cluster randomized trial of a mobile health (mHealth) HIV self-testing strategy among urban refugee and displaced youth in Kampala, Uganda. SRH: sexual and reproductive health.



Treatment Arm 1: HIV Self-Testing Intervention

Participants in this arm will be enrolled into the HIV self-testing intervention group and will receive HIV self-testing kits so they can perform HIV testing. At baseline enrollment, the peer navigator will provide an HIV self-testing kit (OraQuick Rapid HIV-1/2 Antibody Test, OraSure Technologies), which includes an oral swab test stick and tube solutions, a written detailed step-by-step description of how to correctly use the HIV self-testing kit, pictorial and written guides for the HIV self-testing kit, condoms and lubricant, information booklets on HIV and testing, and referral cards with the addresses and phone numbers of local clinics for confirmatory testing. The cards will also have the peer navigator's phone number to allow participants to contact the peer navigator if they need additional information on how to use the kit or need support to go for confirmatory tests at local clinics. Instructions for the kit are in French, Luganda, Swahili, Kirundi, Kinyarwanda, and English and have been pilot tested for clarity and comprehensiveness with peer navigators. A 24-hour contact number will be provided to participants to text if/when they have questions. At follow-up visits, peer navigators will check in with participants about the HIV self-testing kit, distribute another HIV self-testing kit and condoms/lubricant, and screen for adverse events (eg, negative HIV self-testing–related experiences).

Treatment Arm 2: HIV Self-Testing Plus mHealth

Participants in this arm will be enrolled into the HIV self-testing group (as above) and on a web-based SMS platform hosted by WelTel [40,41]. WelTel is a nonprofit agency developing the mHealth intervention, in which participants receive weekly supportive bidirectional text messages asking how they are doing [42]. Participants are requested to reply "fine" or "not fine," and those responding "not fine" will be contacted with support by a peer navigator. Participants in this arm will discuss the weekly WelTel messages with peer navigators and respond to the "not fine" messages within 2 days. If they do not reply to the initial SMS message within the specified timeframe, a peer navigator will follow up with them during that week. The WelTel system will manage the SMS intervention on a structured mobile phone platform (all SMS interactions are logged). WelTel's two-way texting mHealth intervention may prompt participants to engage in HIV self-testing and/or to engage peer navigator support in decision making regarding HIV self-testing practices.

Arm 3: Standard of Care

Participants in this arm will be enrolled into a standard of care group. Participants will receive information about HIV testing, care, and support services at local clinics. They will be provided a pamphlet of information about HIV and HIV prevention strategies (written in French, English, Luganda, Kirundi, Kinyarwanda, and Swahili).

Outcomes

Primary Outcomes

The primary outcomes measured in this trial are as follows:

1. Changes in HIV testing frequency: This is measured as participants' self-reported last HIV test. To capture changes, this measure is assessed at all three study time points (baseline [Time 1], 8 months [Time 2], and 12 months [Time 3]).
2. Changes in knowledge of HIV status: To address social desirability bias challenges regarding self-reported HIV serostatus, multiple steps are employed. First, at each timepoint (Time 1, Time 2, and Time 3), participants are asked their current HIV status. At Time 3, participants are offered a completely voluntary rapid HIV test. Knowledge of HIV status will be assessed as correct for persons who agree to take the rapid test and correctly report their HIV status (prior to receiving the result).
3. Changes in linkage to confirmatory HIV testing: Participants in trial arms 1 and 2 (HIV self-testing and mHealth HIV self-testing intervention) are asked at Time 2 and Time 3 if they used their HIV self-testing kit. For those who respond affirmatively, they will be asked the result, and those who report a positive result will be asked if and where they received confirmatory testing.
4. Changes in linkage to HIV care: Participants who seroconvert during the study are asked the frequency of accessing HIV care service since diagnosis. This will be assessed at Time 2 and Time 3.
5. HIV self-testing kit use: To understand the frequency of HIV self-testing kit use and to reduce social desirability bias regarding HIV self-testing kit use, participants in trial arms 1 and 2 will be followed up 1 month after Time 3 to request for purchasing unused kits back. Participants will not be informed of this as an option prior to this time.

Secondary Outcomes

Secondary outcomes include changes in depression assessed using the Patient Health Questionnaire-9 items (PHQ-9) [43]; condom use self-efficacy measured with the Condom Use Efficacy Scale [44,45]; consistent condom use frequency assessed by asking participants if they used condoms every time (consistently) in the past 3 months; sexual relationship power assessed using the relationship control subscale from the Sexual and Reproductive Power Scale [46]; perceived HIV-related stigma with the perceived HIV-related stigma subscale of Steward et al [47]; and adolescent SRH stigma assessed with the Ugandan Adolescent SRH Stigma Scale [48] adapted from the Adolescent SRH scale by Hall et al [49].

Sample Size and Power Analysis

Cluster sizes of 130 per group (n=390) are required to have 80% power (P<.05) to detect a 25% difference (39% [5] vs 64% tested) in HIV testing between any two groups from three pairwise comparisons (control vs arm 1, control vs arm 2, and arm 1 vs arm 2) for an odds ratio of 1.66. We assume an intraclass correlation coefficient of 0.013 based on HIV research on condom use in sub-Saharan Africa [50]. With 10% attrition, 432 participants (144 per cluster) are required. Computations were performed using RStudio version 3.3.0 (RStudio Team), based on formulae for multiple comparisons of proportions, and adjusted for design effect [51].

Data Collection and Management

Outcome data will be collected at three time points as identified using a tablet-based survey application (QuickTapSurvey, Formstack for Time 1; SurveyCTO, Dobility for Time 2 and Time 3). Baseline data to characterize the study population include demographics and sexual history, which will be collected using these tools. Data will be automatically uploaded onto a secure password-protected server using an SSL certificate and will remain encrypted when not in use.

Data Analysis Plan

Analysis and reporting will be conducted in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines [52] (Multimedia Appendix 1). The analyst will be blinded to group allocation. A flow diagram will be used to illustrate patient flow (screening, randomization, allocation, and follow-up). Baseline data will be reported for all three arms and summarized as mean (SD) or median (first quartile, third quartile) for continuous variables and as count and number (percentage) for categorical variables. Primary analysis will involve intention-to-treat analysis (data from participants will be analyzed according to their allocation, irrespective of whether they actually received that intervention). Between-group comparisons will be performed using multilevel mixed effect logistic or linear regression models (to account for clustering), depending on which outcome is being evaluated. For these models, the intervention group will be entered as a fixed effect. The level of significance will be set at α=.05, but adjusted using the Bonferroni method for secondary outcomes [53]. The results will be expressed as odds ratios or mean differences as appropriate, accompanied by 95% CIs and P values. We will conduct adjusted analysis for the primary outcome (changes in HIV testing frequency) to investigate the role of various covariates in the relative effect. We will build mixed effect multilevel logistic regression models with the intervention group as the independent variable and HIV testing uptake in the past 3 months (yes/no) as the dependent variable. Covariates (eg, age) will be entered as a block. We will explore gender differences in primary and secondary intervention outcomes.

Results

The Tushirikiane trial protocol has been approved by the Research Ethics Board of the University of Toronto (June 14, 2019), Mildmay Uganda Research Ethics Committee (November 11, 2019), and Uganda National Council for Science & Technology (August 3, 2020). The trial is registered at ClinicalTrials.gov (NCT04504097). The Tushirikiane trial launched on February 15, 2020, recruiting a total of 452 participants. Data collection was paused for 8 months owing to COVID-19. Data collection for wave 2 resumed on November 18, 2020, and as of December 10, 2020, a total of 295 participants have been followed up. Data collection for the third, and final, wave will be conducted between February and March 2021. The final follow-up to purchase back unused HIV self-testing kits will occur in June 2021.

Discussion

Study Implications

Although Uganda's Ministry of Health currently recommends HIV self-testing, there are currently no national guidelines surrounding the optimal delivery of HIV self-testing for adolescents, young people, or refugees/displaced persons. This study is unique in Uganda and elsewhere [32] to outline a path to reducing the barriers to HIV testing faced by urban refugee and displaced youth living in slums and informal settlements. Refugee and displaced adolescents and youth are often not included in HIV and other SRH programs [54-56]. There is also a need for age and gender-disaggregated data to inform SRH programs with refugee and displaced youth, and our study will provide such data [57]. Our research has the potential to advance the HIV prevention and care cascades that involve the integration of social science, epidemiological, and health behavior theories in interventions to increase demand for (through HIV knowledge and peer support) and supply of HIV testing and linkage to HIV care and treatment among refugee and displaced youth [58-60]. Routine HIV testing is key to these cascades [61,62]. We address the World Health Organization (WHO) 2016-2021 HIV Global Health Sector Strategies to address youth key populations; low- and middle-income countries; and targeted HIV testing [58,59]. Community partners and knowledge users will be involved in all stages of trial design, conduct, and analysis, as well as dissemination. Should findings indicate increased effectiveness of HIV self-testing over traditional HIV testing strategies, these partnerships will facilitate the scale-up of HIV self-testing implementation for marginalized communities in Uganda.

Ethics

The study population includes young adults (aged 16 years or above) capable of providing informed consent; Uganda's HIV and AIDS Prevention and Control Act permits youth aged 12 years or above to independently access HIV testing and counselling without parental permission. All participants will receive information about the study before being enrolled to ensure understanding of rights for refusal/withdrawal, study processes, and expectations, and to provide written informed consent. At any time during the study data collection period, participants can withdraw from the study before completing the interview with no adverse consequences on the care or services they receive. All data will be stored on password-protected computers. To maintain confidentiality, all participants will be given a unique case ID, and no personal identifying information will be stored with the study data.

The risks associated with the Tushirikiane trial are reasonable. Physical risks exist for participants who conduct HIV testing (standard of care) and/or confirmatory testing (HIV self-testing and HIV self-testing plus mHealth). However, in all cases, HIV testing and confirmatory testing are optional. Further, the results will only be linked to participant ID. Second, an HIV diagnosis may cause stress, anxiety, and fear of stigmatization among participants. Such risks will be mitigated by the clinics conducting testing, which offer confidential pretest and posttest counselling, as well as HIV treatment. All participants will also be provided with a list of community resources regardless of HIV testing outcomes.

Any adverse event will be reported by the peer navigator to the research assistant, who will fill out an adverse event reporting form (Adverse Event Reporting Form) and adverse event narrative form if appropriate (Adverse Event Narrative Form). Adverse events can also be directly reported by study participants via a Tushirikiane hotline, which will be shared with the study participants at enrollment (Template HIV Counselor Hotline Card), can be called toll free, and will be monitored by trained HIV counselors throughout the duration of the study. Any adverse event requiring a narrative form will be reported to the principal investigators within 24 hours.

Dissemination

Regardless of the outcomes, trial results will be published in peer-reviewed scientific journals and disseminated via many methods. The findings will be disseminated (1) to academics and researchers in HIV, sexual health, social work, and adolescent health via presentations at key scientific conferences; (2) to international collaborating organizations, with executive summaries and reports disseminated to UNAIDS, WHO, and United Nations High Commissioner for Refugees; (3) to local organizations, with reports disseminated to the Ugandan National AIDS Control Program, Ministry of Health, and our collaborators; and (4) through a research brief with highlights of the findings in all five languages.

Data Sharing

The final data set will consist of self-reported demographic and social-ecological data from interviews with the participants and laboratory data from HIV confirmatory tests for HIV-positive individuals. Even though the final data set will be deidentified before release for sharing, it is possible to deductively disclose subjects using a combination of common characteristics. Therefore, to access our data, users need to meet our data-sharing agreement that provides for (1) the ability to secure ethics approval from both the user's institution and the University of Toronto research ethics board; (2) a commitment to use the data solely for research purposes and to not identify any individual participant; (3) a dedication to securing the data using appropriate computer technology such as encryption; and (4) a commitment to destroying or returning the data after analyses are completed.

Strengths and Limitations of This Study

The Tushirikiane study is unique in exploring HIV self-testing feasibility and uptake among urban refugee and displaced youth in Kampala, Uganda. Little is known about the preferred HIV testing strategies in this population.

Our three-arm cRCT longitudinal design will allow us to examine changes over time and assess if HIV self-testing alone or HIV self-testing alongside an mHealth component (bidirectional supportive SMS) increases HIV testing uptake and status awareness in comparison with the standard of care.

Our cluster randomization by informal settlements ("slums") mitigates threats to internal validity and experimental contamination due to the shared social and physical

environments between youth in the same or nearby informal settlement.

The primary study limitations are loss to follow-up, missing data points, and study delays due to COVID-19.

Our research will provide gender- and age-stratified analyses, as well as an understanding of the potential added benefits of SMS support strategies alongside HIV self-testing to inform differentiated HIV testing strategies among urban refugee and displaced youth, which can be adapted for diverse contexts.

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Authors' Contributions

Study design: CL, MO, DKM, RH, SM, RL, PK, KM, SB, LM, and TPN. Data collection: DKM, RH, SM, UMK, and TPN. Data management: CL, MO, DKM, RH, IB, RL, UMK, ML, and CM. Manuscript writing: CL, MO, IB, and ML. Manuscript editing: CL, MO, DKM, RH, IB, SM, RL, PK, UMK, ML, KN, CM, SB, TPN, and LM.

Conflicts of Interest

RL is an academic physician-researcher and also has interests in a non-profit and private company social enterprise, WelTel Inc., that develops and provides digital health software. He is not being paid or otherwise compensated by WelTel for this project. No other authors declare a conflict of interest.

Multimedia Appendix 1
CONSORT-EHEALTH checklist (V.1.6.1).
[PDF File (Adobe PDF File), 416 KB - resprot_v10i2e26192_app1.pdf]

Multimedia Appendix 2
CIHR Peer Reviews.
[PDF File (Adobe PDF File), 16 KB - resprot_v10i2e26192_app2.pdf]

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Abbreviations

cRCT: cluster randomized controlled trial
SRH: sexual and reproductive health
UNAIDS: Joint United Nations Program on HIV/AIDS
WHO: World Health Organization
YARID: Young African Refugees for Integral Development

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Protocol

mHealth-Supported Delivery of an Evidence-Based Family Home-Visiting Intervention in Sierra Leone: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Past trauma and exposure to violence have been related to poor emotion regulation and household violence, which can have persistent mental health effects across generations. The Family Strengthening Intervention for Early Childhood Development (FSI-ECD/called Sugira Muryango in Rwanda) is an evidence-based behavioral home-visiting intervention to promote caregiver mental health, positive parenting practices, and early childhood development among families facing adversity. In Sierra Leone and other lower- and middle-income countries, mobile health (mHealth) technology has the potential to improve health care delivery and health outcomes.

Objective: This study aims to (1) apply a user-centered design to develop and test mHealth tools to improve supervision and fidelity monitoring of community health workers (CHWs) delivering the FSI-ECD and (2) conduct a pilot randomized controlled trial of the FSI-ECD to assess feasibility, acceptability, and preliminary effects on caregiver mental health, emotion regulation, caregiving behaviors, and family violence in high-risk families with children aged 6-36 months in comparison with control families receiving standard care.

Methods: We will recruit and enroll CHWs, supervisors, and families with a child aged 6-36 months from community health clinics in Sierra Leone. CHWs and supervisors will participate in 1 problem analysis focus group and 2 user interface/user experience cycles to provide feedback on mHealth tool prototypes. Families will be randomized to mHealth-supported FSI-ECD or standard maternal and child health services. We will collect quantitative data on caregiver mental health, emotion regulation, caregiving behaviors, and family functioning at baseline, postintervention, and 3-month follow up. We will use a mixed methods approach to explore feasibility and acceptability of mHealth tools and the FSI-ECD. Mixed effects linear modeling will assess FSI-ECD effects on caregiver outcomes. Cost-effectiveness analysis will estimate costs across FSI-ECD versus standard care.

Results: Funding for this study was received from the National Institutes of Mental Health on August 17, 2020. Institutional Review Board approval was received on September 4, 2020. Data collection is projected to begin on December 15, 2020.

Conclusions: This study will provide important data on the feasibility, acceptability, and preliminary efficacy of mHealth-supported delivery of an evidence-based family home-visiting intervention in a postconflict LMIC.

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KEYWORDS

mHealth; caregiver mental health; family functioning; early childhood development; community health workers

Introduction

Background

Exposure to war, trauma, and other humanitarian crises can have persistent mental health effects across generations, including intergenerational violence [1-3]. The World Health Organization (WHO) estimates that 35% of women globally report experiencing intimate partner violence in their lifetime, and 75% of children in lower- and middle-income countries (LMICs) experience some form of violent or psychologically damaging discipline at home. Experiencing or witnessing family violence during early childhood increases risks for poor emotion regulation and other psychological problems, including posttraumatic stress disorder, externalizing and internalizing behavioral difficulties, and school problems. In postconflict Sierra Leone, research on the intergenerational impact of the 11-year civil conflict has shown that exposure to violence is related to poor parent/caregiver mental health and harsh parenting practices, which adversely affect child development [4-8]. The 2017 Sierra Leone Multiple Indicator Cluster Survey found that 85% of children aged 3-4 and 67% of those aged 1-2 experience violent discipline [9]. Given that poor caregiver emotion regulation is related to family violence and poor child development outcomes [4,5], evidence-based interventions focused on enhancing caregiver–child interactions (including father/male caregiver involvement), improving caregiver emotion regulation and mental health, and promoting alternatives to harsh discipline practices are urgently needed.

Evidence-Based Family Strengthening

In prior research among families facing adversity in Rwanda, we developed and evaluated the Family Strengthening Intervention for Early Childhood Development (FSI-ECD/*Sugira Muryango*), a home-visiting behavioral intervention delivered by lay workers [10,11]. The FSI-ECD targets caregiver emotion regulation and caregiver–child interactions as major mechanisms to prevent the intergenerational transmission of emotional and behavioral difficulties related to past trauma. It has demonstrated effectiveness in improving caregiver emotion regulation, reducing family violence, and promoting healthy child development [7,11]. The FSI-ECD is a promising approach for targeting underlying mechanisms linked to poor child outcomes [6,7]. Vital for low-resource settings, it can be delivered feasibly by lay workers with strong supervision and quality improvement cycles. Given the limited health infrastructure in many LMICs, including Sierra Leone [12,13], behavioral interventions that can be delivered by well-trained and supervised lay workers, such as community health workers (CHWs), are a more viable option for implementation and sustainment of evidence-based practices.

To further address critical shortages in the mental health workforce in LMICs, intervention delivery strategies must innovate. In Sierra Leone, new government leadership is pursuing mobile health (mHealth) strategies as means to address significant health care workforce limitations that plague delivery of evidence-based behavioral interventions to vulnerable families. Mobile technology has the potential to transform health care delivery and improve health outcomes in Sierra Leone and other LMICs by providing training, supervision, and fidelity supports to enhance quality improvement while interventions are scaled out, but it has not been widely applied to mental health and family-based prevention, particularly in Sub-Saharan Africa [8,14,15]. mHealth supervision and fidelity monitoring tools could enhance quality of service delivery and expand the reach of evidence-based mental health services to vulnerable families by generating a rapid feedback loop between supervisors and facilitators unconstrained by geographical distances. However, successful implementation of mHealth tools in Sub-Saharan Africa has been limited by dependence on a reliable network connection and electricity [8]. Although 83% of adult Sierra Leoneans have access to a mobile phone, most lack internet access, particularly in rural areas [16]. In this context, innovative use of battery-powered tablets with offline functions and access to cloud storage are logistically feasible and could help improve delivery quality and supervision of CHWs.

Study Objectives

The current study aims to (1) pilot a culturally adapted version of the FSI-ECD delivered by CHWs to vulnerable Sierra Leonean families with children aged 6-36 months to assess feasibility, acceptability, and preliminary effects of mHealth-supported delivery of the FSI-ECD on caregiver mental health and emotion regulation, caregiver–child interactions, and family violence in comparison to control families who receive standard care with standard supervision; and (2) develop and pilot innovative and cost-effective mHealth tools to support CHW delivery of the FSI-ECD. Development of mHealth tools will employ a user-centered design approach to design, prototype, and test digital tools that incorporate user feedback from supervisors and CHWs at each stage of development. User-centered design grounds the tool/app development process in the needs and preferences of those who will use the tool to make it more user-friendly, acceptable, and suitable to the real-world needs of the user; it creates a sense of engagement and shared ownership that aids adoption of the innovation [17-19]. We will use participatory methods and best practices in the user interface/user experience (UI/UX) design to engage CHWs and supervisors in the iterative development process to ensure that our mHealth tools and strategies meet their needs, align with local technological capacity and health service

priorities, and support sustained evidence-based practice. The objectives are to develop mHealth tools for supervision, fidelity monitoring, and training of CHWs in Sierra Leone and to provide supervisors with quick visual data displays on CHW performance to inform quality improvement cycles. We will also conduct a preliminary cost-effectiveness analysis to assess the economic value of the mHealth-supported delivery of the FSI-ECD versus standard care with standard supervision.

Methods

Design

This study is approved by the Boston College Institutional Review Board (reference number 21.006.01; Multimedia Appendix 1) and the Sierra Leone Ethics and Scientific Review Committee. The reporting of the trial follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [20] (Figure 1). This trial is registered with the Clinical Trials Registry maintained by the National Library of Medicine at the National Institutes of Health (Trial ID NCT04481399, registered on July 22, 2020). Any subsequent modifications to the study protocol will be reviewed by the Boston College Institutional Review Board and Sierra Leone Ethics and Scientific Review Committee for approval and then submitted to the Clinical Trials Registry as an amendment.

Figure 1. SPIRIT Schedule of Enrollment, Interventions, and Assessments.

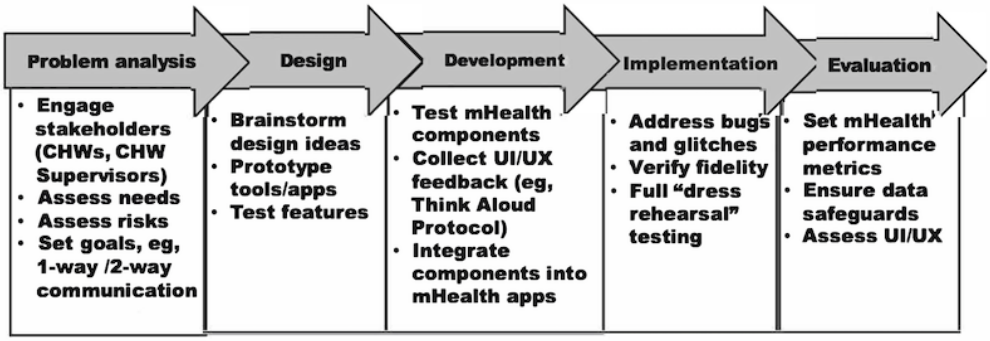
	STUDY PERIOD					
	Enrollment	Allocation	Postallocation			Close-out
TIMEPOINT	*Screening*	0	*Baseline*	*Post intervention*	*3-mo follow-up*	*Wrap-up*
ENROLMENT:						
Eligibility screen	X					
Informed consent	X		X			
Allocation		X				
INTERVENTIONS:						
mHealth-Supported FSI-ECD	←	—	—	—	→	
Standard Care	←	—	—	—	→	
ASSESSMENTS:						
Feasibility of mHealth-Supported FSI-ECD Implementation			X		X	
Emotion Regulation	X		X	X	X	
Home Observation			X	X	X	
Anxiety and Depression			X	X	X	
Intimate Partner Relationships			X	X	X	
Post-Traumatic Stress Symptoms			X	X	X	
Caregiver-Child Interactions			X	X	X	

Overview of Design

We will apply a 5-phase user-centered design approach [21] to develop and test mHealth supervision and fidelity monitoring tools (Figure 2). We will recruit CHWs delivering services to families with children aged 6-36 months (N=6; 3 male/3 female) and CHW supervisors (N=4; 2 male/2 female) to participate in end user focus group discussion sessions. We will hold 3 sessions: an initial problem analysis focus group sessions followed by 2 iterative cycles of UI/UX testing sessions. Problem analysis will seek to understand how CHWs and supervisors might use mHealth tools to enhance fidelity monitoring and supervision and what types of training resources might best support performance. Design of the mHealth tools will be informed by problem analysis findings. Development will test prototyped components of the mHealth tools to integrate audio, replay, visual displays of data, and summary features. UI/UX testing sessions will use Think Aloud Testing Protocols

[22], where participants are instructed to "think aloud" while using mHealth tools to illuminate features that are user friendly versus confusing or hard to use. Assessment of strengths and weaknesses of the mHealth tools and the second round of UI/UX testing will inform further refinements prior to the pilot trial. All sessions will be audiotaped, translated, and transcribed. All UI/UX participants will complete a validated usability scale prior to deployment of the mHealth tools [23].

Figure 2. User-centered Design Process for mHealth Tool Development.



We will conduct a pilot randomized controlled trial to evaluate preliminary mental health benefits of the mHealth-supported FSI-ECD among vulnerable families (N=80) with children aged 6-36 months in the Makeni City region of Sierra Leone. Study research assistants will seek informed consent from families, CHWs, and supervisors for their participation. Families will be randomized to receive the FSI-ECD or standard maternal and child health services delivered by a CHW with standard supervision. To minimize contamination risk, we will use randomization rules developed in our prior work in Sierra Leone (eg, geographic information system mapping to ensure nonadjacency of control and FSI-ECD families). The randomization allocation sequence will be generated via computer-generated random number list in REDCap. Study research assistants and data analysts will be blinded to participant assignment and will assign participants to study condition based on the randomization allocation sequence. Different CHWs will provide the FSI-ECD and standard care to minimize contamination risks.

Setting and Participants

Makeni is the largest city in the Northern Province of Sierra Leone. The city is the capital of Bombali District, and is the economic center of the Northern Province. Makeni is the Provincial Headquarters of the Northern Province of Sierra Leone. The total population is 125,970, of which 124,634 live in urban areas and 1336 live in rural areas [24]. The most common forms of employment are agriculture and trade. Krio is the primary language.

Inclusion criteria for CHW participation in problem analysis and UI/UX testing are as follows: currently providing maternal and child health services to families with children aged 6-36 months in the Makeni region, aged 18 or older, and ability to attend three 90-minute sessions. Inclusion criteria for supervisors are as follows: currently providing supervision to CHWs delivering the aforementioned services in the Makeni region and aged 18 or older. We will exclude individuals who do not meet CHW or supervisor inclusion criteria.

Inclusion criteria for families are as follows: (1) a Sierra Leonean household with cohabitating caregivers (eg, father/mother, mother/grandmother, mother/partner) and child (aged 6-36 months) with both caregivers aged 18 or older; and (2) 1 caregiver scoring at least 62.5 on the Difficulties in Emotion Regulation Scale (DERS). Both caregivers must agree to attend FSI-ECD sessions; however, if 1 caregiver decides to withdraw, the family can still continue to participate. If enrolled families have more than 1 child aged 6-36 months, we will include all eligible children as study participants. We will exclude families who do not meet all inclusion criteria or who experience active family crises (eg, current suicidality or psychosis, serious medical condition, or cognitive impairment as assessed by a study social worker).

We will recruit families from 2 communities within the Makeni region in coordination with the CHW Focal Person, who is the Ministry of Health and Sanitation Community Health Worker Program official responsible for coordinating the work of CHWs and supervisors within peripheral health units. Peripheral health units are key units within the Sierra Leone health care system. They deliver "first-line" care, including prenatal care, routine deliveries, immediate postnatal and neonatal care, community outreach services, routine vaccination, and treatment of childhood illnesses and malnutrition. Peripheral health units maintain records of families in the community who have sought services and we will be able to identify families with a child aged 6-36 months by reviewing their records. We anticipate that engaging at the community level with the peripheral health units will facilitate recruitment and enrollment of our target sample size.

We will recruit CHWs (N=8) and supervisors (N=2) from the 2 identified peripheral health units to deliver the mHealth-supported FSI-ECD and provide weekly supervision. CHW is a volunteer position and there are no educational qualifications that must be met in order to be engaged as a CHW. CHWs and supervisors who participate in problem analysis and UI/UX sessions will be eligible to participate in the FSI-ECD pilot study. Inclusion criteria are CHWs assigned to the peripheral health unit that provides health services in 1 of the 2 communities and 18 years or older. We will exclude CHWs who do not meet inclusion criteria. Inclusion criteria for supervisors are currently overseeing CHWs providing maternal and child health services in 1 of the 2 communities and aged

18 or older. We will exclude supervisors who do not meet inclusion criteria.

FSI-ECD

The FSI-ECD is composed of 4 core components: (1) developing problem-solving, stress management, and emotion regulation skills; (2) cultivating positive parenting skills and fostering father/male co-caregiver engagement; (3) developing communication and conflict resolution skills; and (4) exploring alternatives to harsh punishment and practicing nonviolent child discipline. The FSI-ECD integrates key elements of the evidence-based Family-Based Prevention Intervention [25] and was culturally adapted to the Rwandan context through extensive community-based participatory research methods involving Rwandan community advisory boards. The FSI-ECD is delivered in 12 modules in the home via coaching by CHWs. Sessions are delivered once per week and last approximately 90 minutes. Prior to the trial, we will adapt the FSI-ECD to the cultural context of Sierra Leone. A Community Advisory Board will advise on local parenting and mental health terms and concepts drawing from previously collected qualitative data on parenting in Sierra Leone.

Standard Services

Standard CHW care involves 3 home-visiting, educational sessions delivered to families following childbirth, with weekly supervision via phone or face-to-face. Topics of home-visiting sessions include skilled postnatal care for mothers, early initiation of breastfeeding, nutrition, immunization services, handwashing and hygiene practices, building the capacity of family members to take care of newborns and children under age 5. CHWs also conduct screenings for acute malnutrition and growth monitoring to identify early referrals, and they can provide family planning methods; deworming tablets; and other vitamins for acute malnutrition, dehydration, and antimalaria treatment. Each home-visiting session lasts approximately 60 minutes.

Training and Supervision

CHWs and supervisors will be trained in the core components of the adapted FSI-ECD by FSI-ECD experts. Training will occur 5 days per week over the course of 3 weeks. At the conclusion of training, CHWs and supervisors will complete a competency assessment. CHWs and supervisors will also complete a 1-day technology training on use of the mHealth tools. During FSI-ECD delivery, CHWs and supervisors will participate in weekly 60-minute supervision sessions guided by mHealth tools to support delivery quality. CHWs and supervisors will complete fidelity monitoring checklists that are embedded in mHealth tools, and review of fidelity monitoring data will inform quality improvement feedback cycles during supervision.

Measures

FSI-ECD Outcomes

We will collect quantitative data on caregiver mental health and emotion regulation, harsh parenting practices, the home environment, and family functioning at baseline, postintervention, and 3-month follow-up. All quantitative measures have undergone a thorough development, translation, and validation process [26] in a prior randomized controlled trial in Sierra Leone. The following quantitative measures will be used: the DERS (α=.95) [27], WHO Disability Assessment Schedule (α=.91) [28], the Conflict Tactics Scale (α=.72-.86) [29], Hopkins Symptom Checklist (α=.92) [30], and Post-traumatic Stress Disorder Reaction Index (α=.93) [31]. To assess caregiver–child interactions, we will use the Home Observation for Measurement of the Environment (α=.73) [32] and the Observation of Mother–Child Interaction (α=.83) [33]. We will also collect qualitative data at postintervention via key informant interviews with randomly selected caregivers (4 males/4 females) to assess FSI-ECD feasibility, acceptability, and satisfaction.

mHealth Outcomes

We will collect quantitative data on mHealth tool feasibility, acceptability, adoption, and appropriateness with CHWs and supervisors at baseline and postintervention via quantitative scales developed by researchers at Johns Hopkins Bloomberg School of Health [34]. We will track length of time to deliver FSI-ECD content, use of embedded fidelity monitoring and tracking features, and amount of CHW–supervisor contact via tablet, phone, and face-to-face. Fidelity data will include a CHW-completed electronic fidelity checklist designed to support self-monitoring and performance review with supervisors as well as a supervisor-completed electronic fidelity checklist to be completed while reviewing audiotaped FSI-ECD sessions and discussed during supervision. We will also collect data on mHealth tools postintervention via key informant interviews with CHWs (n=8) and supervisors (n=4) to understand usability of audio/video functions for FSI-ECD delivery, supervision, and quality improvement cycles.

Participant diagnostic and assessment data will be collected via tablets and deidentified. All tablets will be encrypted and password protected using a password known only to the research team. All data on the tablet will remain on the tablet until it is connected to Wi-Fi and uploaded to a secure server. Daily quality assurance and data monitoring checks will determine successful upload of the data, which will be backed up to Box, a secure, HIPAA (Health Insurance Portability and Accountability Act)-compliant, cloud-based storage platform, before it is remotely wiped from the tablet.

Data Analysis

For quantitative data analysis, will use mixed effects linear models to assess the effects of the FSI-ECD on caregiver mental health and emotion regulation, caregiver–child interactions, and parenting practices. These models will account for clustering of families within CHWs delivering services and clustering of outcomes within families across time. If outcomes are skewed and violate the normality assumption for linear models, we will use generalized linear models with a Poisson distribution. We will conduct all analyses on an intent-to-treat basis. Paired *t*-tests (2-tailed) and Wilcoxon signed rank tests will examine postintervention change in quantitative implementation outcomes (ie, feasibility, acceptability, adoption, appropriateness), controlling for baseline scores.

Power calculations for sample size were calculated using the power command in STATA (StataCorp). The proposed pilot study is not powered to detect treatment effects of clinical significance. However, if we assume a standard α level of .05, 80 families with 2 eligible respondents per family on average, and 2 time points, with assumptions of moderate intraclass (within-family) correlation (approximately 0.5), this pilot randomized control trial has power of 0.80 to detect a standardized "medium" effect size of approximately 0.50 [35]. For outcomes with only 1 observation per time point, and using the same assumptions as above, this pilot randomized control trial has power of 0.80 to detect a standardized effect size of approximately 0.6. Multiple imputation will be used to deal with missing data.

Qualitative data analysis of key informant interviews will follow a 3-step analytical strategy derived from thematic content analysis and grounded theory [36,37]. We will use open coding to examine key interview themes (eg, barriers and facilitators to use, feasibility, and acceptability). We will iteratively develop a coding scheme organized by key themes. After we have identified major categories and established a codebook, we will conduct axial coding to link themes in terms of timing, context, and other dimensions. Poor agreement (ie, low κ ratings as scored in MAXQDA [38]) will be grounds for refining the codebook. We will repeat reliability testing until coding is at >80% agreement for all data sources. We will code all data sets in MAXQDA. Mixed methods analysis will synthesize qualitative and quantitative data using embedded quotes and joint display tables [39]. This approach will also be used for qualitative data analysis of key informant interviews with caregivers.

Cost-effectiveness analysis will estimate costs across FSI-ECD versus standard care. We will use budget, expenditure, supervision, and fidelity data to collect implementation, health, and service costs using standard costing methodologies [40]. Costs will include implementation activities (eg, staff and CHW/supervisor trainings, session delivery, supervision) and directly related recurrent or capital items (eg, tablets, tech support, broadband access, travel supplies). Costs of digital tools will be included as a capital item and amortized based on project duration. Service delivery costs will rely on in-country data or standard costs provided by WHO-CHOosing Interventions that are Cost-Effective published costs data. Outcomes will include a functional impairment measure (WHO Disability Assessment Schedule) that can be converted to quality-adjusted life years [41]. We will use standard incremental cost-effectiveness analysis to compare mHealth-supported delivery of the FSI-ECD to standard care and capture marginal variations in costs and effectiveness using incremental cost-effectiveness ratios. Differences in intervention cost will be divided by differences in intervention effectiveness to calculate incremental cost-effectiveness ratios that can be used to understand the cost of the intervention per unit of outcome (cost per quality-adjusted life year). We can compare this to the standard willingness to pay threshold and to alternative programs to determine which programs are relatively more cost-effective.

Ethical Approval and Consent to Participate

This study received ethical approval from the relevant College Institutional Review Board and the Sierra Leone Scientific Review Committee (Multimedia Appendix 1). All participants provided verbal consent to participate due to low literacy levels. This procedure was approved by both ethics committees.

Availability of Data And Materials

Data sharing will be in accordance with the NIH Data Sharing Policy and Implementation Guidance and more specifically the "Data Sharing Expectations for National Institute of Mental Health (NIMH)-funded Clinical Trials." The data generated in this study will be entered into the NIMH Data Archive as required as prescribed by the Notice of Award as well as presented at national or international conferences and published in a timely fashion. All final peer-reviewed manuscripts that arise from this proposal will be submitted to the digital archive PubMed Central. Published data will be available in print or electronically from publishers, subject to subscription or printing charges. Research data that document, support, and validate research findings will be made available after the main findings from the final research data set have been accepted for publication.

Results

Funding for this study was received from the National Institute of Mental Health on August 17, 2020 (Multimedia Appendix 1). Institutional Review Board approval was received on September 4, 2020. At the time of manuscript submission, the study has not yet initiated baseline data collection. Data collection is projected to begin on December 15, 2020. Table 1 presents information on the timeline of study activities across the 2 years of the project.

Table 1. Project activities and timeline.

Quarter	Year 1				Year 2			
	1	2	3	4	1	2	3	4
AIM 1: mHealth tool/app development								
Focus group: UI[a]/UX[b] participant recruitment	X							
Problem analysis		X						
Design and development		X	X					
AIM 2: FSI-ECD[c] adaptation and pilot study								
FSI-ECD adaptation	X	X						
CHW[d] and supervisor recruitment		X						
CHW and supervisor FSI-ECD training (3 weeks)			X					
Family recruitment, enrollment, and baseline diagnostics			X					
FSI-ECD implementation and postintervention evaluation				X	X			
FSI-ECD 3-month follow-up						X		
Data analysis and dissemination						X	X	X

[a]UI: user interface.

[b]UX: user experience.

[c]FSI-ECD: Family Strengthening Intervention for Early Childhood Development.

[d]CHW: community health worker.

Discussion

Possible Challenges

There are several potential challenges that may arise during study implementation. In Sierra Leone, many caregivers are involved in employment that requires a high level of daily mobility, such as trade and agriculture. Some caregivers travel across districts, regions, or to neighboring countries for several weeks in order to work. In this work context, we may experience some challenges recruiting and retaining caregivers because participation in the FSI-ECD requires caregivers to attend twelve 90-minute sessions delivered once per week. Although the FSI-ECD may provide long-term benefits for caregiver mental health and child development, these benefits may not be a sufficient incentive for study participation. To help address this challenge, we will encourage highly flexible scheduling to accommodate the working hours of caregivers. The home-visiting nature of the FSI-ECD is also intended to improve service access for families with young children and will relieve the burden of traveling to attend services.

Technology literacy levels and potential technical issues that may occur with the mHealth tools could also pose challenges to this study. To address this, we will provide a 1-day technology literacy training on the use of mHealth tools and basic skills with tablet use. We will also provide ongoing technical support to troubleshoot any technical issues. It is possible that poor connectivity may impede rapid resolution of technical issues, because technical assistance will be remote. However, given that CHWs and supervisors will not need to use mHealth tools on a daily basis, our team should be capable of reasonably resolving any issues with enough time to ensure study activities proceed as planned. We will also train the study data manager in use of the mHealth tools to support greater in-country expertise. We will document any technical issues and keep a log of the strategy to resolve them in the event that the same issue is encountered on a subsequent occasion. To address potential difficulties with internet connectivity, we will place a modem for CHWs and supervisors in the peripheral health unit where they are based. Battery-powered tablets with offline functions and access to cloud storage will also ensure that mHealth tools can be feasibly used and data securely stored until connectivity is available.

Study Strengths

This study has several strengths. We propose to recruit and enroll CHWs and supervisors, government health employees who work in the communities where they reside, to deliver the FSI-ECD. CHWs will likely already have familiarity with many families in their community before study recruitment and enrollment begins, which may facilitate recruitment and engagement of caregivers in study activities. CHWs will also be familiar with the social norms, typical work schedules, and family habits of their community members, which may also help increase engagement and retention of families in study activities.

Conclusion

This study has the potential to build urgently needed capacity for both delivery of evidence-based mental health services to reduce family violence and harsh parenting practices and for effective use of mHealth strategies to improve lay worker health service delivery. This study will provide important data on feasibility, acceptability, and cost of both mHealth tools and mHealth-supported FSI-ECD. If mHealth tools are feasible, acceptable, and support high-quality FSI-ECD delivery, this

platform could be used to improve efficiency and quality of service delivery for other CHW-delivered services in similar settings. The mHealth tools might also help expand the reach of evidence-based mental health services to vulnerable families in more rural areas by generating a more rapid feedback loop between supervisors and CHWs unconstrained by geographical distances. Finally, applying mHealth tools for supervision and quality improvement has the potential to reduce long-term costs associated with traditional modes of fidelity monitoring and supervision, thus enabling greater scalability in a setting with limited behavioral health professionals.

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Authors' Contributions

AD contributed to conception and design of the work and to drafting and revising the manuscript. CS, RE, and MJ contributed to drafting the manuscript. TB contributed to conception and design of the work and revising the manuscript. All authors approved the submitted version of the manuscript and agree to be personally responsible for their own contributions.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Boston College Institutional Review Board Approval.
[PDF File (Adobe PDF File), 4815 KB - resprot_v10i2e25443_app1.pdf]

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Abbreviations

CHW: community health worker
DERS: Difficulties in Emotion Regulation Scale
FSI-ECD: Family Strengthening Intervention for Early Childhood Development
LMIC: lower- and middle-income country
UI/UX: user interface/user experience
WHO: World Health Organization

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Protocol

Effectiveness of an Integrated Engagement Support System to Facilitate Patient Use of Digital Diabetes Prevention Programs: Protocol for a Randomized Controlled Trial

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Abstract

Background: Digital diabetes prevention programs (dDPPs) are effective behavior change tools to prevent disease progression in patients at risk for diabetes. At present, these programs are poorly integrated into existing health information technology infrastructure and clinical workflows, resulting in barriers to provider-level knowledge of, interaction with, and support of patients who use dDPPs. Tools that can facilitate patient-provider interaction around dDPPs may contribute to improved patient engagement and adherence to these programs and improved health outcomes.

Objective: This study aims to use a rigorous, user-centered design (UCD) methodology to develop a theory-driven system that supports patient engagement with dDPPs and their primary care providers with their care.

Methods: This study will be conducted in 3 phases. In phase 1, we will use systematic UCD, Agile software development, and qualitative research methods to identify *key user* (patients, providers, clinical staff, digital health technologists, and content experts) requirements, constraints, and prioritization of high-impact features to design, develop, and refine a viable intervention prototype for the engagement system. In phase 2, we will conduct a single-arm feasibility pilot of the engagement system among patients with prediabetes and their primary care providers. In phase 3, we will conduct a 2-arm randomized controlled trial using the engagement system. Primary outcomes will be weight, BMI, and A_{1c} at 6 and 12 months. Secondary outcomes will be patient engagement (use and activity) in the dDPP. The mediator variables (self-efficacy, digital health literacy, and patient-provider relationship) will be measured.

Results: The project was initiated in 2018 and funded in September 2019. Enrollment and data collection for phase 1 began in September 2019 under an Institutional Review Board quality improvement waiver granted in July 2019. As of December 2020, 27 patients have been enrolled and first results are expected to be submitted for publication in early 2021. The study received

Institutional Review Board approval for phases 2 and 3 in December 2020, and phase 2 enrollment is expected to begin in early 2021.

Conclusions: Our findings will provide guidance for the design and development of technology to integrate dDPP platforms into existing clinical workflows. This will facilitate patient engagement in digital behavior change interventions and provider engagement in patients' use of dDPPs. Integrated clinical tools that can facilitate patient-provider interaction around dDPPs may contribute to improved patient adherence to these programs and improved health outcomes by addressing barriers faced by both patients and providers. Further evaluation with pilot testing and a clinical trial will assess the effectiveness and implementation of these tools.

Trial Registration: ClinicalTrials.gov NCT04049500; https://clinicaltrials.gov/ct2/show/NCT04049500

International Registered Report Identifier (IRRID): DERR1-10.2196/26750

(JMIR Res Protoc 2021;10(2):e26750) doi:10.2196/26750

KEYWORDS

mobile health; mHealth; eHealth; diabetes prevention; type 2 diabetes mellitus; mobile phone

Introduction

Background

More than 80 million US adults are considered prediabetic. Without treatment, an estimated 15% to 30% will develop diabetes over the next 5 years [1]. The epidemic of prediabetes is driving the morbidity and mortality of the downstream manifestations of type 2 diabetes (DM2) and cardiovascular disease, of which there are 2 to 3 times increased odds in persons with prediabetes [2,3]. Thus, effective, and scalable management solutions are greatly needed.

Evidence-based interventions to prevent DM2 have focused on behavior change therapies including weight loss, dietary changes, and exercise. This focus on behavior change was in response to findings from seminal research in Finland and the United States, which demonstrated that intensive lifestyle changes (including a low-fat diet, 150 min per week of moderate exercise, and a target 7% weight reduction) were as effective as medication in preventing the progression to DM2 in at-risk patients [4]. In response to these findings, the Centers for Disease Control and Prevention (CDC) developed a national diabetes prevention program (DPP) in 2010 that was aimed at providing patients with comprehensive, research-based, cost-effective programs to help prevent diabetes. To date, more than 1500 organizations nationwide have partnered with the CDC to deliver DPP and more than 100,000 individuals have participated in one of these programs [5].

Digital Diabetes Prevention Program Platforms

The DPP curriculum has been successfully adapted to a variety of digital platforms, known as digital DPPs (dDPPs). Several commercial dDPP vendors are currently available to consumers (Noom, Livongo, and Omada). To varying degrees, the core elements of these programs include (1) a structured lesson plan on diabetes prevention, weight loss, exercise, and other areas of lifestyle modification adapted from the CDC program; (2) a system of activity, steps, meal, or other feature tracking, which patients can either automatically or manually upload to their device; and (3) a personalized coaching and social support network.

Early data have demonstrated the effectiveness of dDPPs in achieving weight loss, A_{1c} reduction, and other key diabetes health outcomes at 6 months and 1 year [6-8]. These digital platforms also offer benefits to patients in terms of accessibility, convenience, and personalization, which make them attractive alternatives to the more resource-intensive in-person DPPs. This potential has been further highlighted by the COVID-19 pandemic, in which disruptions in continuity of care for chronic disease management and elevated barriers to in-person health activities such as fitness classes and group nutrition counseling have driven more people to digital platforms for health behavior change [9].

Digital Health Engagement: Challenges for Patients and Providers

Despite the popularity and effectiveness of digital health interventions such as dDPPs, the integration of these tools into clinicians' armamentaria for disease management and healthy behavior change has been limited [10]. The reasons for this include technical barriers, suboptimal user experience, entrenchment of practice habits and preferences, perceived administrative burden, and unfavorable reimbursement environments. In particular, user engagement in digital health tools represents a critical, but challenging, component of the effective translation of evidence-based behavioral interventions into pragmatic, scalable digital solutions [11,12]. Although regular interaction with digital health tools for weight loss and diabetes prevention has been shown to improve targeted health outcomes with a tendency toward a dose-response relationship [13-15], low rates of long-term engagement are known barriers to achieving and maintaining these outcomes [16-18]. Tools to identify and measure engagement have been lacking, in part, because of the lack of conceptual clarity and precision in defining the features of engagement, and gaps remain in the understanding of the links between specific engagement behavior and the achievement of target health goals [19-21]. For providers, poor integration of dDPPs into the existing health information technology (HIT) and electronic health record (EHR) workflows negatively impacts the ability to incorporate relevant aspects of the programs into patient care, communication, or education. This results in missed opportunities for comprehensive care delivery in diabetes

prevention, as providers are unable to overcome barriers in technology, workflows, and competing priorities to effectively leverage digital health tools. Integrated clinical tools that can facilitate patient-provider interaction around dDPPs may contribute to improved patient engagement and adherence to these programs and improved health outcomes by addressing some of these issues.

Objectives

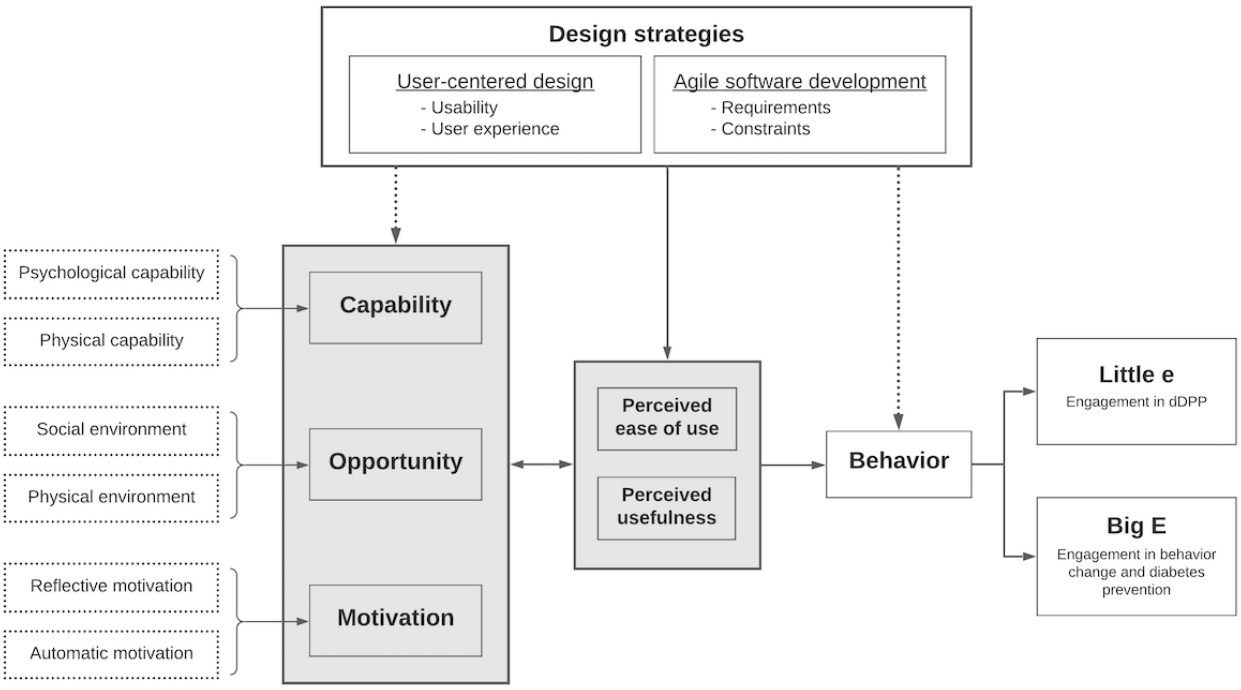
Few studies have investigated integrating consumer-facing digital health programs such as dDPP platforms into existing clinical systems, such as the EHR, or into clinical workflows of ambulatory care practices to facilitate patient-provider interaction with these tools. We hypothesize that existing digital technology, such as text messaging systems, patient portals, and EHR integrations, can support both clinicians and patients by improving communication, education, and shared decision making around digital behavior change tools. The purpose of this study is to design and test a novel clinical tool to enhance engagement with digital behavior change efforts in diabetes prevention.

Methods

The Integrated Framework for the Development of Digital Health Behavior Change Interventions

The dDPP engagement intervention uses an integrated framework that combines established theoretical models for behavior change with effective digital health implementation strategies (Figure 1). This combination leverages both theoretical and pragmatic approaches to the development, implementation, and evaluation of digital behavior change tools and provides a structure for both outcomes and process measures.

Figure 1. The integrated framework for the development of digital health behavior change interventions. dDPP: digital diabetes prevention program.

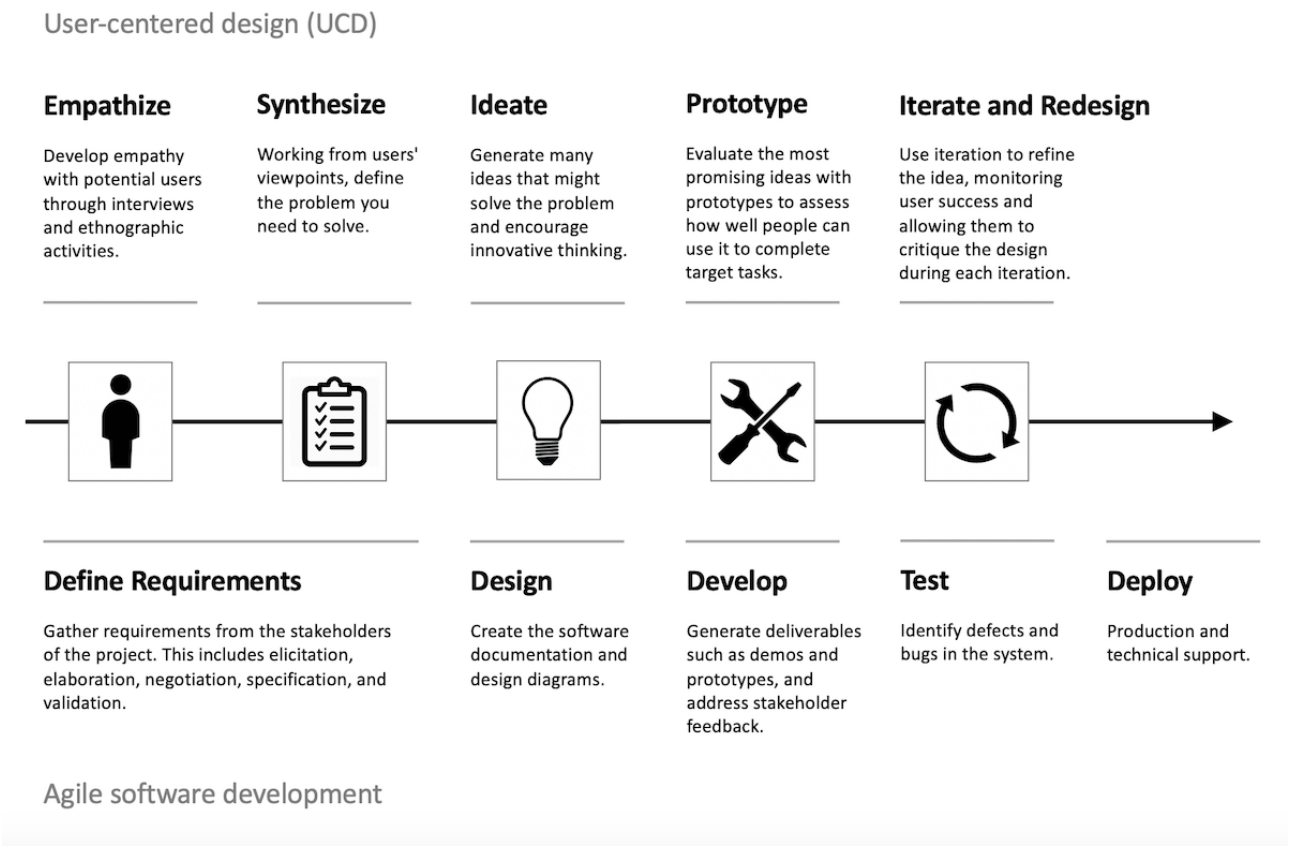


This integrated framework adapts the Capability, Opportunity, and Motivation Model of Behavior Change (COM-B); the Technology Acceptance Model (TAM); and the Johnson and Johnson (J&J) approach to engagement in digital behavior change interventions. COM-B is a comprehensive model developed by Michie et al [22] who identify 3 components of behavior (capability, opportunity, and motivation) that may be activated and/or suppressed to elicit targeted actions and effect change. This model is widely used in behavior change health research and has been proven effective for designing health interventions targeting disease prevention [23-26]. The TAM is an information technology framework based on the Theory of Reasoned Action that conceives of beliefs and attitudes as determining intentions, which in turn dictate behavior. It asserts that perceptions of usefulness and ease of use by end users will directly influence intention to use new technology, leading in turn to its adoption [27,28]. TAM and its subsequent versions TAM2 and TAM3 have been widely applied to explain the adoption of HIT [29,30]. The J&J approach to digital health engagement derives from the belief that user engagement with digital behavior change interventions (DBCIs) is a precursor to improved health outcomes. Engagement with DBCI can be divided into 2 types—*Big E* and *Little e*—with *Big E* describing engagement with targeted health behavior (eg, weight loss) and *Little e* representing engagement with the digital behavior change intervention itself (eg, weight tracking) [19]. This combined framework leverages the core relevance of older, well-accepted models (particularly TAM, which was first developed in the 1980s) while acknowledging the innovative contributions of later theories that address new areas of exploration in digital behavior change, particularly digital app development.

In addition to our theoretical model, we use complementary strategies of user-centered design (UCD) and Agile project

management for the design, development, and implementation of our engagement intervention (Figure 2). UCD and the related Design Thinking (DT) process have emerged as novel frameworks for product development and research in health care, particularly in the areas of health care technology and digital health product development [31]. UCD uses repeating cycles of ideation, prototyping, testing, and refinement to develop digital health interventions in collaboration with end users (eg, patients, providers, health administrators, technologists, other stakeholders), with the goal of building products that are appropriate, acceptable, and usable for those users. The iterative nature of UCD also allows for continual innovation, adaption, and refinement of products over time. Agile is a process derived from software development that involves the identification and review of key requirements (eg, needs, preferences, expectations of users) and the continuous generation of partial deliverables for stakeholders and end users. Agile processes include users at every stage of product development and allow stakeholders to be actively involved in the development process, from inception to implementation. Decisions and changes to a product are discussed among the multidisciplinary team to arrive at the best solution for the study intervention. As the intervention evolves, the computational system will evolve to address the changes. Applying the strategies of UCD and Agile facilitates the development of targeted, acceptable, and adaptable digital health interventions, thereby improving the likelihood of both effectiveness and adoption and adherence by users.

Figure 2. User-centered design and Agile software development.



dDPP Platform: Noom

Our study (NCT04049500) will use the commercially available application Noom to provide patients with a dDPP platform. Noom is a mobile health behavior change lifestyle app based on the CDC's DPP that allows users to log their meals, weight, and exercise and physical activity minutes. Noom connects users with an individual behavior change coach and support group and provides a DPP curriculum through daily articles that cover topics including diet, exercise, and healthy behavior psychology. The core philosophy of Noom is to work with the user to adopt a healthier lifestyle in a way that best fits the user's individual life. Preliminary studies of Noom showed high levels of effectiveness and acceptability compared with in-person DPPs. In overweight or obese adults with prediabetes, participation in Noom was associated with significant weight loss at 24 and 65 weeks, which exceeded the CDC DPP 5% weight loss requirement [7,32]. In one study, participants exhibited a dose-dependent response with greater mean weight loss at 65 weeks in those who engaged more in the program [32]. In addition, certain metrics of in-app engagement such as weekly logged meals, weigh-ins, and group posts were shown to predict weight loss [32]. Noom is a well-established commercial dDPP platform with a growing market share and considerable brand recognition and robust customer and technical support.

Study Overview

This study will consist of 3 phases.

- *Phase 1* will combine a theory-based approach to behavior change with UCD and Agile software/technical strategies to
  - Identify the needs, requirements, preferences, and constraints of users (patients, clinical providers, ambulatory practice management and technologists, dDPP coaches, and technical teams).
  - Co-design a patient- and provider-facing engagement intervention (ie, mobile app, text messaging system, EHR visualization) to support patients' use of the dDPP and assess its usability via iterative prototyping and user testing.
- *Phase 2* will consist of a single-arm feasibility pilot among patients with prediabetes using the engagement intervention tool and a validated third-party vendor dDPP platform to assess the preliminary effectiveness of the engagement system and further refine the intervention.
- *Phase 3* will consist of a two-arm randomized controlled trial (RCT) to evaluate the impact of the engagement intervention tool plus the dDPP platform versus the dDPP platform alone on health outcomes (weight, BMI, and A_{1c}) and engagement in the dDPP.

Inclusion and Exclusion Criteria for Patients and Providers

Eligible patients will have been diagnosed with prediabetes (A_{1c} level of 5.7-6.4 in the last year) or have risk factors for diabetes (obesity and family history). In addition, they must have access to smartphones or internet-connected tablets and be able to read and write English. We will exclude patients who have ever been diagnosed with diabetes (A_{1c} level>6.4) or those with contraindications to weight loss, dietary adjustments, or moderate physical activity. Patients whose weight may vary considerably over the study's timeframe for reasons other than the intervention (eg, cancer, pregnancy, ascites, severe congestive heart failure) and patients with severe psychiatric disease, dementia, or vision or other impairments that would prevent them from being able to access and use the dDPP app will also be excluded.

Eligible providers will have at least 2 years of experience providing care to patients with prediabetes or risk factors for diabetes in the outpatient setting.

Phase 1: Intervention Design

Study Design

In this phase of the study, we will employ UCD techniques to identify use cases, needs (requirements), preferences, and constraints of a targeted digital engagement intervention and use Agile methodologies to guide the intervention's technical development.

Setting and Participants

This study will be conducted within the ambulatory practice network of New York University Langone Health (NYULH). The network cares for more than 7.64 million diverse patients throughout New York, New Jersey, and Florida and includes more than 8000 health care providers. Practice sites include academic faculty practices, community clinics, and Federally Qualified Health Centers. The entire ambulatory network shares a single integrated EHR (Epic).

Enrollment for the intervention design and development phase will include 25 to 30 diverse stakeholders or *key users*—patients and health care providers who meet our inclusion criteria, health technologists, behavioral change theorists, and dDPP vendor staff (coaches and developers). Sample size estimates for this phase were based on best practices for maximizing the power of qualitative research, which recommend 6 to 8 participants per qualitative method, with additional participants as needed to achieve goal data collection and/or thematic saturation. Previous UCD studies suggest that 2 to 3 cycles of user testing are required to reach saturation [33].

Procedures and Data Collection

In this phase, we will apply the UCD model of *empathize, define, ideate, prototype, and test* to iteratively gather information, define, design, and refine the engagement intervention. This method will be applied over several cycles until a minimum viable product (MVP) of a workable intervention prototype is developed. The tools deployed for this process (eg, DT workshops, think-alouds, and usability testing) have been described extensively elsewhere and have been used with success by this and other research teams in the development of digital health technologies [33-37].

In the *empathize* and *define* stage, we will conduct focus groups and interviews to capture experiences and baseline needs of key users including patients, providers, technologists, and content experts in diabetes prevention, digital health engagement, and behavior change theory. This information will be used to inform the focus of the subsequent stages. In the *ideate* stage, we will use a series of structured DT workshops developed in response to results from the previous stage to engage a multidisciplinary group in the organized predesign of possible intervention solutions. Specific ideation sessions will focus on the patient- and provider-facing components of the engagement intervention and interactions of the intervention with the commercial dDPP platform.

In the *prototype* and *test* stages, a select number of solutions will be chosen by the multidisciplinary group and the research team for further development to be undertaken by the research and technical teams. These prototypes will undergo a series of structured think-aloud and usability testing sessions with key users (patients and providers) and will be iteratively refined based on results from these sessions until no further substantive changes are required and an MVP is developed. Usability testing will include both the intervention itself and the intervention integrated with the commercial dDPP platform. Usability testing participants will be asked to complete demographic surveys and pre- and posttesting surveys.

Data Analysis

Qualitative data from interviews, focus groups, DT workshops, and usability testing will be recorded, transcribed, and coded both deductively to evaluate relevant domains of our integrated theoretical framework (eg, user requirements, preferences, and constraints; barriers and facilitators to tool use; ease of use,

usability) and inductively to identify emergent themes and concepts. Coders will meet to review their coding, conduct team debriefing meetings, and reach a consensus on code names and meanings. Once all transcripts have been collaboratively coded, analytic domains will be identified and major and minor thematic areas will be described. Quantitative data from user testing surveys will be analyzed using basic statistical methods to identify significant associations between intervention use and relevant demographics.

Results from the qualitative and quantitative data analysis will be used to identify key *user stories*, a core technique in Agile methodologies for the identification of units of technical development work through the lens of a user [38,39]. User stories will be converted by the technical team into a series of discrete technical requirements and constraints that will be used to inform the technical build of the engagement intervention. User stories, requirements, and technical work or *tasks* will be tracked and completed using Agile project management software (ClickUp).

Phase 2: Feasibility Pilot

Study Design

Following phase 1 development of an intervention MVP, we will conduct a single-arm pilot test to further evaluate the feasibility and the process of implementing the intervention. The findings will inform additional refinements in advance of the RCT.

Setting and Participants

The study will take place across 2 ambulatory care practices within the NYULH ambulatory network, selected based on their practice size and volume of patients with prediabetes. In total, 20 patients who meet the inclusion criteria will be enrolled; 5 to 8 providers whose patients were enrolled in the study will also be enrolled. The sample size is based on best practices for maximizing the power of qualitative research and estimates of the number of users needed to inform additional rounds of prototype refinement. For feasibility studies, 24 to 50 participants are generally recommended [40]. Additional patients and providers may be recruited until thematic saturation is met and/or no further refinements to the intervention are identified.

Procedures and Data Collection

Eligible patients will be identified through (1) the review of patient data in the EHR and (2) provider referrals. Eligible participants will be consented by a member of the research team. Consented patients will be enrolled in the commercial dDPP and receive the patient-facing engagement intervention developed in phase 1. Patients will receive information and training on both the national DPP and the intervention dDPP and will be guided through downloading and enrolling in the dDPP platform. Patients will also receive wireless connected step trackers and weight scales and will be instructed on how to connect their devices to their dDPP account and upload their health data. Eligible physicians whose patients have been enrolled in the study will be included in the study and will receive the provider-facing engagement intervention developed in phase 1.

Patients and providers will be asked to complete surveys at various points throughout the study.

Patient-level data include the following:

- Participant demographics: a self-report survey will collect patient sociodemographic data including age, sex or gender, race or ethnicity, and occupation. This will be compared with the patient data available in the EHR.
- Baseline *engagement readiness* survey: a self-report survey of areas related to digital engagement and health behavior change, including digital literacy, technology readiness, disease self-management and self-efficacy, quality of life, time management, and perceptions of their provider.
- Use behavior: patients' dDPP use behavior will be measured by the research team at regular intervals throughout the study period, including the following dDPP features: meals logged, steps logged, exercise and/or physical activity logged, weights logged, and interactions with other dDPP features. Patients will also complete quarterly self-reports of engagement in the dDPP, including features used and motivation to use features.
- TAM survey: self-reported responses to questions derived from the validated TAM survey that assesses the perceived ease of use, usefulness, and quality of the patient-facing engagement intervention. This survey will be administered quarterly throughout the patients' participation in the study.
- COM-B survey: a self-report of questions adapted from the well-established COM-B framework and related questionnaires, assessing capability, opportunity, and motivation of patients to (1) use the dDPP and (2) engage in health behavior change around diabetes prevention.

Provider-level data include the following:

- Provider demographics: a self-report survey will collect relevant provider demographics, including years of practice, practice type, and patient panel information.
- Use behavior and usability testing: providers will be interviewed at regular intervals regarding their use of the provider-facing engagement intervention, impact on patient management, impact on clinical workflows, and overall experience and evaluation.
- TAM survey: a self-report of questions derived from the validated TAM survey that assesses the perceived ease of use, usefulness, and quality of the provider-facing engagement intervention. This survey will be administered quarterly throughout the providers' participation in the study.

Data Analysis

We will use descriptive statistics to summarize all patient- and provider-level outcomes and assess their relationship to patient engagement and activity data derived from the dDPP platform. All qualitative data collected via surveys will be analyzed using deductive and inductive (grounded theory) approaches, as described in phase 1. The results of quantitative and qualitative analyses in phase 2 will inform intervention approaches and assessments in phase 3.

Phase 3: RCT

Study Design

In phase 3, we will conduct a two-arm pragmatic RCT to evaluate the impact of the engagement intervention tool plus the dDPP platform versus the dDPP platform alone on relevant prediabetes health outcomes and patient engagement in the dDPP.

Setting and Participants

The study trial will use a practice-level cluster-randomized design, with 1:1 randomization of 40 primary care practices resulting in 20 clinics per study arm. Randomization will be stratified by clinic size to ensure even distribution of different-sized clinics to the two study arms. The proposed sample size provides 80% power to detect a 30% increase in dDPP session completion and a 2 kg increase in 12-month weight loss in the intervention arm relative to the control. This calculation assumes 20% attrition, two-sided tests with a type I error rate of 0.05, and an intraclass correlation coefficient of 0.05.

We will recruit patients who meet the inclusion criteria with primary care providers at the study sites through the patient portal, an increasingly common and effective approach for recruitment [41-43], and through population-based outreach from NYULH prediabetes registries with assent from primary care providers. Intervention participation will last 12 months.

Patients enrolled in the intervention arm will receive access to the dDPP platform and the engagement system developed and refined in phases 1 and 2. Patients in the control arm will receive the dDPP alone. Providers in both arms will receive information on the study and educational material for their patients. Patients will receive enrollment and onboarding information and training for dDPP, the engagement system, and the home devices (weight scales and pedometers or fitness trackers), as outlined and refined in phase 2. In addition to the home devices, upon enrollment, patients will be provided a home A_{1c} testing kit and instructions for its use for the study.

Procedures and Data Collection

Eligible patients will be identified and enrolled as in phase 2, with applicable modifications as identified through phase 2 study design review and optimization.

The main health outcomes assessed in phase 3 are listed in Table 1 and correlate to health measures most commonly monitored in patients with prediabetes and goal outcome measures assessed by the dDPP.

Table 1. Phase 3 study outcomes.

Construct and measure	Data source	Collected at (months)
Clinical outcomes		
Weight reduction (kg)	Noom (via a wireless scale)	Baseline, 6, and 12
Physical activity (steps per day)	Noom (via a wireless pedometer)	Baseline, 6, and 12
A_{1c} (%)	A_{1c} home test kit	Baseline, 6, and 12
Engagement outcomes		
Patient engagement	Noom	Weekly
Number of dDPP[a] log-ins	Noom	Weekly
Number of dDPP lessons completed	Noom	Weekly
Perceived provider involvement with dDPP progress	Patient portal 1-item survey	3, 6, 9, and 12

[a]dDPP: digital diabetes prevention program.

Changes in body weight will be our primary weight-based outcome. Second, we will assess the achievement of a 7% weight loss goal (the DPP weight goal). Weight will be collected from a Bluetooth-linked wireless weight scale, a validated process that automatically reports weigh-ins to the dDPP platform server [6,44-46]. In addition to providing the scale and weight measurement protocol, regular checks of weight data by research staff will be conducted to identify and follow up on values that appear invalid and comparisons with EHR-based data from clinical visits during the study period. Physical activity will be assessed using validated accelerometers or pedometers integrated into the dDPP platform [47-50]. A_{1c} will be assessed using home A_{1c} devices, which have been shown to be safe and equivalent to laboratory testing and are increasingly used in pragmatic digital studies to avoid unnecessary burden on participants [44,51,52].

Patient engagement in the dDPP will be measured using data on log-ins, lesson completion, feature interactions, and messages with coaches and social groups. These data will be reported at regular intervals from the dDPP using a secure application programming interface. Perceptions of engagement will be assessed at both patient and provider levels via a survey at 6- and 12-month intervals. To assess the determinants, process, and outcome measures associated with our theoretical model (capability, opportunity, motivation, ease of use, and usability) and relevant implementation outcomes (acceptability, adoption, cost, and sustainability), patients and providers will be asked to complete the surveys outlined in phase 2, with applicable modifications as identified through phase 2 design review and optimization. Data collection will occur at study enrollment (baseline) and 6- and 12-month intervals.

Data Analysis

All data will be descriptively summarized using frequencies and percentages for categorical variables and means and SDs for normally distributed data or median and IQR for skewed continuous variables. All available data will be included in data listings and tabulations with the number of missing values indicated. All analyses will follow the principle of intention-to-treat. Before analyzing the data, we will compare drop-out and missing data across study arms to assess whether any patient characteristics were associated with the missing data and, if necessary, perform additional analyses using multiple imputation methods.

The primary clinical outcomes (weight reduction or BMI, physical activity, and A_{1c}) will first be analyzed as continuous variables using generalized estimating equation (GEE) models. Each GEE model will include a categorical indicator variable for the randomized study arm (control as reference), a variable corresponding to measurement time (baseline as reference), and an interaction term of the 2 variables. We will explore adjusting for any baseline demographics, use behavior, and survey responses that may be unbalanced between study arms. A Bonferroni-Holm correction method for multiple comparisons will be used to control the type I error rate of 0.05. A similar GEE model with a logit link function will be used to analyze the achievement of a 7% weight loss as a binary dependent variable.

We will also explore the extent to which engagement with the program acts as a mediator. We propose using a single mediator causal model approach with bootstrap-derived confidence intervals to measure the intervention's effect on weight loss, physical activity, and A_{1c} through the specific mechanism of patient engagement.

Privacy and Security

Privacy and security of users' data will be maintained by both the primary research team and the dDPP vendor in accordance with institutional and industry standard practices. We will ensure that participating patients and providers are informed of potential data requirements, usage, storage, and safety policies related to their study participation and follow standard procedures to address privacy breaches if they occur. All trial data will be saved on a dedicated server, available only to the study staff. Data will not be shared with third parties.

Informed Consent and Ethics Approval

Approval will be obtained through the NYULH Institutional Review Board. Participation in this trial is voluntary, and all eligible patients will be informed about the aims, risks, and benefits of the trial. Patients will be provided with written information and a consent form and given time to review the materials fully and ask questions before consenting. All patients can decline to participate in this trial and can withdraw consent at any time without penalty.

Results

The project was initiated in 2018 and funded in September 2019. Enrollment and data collection for phase 1 began in September 2019 under an Institutional Review Board (IRB) quality improvement waiver granted in July 2019. As of December 2020, 27 patients have been enrolled and first results are expected to be submitted for publication in early 2021. The study received IRB approval for phases 2 and 3 in December 2020, and phase 2 enrollment is expected to begin in early 2021.

Discussion

This proposed research will identify the needs and perspectives of key stakeholders in diabetes prevention management and incorporate them into the design and development of a targeted solution to support patient engagement and clinical integration of dDPP platforms. We will use the findings of this study to inform a larger scale study to assess the effectiveness and implementation of this intervention in routine ambulatory practices and diabetes prevention care. This type of technologically integrated support system has the potential to improve both patient engagement in an evidence-based dDPP and the experience of care by providing more seamless access to crucial elements of diabetes prevention for both patients and providers. This in turn may facilitate both disease management and the patient-provider relationship and ultimately improve health outcomes.

Strengths

The strengths of this research include its pragmatic, multiphased UCD, which allows for iterative development and testing of digital interventions before deployment in a full RCT, thereby improving the likelihood of successful deployment and reducing the risks of technical problems, bias, or error in the clinical trial phase. Our use of an integrated theoretical framework that combines behavioral theory with UCD and Agile approaches will ensure that our intervention is both pragmatically and theoretically appropriate. Our partnership with a well-established third-party dDPP vendor leverages existing technology that has considerable market penetration and brand recognition and has been effectively user tested and validated in the consumer marketplace, rather than requiring the development of an in-house dDPP product. The extensive experience of this research team in developing, deploying, and evaluating digital health technologies will facilitate optimal study rollout [36,37,53-61].

Limitations

There are several potential limitations to this study. First, we are only recruiting a small number of patients in phase 1 to identify the requirements of our intervention, which may not be representative of the broader population of patients with prediabetes in our health system. Therefore, it is possible that the features of our intervention will not apply to a larger or more diverse population. To address this, we have partnered with our system's patient advisory committee, which is composed of representative samples of patients who act as patient advocates in research study design. The planned randomized trial will help us gain additional insights into the generalizability of our intervention. Second, although we are able to adapt the components of our intervention to the requirements of our users, we are unable to make changes to the third-party dDPP platform we have partnered with. It is possible that barriers to engagement

and health behavior change will be driven by features of the dDPP platform, rather than our intervention. To address this, our process and outcome instruments will explicitly include questions of usability, ease of use, user experience, capability, opportunity, and motivation for both the *Little e* interventions (our engagement system *and* Noom) and *Big E* (diabetes prevention and lifestyle modification) to allow for analysis of each element. Finally, although the science of patient engagement is becoming more robust, there is still incomplete understanding of the moderators and mediators of engagement in digital applications, particularly digital health tools. It is possible that our study measures and instruments will not completely capture the nuances of user experiences, preferences, drivers, and behavior patterns that comprise engagement in digital behavior change technology or that then translate to behavior change itself. We have attempted to address this by enlisting experts in diverse fields of behavior change, patient engagement, behavioral economics, and digital technology and elsewhere to develop theoretically grounded, contextually relevant methods and measures.

Conclusions

Our findings will help develop, evaluate, and validate technology that facilitates patient engagement in digital behavior change interventions for diabetes prevention and integrates dDPP platforms into existing clinical workflows for providers. Integrated clinical tools that can facilitate patient-provider interaction around dDPPs may contribute to improved patient adherence to these programs and improved health outcomes by addressing barriers faced by both patients and providers. Further evaluation with pilot testing and a clinical trial will assess the effectiveness and implementation of these tools.

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Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control and Prevention
COM-B: Capability, Opportunity, and Motivation Model of Behavior Change
DBCI: digital behavior change intervention
dDPP: digital diabetes prevention program
DM2: type 2 diabetes mellitus
DPP: diabetes prevention program
DT: Design Thinking
EHR: electronic health record
GEE: generalized estimating equation
HIT: health information technology
IRB: Institutional Review Board
J&J: Johnson and Johnson
MVP: minimum viable product
NYULH: New York University Langone Health
RCT: randomized controlled trial
TAM: technology acceptance model
UCD: user-centered design

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Protocol

A Multicomponent Intervention to Reduce Screen Time Among Children Aged 2-5 Years in Chandigarh, North India: Protocol for a Randomized Controlled Trial

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Abstract

Background: Excessive digital screen exposure (≥1 hour per day) is associated with limited growth and development in children.

Objective: This study aims to develop and assess a multicomponent intervention program's effectiveness in reducing excessive screen time among children aged 2-5 years.

Methods: A theory-based multicomponent intervention known as Program to Lower Unwanted Media Screens (PLUMS) at the household level has been developed. It is based on the social cognitive theory for children and self-determination theory for caregivers. After pretesting, a randomized control trial will be conducted to assess this intervention's effectiveness among healthy children aged 2-5 (±3 months) years and their primary caregivers who have at least one digital media gadget at home in zone three of Chandigarh (population of 2,730,035). A sample size of 428 children is estimated per arm. PLUMS includes disseminating specific information, education, communication in the form of videos and posters to the primary caregivers, and conducting motivational interviewing as and when needed. Children will be provided suggestions for playful activities as alternatives to digital media gadgets. The primary outcome is the mean change in the duration of screen time, and secondary outcomes are sleep duration and patterns, emotional-behavioral problems, and level of physical activity of the children. Per-protocol and intention-to-treat analyses will be conducted using SPSS for Macintosh, Version 25.0.

Results: The intervention package will be disseminated once a week for 8 weeks to the participants via the caregivers' preferred means of communication. The endline assessment will be done immediately postintervention and after the 6 months of follow-up. The Institute's ethics committee, Postgraduate Institute of Medical Education and Research, Chandigarh, India, has approved this study (INT/IEC/2019/000711). The Indian Council of Medical Research, New Delhi (3/1/3/Next-100/JRF-2015/HRD), and PGIMER, Chandigarh (71/2-Edu-16/92, Dated 08/01/2018) funded this study.

Conclusions: PLUMS might be effective in reducing excessive screen time among children aged 2-5 years in a North Indian Union Territory.

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KEYWORDS

multimedia; digital-media; preschooler; sedentary behaviors; toddler; sedentary; screen; children; youth

Introduction

Background

The overall impact of sedentary behaviors on health across the lifespan has gathered widespread recognition, as it plays a significant role in most noncommunicable diseases (NCDs) [1]. The Sustainable Development Goals 2030 [2] envisions reducing premature mortality from NCDs by one-third via the prevention, treatment, and promotion of mental health and well-being. Around 34% to 94% of children aged 2 to 5 years remain sedentary during the day [3]. The prevalence of television (TV) viewing for more than 2 hours per day was reportedly 83% in the United States [4] and up to 82% in Canada [5] in children less than 5 years old and 78% in Australia [6] among children aged 3 to 5 years. A Thai study reported that children aged 1 year viewed TV for 1.23 (SD 1.42) hours per day, which increased to 1.69 (SD 1.56) hours per day when they turned 2 years old [7].

Early childhood is a crucial period that is marked by rapid growth and development [8]. Therefore, it is essential to correct an excessively sedentary lifestyle at an early age. These sedentary pursuits may have specific health consequences during this period and later in life [9]. The health effects of excessive screen time (ST) include behavioral problems; poor language, cognitive development, skills, memory, and executive function; lower social competence; sleep disturbances; depression; and low self-esteem [10-17]. In light of this, the present randomized controlled trial was planned with an assumption that ST might be causally associated with emotional behaviors, sleep behaviors, and children's level of physical activity. ST of more than 1 hour per day among children aged 2-5 years is deemed excessive as per the American Academy of Pediatrics [18]. Similar guidelines are available in many developed countries (Australia [19], New Zealand [20], France [21], Italy [22], Canada [23], and World Health Organization [24]) for children aged 2-5 years.

Need for the Trial

A recent review [25] of intervention studies to reduce ST conducted in the last decade (2008-2018) has shown that all the studies (n=16) were conducted in developed countries. Behavior change theories were incorporated in most of the interventions. Educational material was shared with parents with or without their children. Nearly all the significant studies incorporated a postintervention follow-up. Published literature on ST reduction in low- and middle-income countries among young children is scarce [26,27]. Also, there is minimal evidence on the burden, impact, and effectiveness of interventions to reduce ST in Indian settings. Although some of the studies conducted in India have measured change in ST in young children, it was observed only as a secondary outcome [28]. As the number of TV users in India is almost equal to its population [27], designing an intervention to reduce ST among young children becomes more important. Given the Covid-19 pandemic situation, most children's digital-screen exposure occurs at home as families are stuck at home with these media gadgets. Parents are an essential liaison of change between the child and health care worker [29]. Therefore, there is an urgent need to devise interventions for those of a younger age in the home environment to prevent adverse health consequences later in life.

Study Objectives

Given this background, the current study aims to develop a Program to Lower Unwanted Media Screens (PLUMS) to reduce ST among children aged 2-5 years and assess the effectiveness of PLUMS on reducing ST among children in Chandigarh, Union Territory, North India. Effectiveness of the intervention will be determined using the percentage risk reduction of mean ST in the intervention group compared to the control group. As excessive ST is a much less emphasized epidemic, this study's results might focus policy makers on this issue and help them formulate guidelines regarding ST use among young children in India and other low- and middle-income countries.

Methods

The intervention study will be conducted in 2 phases, including the preintervention phase used to develop the intervention and intervention phase, as described in the following sections.

Phase I. Preintervention Phase

The multidimensional intervention package was designed in 3 stages, including literature review, formative research, and pretesting. All 3 stages were completed. The brief methodology and results of each stage are described in the following sections.

Stage I: Review of Literature

In the first stage, the draft PLUMS, including parent and child modules, was prepared after reviewing the existing literature from 2008-2018. Effective community-based interventions to reduce ST in children and the most commonly used theories or models to design the intervention program were identified [25,30]. The following 3 theoretical models were used: social cognitive theory, self-determination theory, and transtheoretical model of behavior change. Social cognitive theory and self-determination theory were used to develop the intervention, and the transtheoretical model of behavior change was used to understand the stage of behavior change of the caregivers, so that the intervention could be customized accordingly. These theoretical models are described in the following paragraphs.

Social cognitive theory was used to modify preschoolers' cognitive development by developing targeted strategies to modify the behaviors of the caregivers and children regarding ST or the home media environment. Bandura's social cognitive theory explains how learning occurs in a social context with a reciprocal and dynamic interaction of the person (here child or caregiver), behavior, and environment. This theory supports a causation model that involves triadic reciprocal determinism between behavioral (expectations, goals, and self-perceptions), personal (cognition, outcome expectation, and efficacy expectation), and environmental factors (reinforcement and observational learning). These factors influence each other bidirectionally (Multimedia Appendix 1). When designing the intervention, we used this theory's framework of modeling (by the caregivers and health care worker), production (alternatives to ST, such as activities given to children or suggested by them),

retention (repeated positive feedback provided by a health care worker), and reinforcement (rewards for encouraging positive behavioral outcomes offered by the health care worker) in observational learning, which is pivotal due to the limited cognitive development of preschoolers [18].

Self-determination theory was used to design the strategies to keep the caregivers motivated to limit the ST among the children and modify the home media environment. Self-determination theory [31] targets 3 primary needs: competence, autonomy, and internalization of the learned concepts leading to desired outcomes. This theory postulates that individuals are better motivated if they satisfy these 3 psychological needs, in turn, leading to positive health outcomes. High-quality learning and favorable outcomes have been observed with the combination of self-determination theory and motivational interviewing [32]. The 4 major motivational interviewing components are empathy, developing discrepancy, "rolling with resistance," and supporting self-efficacy [33]. So, motivational interviewing, along with self-determination theory [34], will be used with the caregivers. Theory-based motivational interviewing will herald the researcher to instruct the caregivers (Multimedia Appendix 2). These motivated and self-determined caregivers will then role-model learned behaviors at home to realize the same in their children and subsequently change the home environment [31].

Last, the transtheoretical model of behavior change by Prochaska et al [33] will be used to modify the caregivers' behaviors. The stage of change will be identified for each caregiver as per the transtheoretical model (Multimedia Appendix 3). The caregivers will be educated and guided towards the desired behavior, eventually preventing relapse.

Stage II: Formative Research

In the second stage, the children's primary caregivers and trained clinicians suggested workable alternatives to ST for children as a result of the formative research. The ideas gathered were refined by an expert panel.

A qualitative study was conducted among parents of children aged 2-5 years and service providers working in a tertiary care hospital in Chandigarh, India. In-depth interviews were conducted (30-40 minutes) with caregivers (n=20) attending the outpatient department. Two focus group discussions were conducted (40-60 minutes) with the service providers (n=11) at a predecided venue and time. The interviews were conducted in the participant's preferred language until data saturation using pretested guides (Multimedia Appendix 4). These interviews were audio-recorded with prior informed consent. Subsequently, thematic analysis was done on the transcribed and translated English versions.

To review and modify the activities and methods proposed by caregivers and clinicians, a consultation meeting with 3 experts (professor-level) from psychiatry, child psychology, and public health was conducted. To decelerate excessive and unregulated ST, the clinicians proposed to increase the quality of family time at home with structured parenting approaches. Caregivers should presume responsibility and effectively use leisure time for children and themselves with health care providers' help when necessary.

The qualitative data obtained through formative research were transcribed and translated into the English language. Thematic analysis of the data was done manually based on grounded theory. Two authors coded the data independently. Both deductive and inductive logic was applied to reason the acceptability and experience of the participants.

The background information of the participants of the in-depth interview and focus group discussions is given in Supplementary Table 1 in Multimedia Appendix 5.

Among the 20 participants in the in-depth interviews, 14 were mothers, and 6 were fathers. The caregivers had a mean age of 34.2 years. Half (10/20, 50%) of the caregivers were educated until the post-graduate level, 50% (10/20) were working, and 40% (8/20) were public health experts. Most (15/20, 75%) of the mothers were the primary caregivers. They were directly involved in their child's behavior modification and introduced media gadgets to them. Digital media exposure usually occurred at home under adult supervision, and aversive measures were frequently used to regulate media gadgets. Most of the caregivers reported negative consequences of excessive ST on their child's health like a change in sleep patterns, learning bad language, impaired emotional behavior, increase in sedentary behaviors, and deterioration in concentration; however, a few perceived a gain in knowledge and development of skills.

In the focus group discussions, the service providers (n=11) had a mean age of 29 years. They were mostly unmarried (9/11, 82%), female (7/11, 64%), and working as junior residents (6/11, 55%). Of the resident doctors, 7 were from the Department of Pediatrics, and 4 were from psychiatry. The clinicians had learned about managing such cases from research articles, methods taught by their seniors, and practical things that worked for their children. Also, they had adapted themselves to the guidelines from developed countries as none exist in India.

Regarding the intervention for children to reduce ST, they reported that at home, adults should instill healthy habits, develop hobbies, and communicate ill effects of excessive usage to their children using role modeling. At the school level or hospital level, a designated person should advise in a stepwise fashion using face-to-face communications with consistent modes of communication preferred by the participant. The intervention package was adapted as per the results of the qualitative study.

Stage III: Intervention: Program to Lower Unwanted Media Screens (PLUMS)

Two modules, one for the caregivers or parents and another for the children, were developed as part of the PLUMS intervention. The strategies were incorporated separately for caregivers and children. These modules have theme-based activities for the children and videos for the parents or caregivers to engage the children in media screen–free activities. PLUMS will be implemented for 8 weeks (2 months) and will consist of 8 themes. Details of these modules are provided in Supplementary Table 2 in Multimedia Appendix 5.

In the caregivers' module, online videos will be disseminated weekly for 8 weeks via the parent's preferred mode of communication. We developed the videos in Hindi and the English language. We developed 1 introductory video and 7 small video sessions based upon the weekly theme. Caregivers can go through the session in their own time as per their convenience, except for the introductory video. The introductory video is planned to be watched with the lead author for a better understanding of the caregivers. The introductory session will last 15-20 minutes, and the 7 weekly videos are 5 minutes long. These online video sessions' primary objective is to help the parents change the home media environment, provide alternatives to ST, provide tips and cues for parenting skills, and engage the child in media-free activities of their choice. These videos will also provide 10 alternative activities per week for children. The caregivers will be encouraged to reward the children for abiding by the rules and accomplishing goals [35].

The child module's lesson plans were drawn from educational disciplines like skill building, motor coordination, learning, goal setting, music, dance, arts, and crafts. This module contains activities for the child that need the caregiver's supervision. To capture the child's interest and channel their energy, specific activities have been selected. This module emphasizes observational learning and increasing the attention span of the child [36]. The curriculum will also allow children to repetitively and effectively learn the desired behavior(s) to facilitate the production and retention processes [36]. We will be providing the following resources as an alternative to screen time for the children: a reading book called "Chika Chika Boom Boom"; pretested and self-developed comic book on the consequences of ST; and coloring book with crayons.

Stage IV: Pretesting the Intervention

In the third stage, the PLUMS intervention, with its parent and child modules, was pretested among 10 families to assess the feasibility, acceptability, and adherence to the intervention plan. After the pretesting, the videos' language was further simplified to match the parents' understanding. The introductory video's duration was reduced from 18 minutes to 12 minutes, as suggested by the families. The videos were made attractive by adding animations, bright colors, background music, and live videos of children (regarding behaviors) recommended by the parents. Additional indoor alternatives to ST were included for the children, as parents could not take the child for outdoor play due to Covid-19 pandemic restrictions. The child module now has 10 activities to choose from instead of 1 per day, as was planned earlier. The children will also be given a coloring book with crayons. The intervention was acceptable and feasible, and the caregivers were ready to adhere to the proposed plan.

Finally, the modified intervention module will be used in the main intervention study.

Phase II: Intervention Study

Study Setting

This study will be conducted in Chandigarh, a North Indian Union Territory. It has a population of about 1,055,450 as per the 2011 census [37]. It is divided into 4 zones. This study will be conducted in Zone three, a field practice area of the Department of Community Medicine and School of Public Health, Postgraduate Institute of Medical Education and Research, Chandigarh, India (Multimedia Appendix 6). It has a population of 250,000 as per the 2018-2019 annual health survey. There are approximately 8681 children aged 2-5 years in this area.

Study Design

The intervention study is a randomized controlled trial.

Study Population

The study population includes the families (N=8681) with children aged 2-5 years (±3 months). The primary caregiver was considered the person who spent most of the time with the child and was involved in the child's decision making for various activities. Inclusion criteria are families who consent to be part of the study, are residents of the study area in Chandigarh for at least the past 6 months, and who intend to stay in Chandigarh through the intervention and follow-up period. Children previously diagnosed (as per medical records) with long-term or chronic illnesses will be excluded from the study.

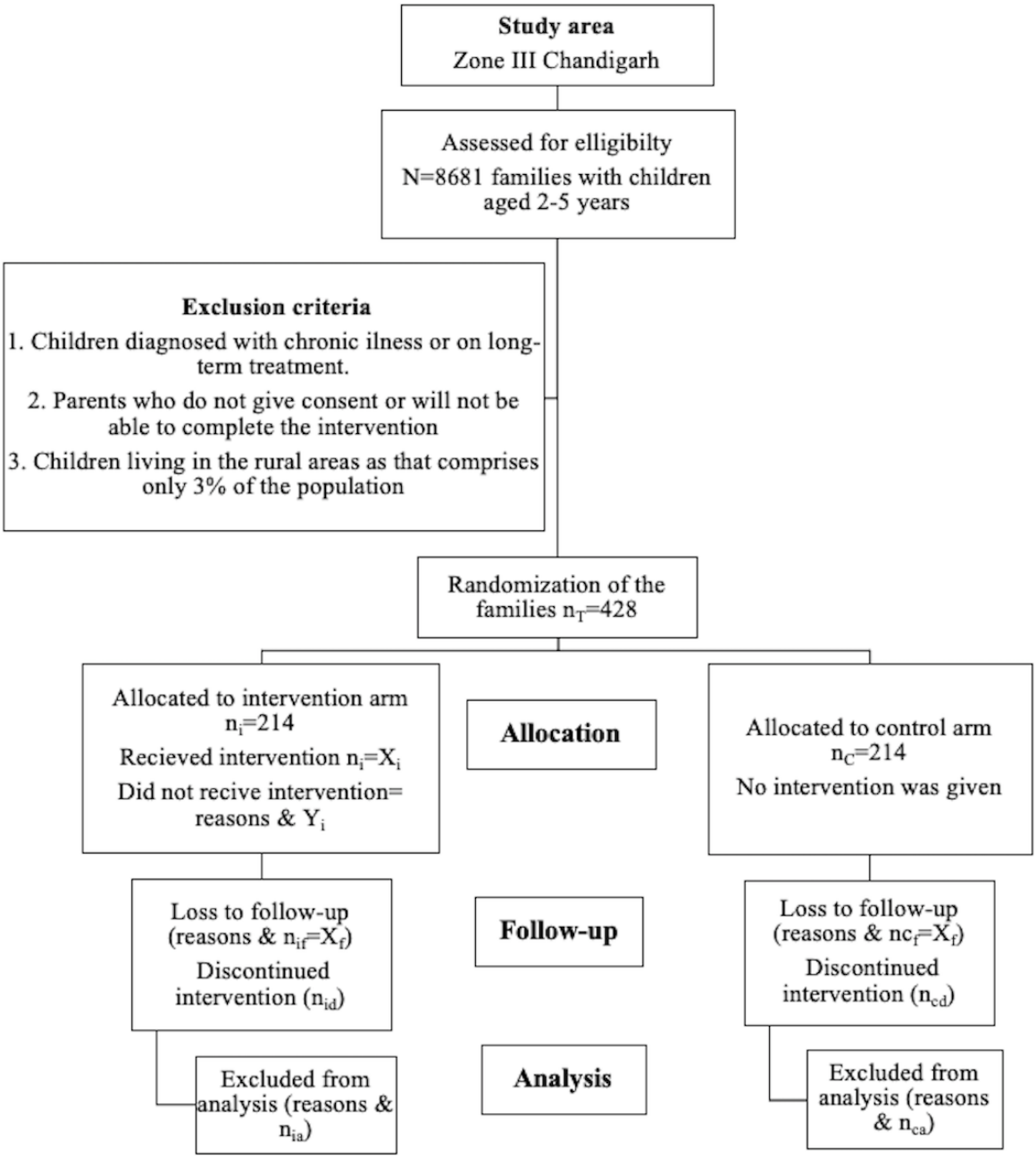
Sample Size

The sample size for the individual level randomization was estimated using the following formula [38]: $n_I = (\sigma_1^2+\sigma_2^2)(Z_{1-\alpha/2}+ Z_{1-\beta})^2/\Delta^2$, where n = sample size, σ_1 = standard deviation of the control group and assumed to be 2.09 [39], σ_2 = standard deviation of the intervention group and assumed to be 1.46 [40], Δ = difference in group means of the average ST and assumed to be 0.54 [39], $Z_{1-\alpha/2}$ = two-sided Z value (Z = 1.96 for the 95% CI), and $Z_{1-\beta}$ = power (80%). Hence, n_I was 170 participants per arm. Considering a 10% attrition rate due to loss to follow-up and 15% nonresponse or refusal rate, the sample size per arm was calculated as 214.

Sampling Technique

The list of eligible families (ie, parents who have children aged 2-5 years) will be obtained from the area's annual health survey report. Families will be randomly selected using the list obtained from the auxiliary nurse midwife. Eligible families providing consent and willing to complete the intervention and follow-ups will be enrolled in the study and randomized into one of 2 groups: control and intervention. The sampling technique and randomization of families using the Consolidated Standards of Reporting Trials (CONSORT) statement is shown in Figure 1 [41].

Figure 1. CONSORT statement flow diagram for the intervention study.



Randomization

Computer-generated randomization will be done to select families for the intervention and control arms. However, restricted randomization will be done so that intervention and control groups have a similar number of families from high, middle, and low socioeconomic groups. Geographical differences (urban and slum areas) in the study area will also be considered during randomization to avoid contamination. A computer-generated sequence will be used to allocate the families in the intervention and control groups. The person generating the list of sequences, collecting data, and disseminating the intervention will be the same; hence, concealment might not be possible. Moreover, as the intervention package comprises information, education, and communication material, concealment might not be possible. Data collection and delivery of the intervention will be done only after the family's allocation in the intervention or control arm.

Blinding

Blinding will not be possible as the investigator will know the participants in the intervention group because he or she will motivate them to continue the intervention at each step. Also, the participants will know that they are being given an intervention to reduce the ST of their children. However, data entry will be performed by a data entry operator who will be blinded.

Stages of the Study

The intervention study will be conducted in 3 stages: baseline assessment, implementation of the intervention, and postintervention assessment.

Baseline Assessment

The baseline data were collected from December 2019 to March 2020. During the baseline assessment, the mean ST, prevalence of excessive ST and its correlates, mean duration of physical activity, emotional problems, and sleep disturbances in both the intervention and control arms were measured.

To assess mean ST, physical activity, and prevalence of excessive ST, a pretested, validated, semistructured, bilingual (English and Hindi languages) digital screen exposure questionnaire (DSEQ) was used (Multimedia Appendix 7). The DSEQ was developed in 5 phases. In phase 1, a draft questionnaire was developed by reviewing the literature on existing tools (n=2) from 2009 to 2017. In phase 2, 9 experts assessed the draft Hindi and English questionnaires' face and content validity. Face-to-face interviews with primary caregivers (n=30) were conducted in a tertiary care hospital for acculturation. In phase 3, a pilot study was conducted among randomly selected families to evaluate the feasibility of the DSEQ in field settings. During phase 4, test-retest reliability was assessed among 30 primary caregivers selected randomly in another urban cluster. In phase 5, the internal consistency of the DSEQ was checked by conducting a cross-sectional study among 400 randomly selected, primary caregivers in Chandigarh, North India. The DSEQ has good internal consistency (Cronbach α=0.73-0.82) and inter-rater agreement (kappa 0.75, 95% CI 0.72-0.78).

The DSEQ was used to collect information from the primary caregivers of the children on (1) sociodemographic profile including family type and socioeconomic status (BG Prasad classification, 2016) [42], (2) digital screen exposure and home media environment, (3) level of physical activity of the child, (4) child's media-related behaviors, and (5) parental perceptions and literacy regarding digital screen exposure. We recorded the duration and content of media watched by the child on a typical day. The objective criterion to measure ST was the number of hours the child watched a specific TV program. Cinema and movies were excluded from the ST measurement to calculate the actual average of ST for a regular day. Besides, cinema and movies are not watched daily and might falsely increase ST.

We used the 5 progressive physical activity levels among preschoolers given in the Preschool Physical Activity Questionnaire (PrePAQ) to assess physical activity. The PrePAQ categorizes activity into stationery (no action), sedentary (limb or trunk movement), slow-paced (moving easily or slowly), medium-paced (moving at a moderate pace), and fast-paced (quick pace or hard effort) [43].

The standard Preschool Child Behavior Check List was used to assess the child's emotional and behavioral development. It has been validated in an Indian setting and has the right internal consistency (Cronbach α=0.95) [44]. It consists of 100 items with a 3-step response scale (0, 1, and 2). These items are scored as being absent (score, 0), occasionally present (score, 1), and very often present (score, 2).

The sleep disturbances scale for children was used to measure the child's sleep patterns. It is a 26-item Likert-type scale that measures specific sleep disorders along with overall sleep disturbances in children. It has been validated and has an internal consistency of 0.71-0.79, test-retest reliability of 0.71, and diagnostic accuracy of 0.91 [40].

The lead author visited the homes of the study families and conducted face-to-face interviews during the baseline assessment.

Implementing the Intervention

In this stage, the PLUMS intervention will be delivered over an 8-week period at the household level in the intervention arm, as already described (Supplementary Table 2 in Multimedia Appendix 5). The objectives of the intervention are to reduce the ST of children [18], enable the caregivers with positive parenting skills and ST literacy, and propose unplugged family time in the home environment.

Participants in the intervention arm will also be classified into 5 behavior stages of change as per the transtheoretical model [45]. In the control arm, routine home-based and facility-based health services will be continued by the local auxiliary nurse midwife under the public health system. Compliance of the intervention will be checked via a proforma from parents (Supplementary Table 3 in Multimedia Appendix 5) and via a journal, videos, or pictures maintained by families.

Postintervention Assessment

In this stage, the same questionnaire for ST and its correlates as used in the baseline assessment will be administered to the intervention and control groups immediately and 6 months postintervention. Hence, primary and secondary outcome measures will be assessed at these 2 time points. In addition to the 2 months of active intervention, the researcher will maintain contact with the intervention arm group participants during the 6-month follow-up period. A passive intervention via information education material (text messages, telephone, emails, or mail) to parents will be given during the follow-up period.

This intervention study will take place over a period of 8 months. The baseline data collection will take place before the intervention (t_0). The postintervention phase (t_1) and follow-up assessment will be done at 6 months (t_2), as shown in Supplementary Table 4 in Multimedia Appendix 5, as per the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [46].

Outcomes

The primary outcome (caregiver-reported) measure will be the mean change in ST (in minutes) per day separately for weekdays and weekends. The secondary outcomes (caregiver-reported) will be the mean change in the duration of physical activity (in minutes), proportion of children with emotional behavior problems, and sleep disturbances. For emotional behavior and sleep disturbances, the change in scores as per the tools will be noted, as mentioned earlier.

Data Management and Analysis

Quantitative data from the intervention study will be entered into Microsoft Excel and analyzed using SPSS for Macintosh, Version 25.0 (IBM Corp, Armonk, NY). ST on a weekday and

weekend day will be calculated separately as per available literature [47]. So, the average ST (by viewing any type of media gadget) per day in a week will be calculated, and because there are 5 weekdays (Monday to Friday) and 2 weekend days (Saturday and Sunday) in a week, the weighted average ST per day in a week will be calculated as: Average ST per day (minutes) = [(Weekday ST in minutes x 5) + (Weekend ST in minutes x 2)]/7.

Continuous variables will be summarized as means with interquartile ranges and standard deviations. Correlations between a continuous variable and other variables will be estimated. Categorical variables will be summarized as proportions, and differences between groups will be tested using chi square tests. The data will be analyzed as per intention-to-treat analysis (for their initially assigned study arm) and per-protocol analysis. Relative risks and their effect sizes, together with the corresponding 95% CIs, will be estimated. The effectiveness of the intervention will be estimated by calculating the relative risk reduction (1-relative risk). A *P* value <.05 will be considered statistically significant for all analyses.

Information regarding PLUMS will be shared in the first communication and then reinforced every week for 8 weeks. So, participants who withdraw from the trial after the third week will be included in the analysis. Participants who withdraw any time before the third week will be excluded from the analysis.

Caregivers' knowledge will be analyzed at the end of the intervention if no associations are observed. The proforma on behavior change will be completed at baseline (t_0) and endline (t_1) to determine the stage of change the families are at postintervention.

A feedback/compliance questionnaire (Supplementary Table 3 in Multimedia Appendix 5) will be given to the caregivers at each counseling session (weekly) to check their fidelity. The child's fidelity, including the level of engagement, will be checked with personalized journals comprising the activities they performed during the given intervention. The parents will be contacted via their preferred mode of communication weekly to keep them motivated and disseminate the next week's intervention module.

Ethics and Dissemination

Ethical approval was obtained from the institutes' ethics committee: Postgraduate Institute of Medical Education and Research, Chandigarh, India (INT/IEC/2019/000711, Dated 02/04/2019).

Results

Enrollment of all participants (n=440) was completed during the baseline assessment. The intervention phase could not be started due to restrictions imposed under lockdown to contain the Covid-19 pandemic. Considering the Covid-19 pandemic and likely change in the ST and physical activity of the children, we will measure the ST and physical activity again before delivering the intervention. The intervention was started in November 2020. It will be implemented for 8 weeks. The endline assessment will be done immediately postintervention and after the 6 months of follow-up. The results will most likely be published by 2022.

Discussion

Principal Findings

Developing countries have seen a recent explosion in digital media, leading to increased ST and sedentary behavior in the younger generation [47]. However, the exact burden and impact of excessive ST exposure, especially among young children, are not well known. An Indian study concluded that 60% of the children (2-5 years) in North India used digital media gadgets for more than 1 hour per day. Bansal et al [48] from South India reported a 72% prevalence of ST for more than 1 hour per day (mobile usage only) among children younger than 15 years [48]. In addition, Indian children (3-11 years old) [49] and Korean children (2-5 years old) [47] experience ST of <1.4 hours per day and <1.21 hours per day, respectively. Since few local studies were available, the present study was planned to reduce the average mean duration of ST in children rather than the proportion.

Previous studies [38] have focused on the usage and impact of TV viewing in children; however, this study includes all digital media types being used by young children (3-5 years old). A systematic review suggested that the most effective interventions for ST reduction in children (0-5 years old) were ≥6 months in duration and conducted in a community setting [30]. Hence, in this study, a home-based intervention was developed to generate evidence on its effectiveness in reducing ST among young children from developing countries. This intervention includes providing feasible alternatives to ST and spending quality family time to strengthen parent-child bonding. Engaging children in goal setting [50] to decrease ST has been proven an effective measure. Also, the intervention plans to design workable measures to limit ST and improve the parent-child relationship in low- and middle-income countries. Further, involving children in alternative activities channels their energy, boosts their confidence, and decreases ST. Since there is evidence that there is a significantly higher risk of abnormal sleep with a TV in the bedroom [50], the interventions in this study include advising caregivers about changing the home media environment to decrease overall ST for children.

With advancements in technology, many newer media gadgets have been introduced in the younger generation's digital-media ecosystem [51]. The existing literature suggests that sedentary behaviors due to excessive media gadget use in children may adversely affect their overall health and social outcomes; however, the pros and cons of their use have not been well understood [52]. Given this, the present study was planned as a home-based intervention study over 6 months to reduce ST among young children. Randomized controlled trials are a punctilious way of determining a cause-effect relation between treatment and outcome [53]. The present study will adhere to the latest American Academy of Pediatrics guidelines [18], which state that children aged 2-5 years should not be exposed to more than 1 hour of high-quality educational ST. To ensure the participants' compliance with PLUMS, the intervention plan is intended to be delivered at a place convenient to the

participants. The caregivers will be counseled at the time and place of their choice.

Strengths

The strengths of this study are that the participants represent Chandigarh's population; hence, the study results can be generalized. There are no published intervention studies from India in this age group and on ST [25]. This study will be the first study that provides a home-based intervention plan to families based upon commonly used theories (transtheoretical model of behavior change [33], social cognitive theory [54], and self-determination theory [25]). This intervention complies with the latest American Academy of Pediatrics guidelines (2016), while previous studies were based on older guidelines. Also, this intervention study focuses on enhancing parents' literacy concerning ST and will eventually have a long-term effect.

Limitations

Social desirability bias might result in caretakers changing some responses. Last, as there is no reliable measure of child ST, recall bias might be introduced because we are relying on the parents' memory. However, to overcome these biases, the investigator recorded all the programs the child watched in the last week and the approximate duration of these programs. Then, to prevent recall bias, TV diaries were proposed to capture the children's actual ST during the day. We will develop a journal comprised of daily activities for children. This journal will cross-check compliance with the intervention and activities preferred by the children at home. Last, there are limited validated tools in literature, so the DSEQ was developed, validated, and pretested to measure ST.

Conclusion

The results from this study might guide policymakers to formulate guidelines on preventing excessive digital screen exposure among young children, the media content watched by children, and the importance of ST on growth and development in childhood, especially in the context of low- and middle-income countries. The results will also facilitate the implementation of an ST reduction intervention program among children aged 2-5 years, which may help prevent NCDs and the attainment of sustainable development goals.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Social Cognitive Theory (SCT) for designing the intervention.
[PNG File , 298 KB - resprot_v10i2e24106_app1.png]

Multimedia Appendix 2
Self-determination theory for motivational interviewing.
[PNG File , 342 KB - resprot_v10i2e24106_app2.png]

Multimedia Appendix 3
Transtheoretical model for stages of change.
[PNG File , 273 KB - resprot_v10i2e24106_app3.png]

Multimedia Appendix 4
Qualitative interview guides.
[DOCX File , 19 KB - resprot_v10i2e24106_app4.docx]

Multimedia Appendix 5
Supplementary tables.
[DOCX File , 33 KB - resprot_v10i2e24106_app5.docx]

Multimedia Appendix 6
Map of Chandigarh showing the study area.

[PNG File , 2295 KB - resprot_v10i2e24106_app6.png]

Multimedia Appendix 7
Digital Screen Exposure Questionnaire-DSEQ.
[DOCX File , 229 KB - resprot_v10i2e24106_app7.docx]

Multimedia Appendix 8
Peer-review reports from the PGIMER Doctoral Committee.
[PDF File (Adobe PDF File), 5062 KB - resprot_v10i2e24106_app8.pdf]

Multimedia Appendix 9
CONSORT 2010 checklist of information to include when reporting a randomized trial.
[PDF File (Adobe PDF File), 67 KB - resprot_v10i2e24106_app9.pdf]

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Abbreviations

CONSORT: Consolidated standards of reporting trials statement
DSEQ: Digital Screen Exposure Questionnaire
NCD: noncommunicable disease
PLUMS: Program to Lower Unwanted Media Screens
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
ST: screen time
TV: television

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Protocol

A Web-Based eHealth Intervention to Improve the Quality of Life of Older Adults With Multiple Chronic Conditions: Protocol for a Randomized Controlled Trial

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Abstract

Background: Multiple chronic conditions (MCCs) are common among older adults and expensive to manage. Two-thirds of Medicare beneficiaries have multiple conditions (eg, diabetes and osteoarthritis) and account for more than 90% of Medicare spending. Patients with MCCs also experience lower quality of life and worse medical and psychiatric outcomes than patients without MCCs. In primary care settings, where MCCs are generally treated, care often focuses on laboratory results and medication management, and not quality of life, due in part to time constraints. eHealth systems, which have been shown to improve multiple outcomes, may be able to fill the gap, supplementing primary care and improving these patients' lives.

Objective: This study aims to assess the effects of ElderTree (ET), an eHealth intervention for older adults with MCCs, on quality of life and related measures.

Methods: In this unblinded study, 346 adults aged 65 years and older with at least 3 of 5 targeted high-risk chronic conditions (hypertension, hyperlipidemia, diabetes, osteoarthritis, and BMI ≥30 kg/m2) were recruited from primary care clinics and randomized in a ratio of 1:1 to one of 2 conditions: usual care (UC) plus laptop computer, internet service, and ET or a control consisting of UC plus laptop and internet but no ET. Patients with ET have access for 12 months and will be followed up for an additional 6 months, for a total of 18 months. The primary outcomes of this study are the differences between the 2 groups with regard to measures of quality of life, psychological well-being, and loneliness. The secondary outcomes are between-group differences in laboratory scores, falls, symptom distress, medication adherence, and crisis and long-term health care use. We will also examine the mediators and moderators of the effects of ET. At baseline and months 6, 12, and 18, patients complete written surveys comprising validated scales selected for good psychometric properties with similar populations; laboratory data are collected from eHealth records; health care use and chronic conditions are collected from health records and patient surveys; and ET use data are collected continuously in system logs. We will use general linear models and linear mixed models to evaluate primary and secondary outcomes over time, with treatment condition as a between-subjects factor. Separate analyses will be conducted for outcomes that are noncontinuous or not correlated with other outcomes.

Results: Recruitment was conducted from January 2018 to December 2019, and 346 participants were recruited. The intervention period will end in June 2021.

Conclusions: With self-management and motivational strategies, health tracking, educational tools, and peer community and support, ET may help improve outcomes for patients coping with ongoing, complex MCCs. In addition, it may relieve some stress on the primary care system, with potential cost implications.

Trial Registration: ClinicalTrials.gov NCT03387735; https://www.clinicaltrials.gov/ct2/show/NCT03387735.

International Registered Report Identifier (IRRID): DERR1-10.2196/25175

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KEYWORDS

eHealth; telemedicine; aged; geriatrics; multiple chronic conditions; depression; social support; quality of life; primary care; health expenditures; mobile phone

Introduction

Background

Multiple chronic conditions (MCCs) are both common among patients aged 65 years and older and expensive to manage. Two-thirds of Medicare beneficiaries have more than one chronic condition, such as diabetes or high blood pressure, and they account for more than 90% of all Medicare spending [1-3]. According to the latest available numbers from the Centers for Medicare and Medicaid Services, per-capita spending in 2017 increased exponentially with the number of chronic conditions, from US $2032 for patients without MCCs to US $32,247 for patients with 6 conditions or more. Patients with ≥6 chronic conditions, making up just 17% of beneficiaries, accounted for 53% of expenditures [1]. In summary, the impact of MCCs on health care use and costs is immense.

For the individual patient, MCCs are equally consequential. MCCs are associated with lower quality of life, poorer response to treatment, worse medical and psychiatric outcomes, higher mortality, and greater financial burden for both patients and families [4]. In addition, numerous studies indicate that chronic conditions contribute to loneliness and that loneliness in turn contributes to reduced functionality and chronic illness [5-7].

MCCs are not simply aggregates of several distinct conditions. They represent overlapping conditions that often have common root causes and, when grouped together, can severely impact a patient's treatment options as well as quality of life. Primary care providers face many challenges in treating patients with MCCs, particularly how to address the complexity and chronic nature of MCCs within the constraining time frames typically allotted in primary care settings [8-12]. As such, most providers necessarily focus on managing medication and laboratory results for MCCs, with little time left for self-management strategies and skills [13]. However, treatment adherence, health tracking, and feedback to clinicians are likely to be particularly important for patients with MCCs, given the challenges of polypharmacy and multiple ongoing treatment needs. In addition, patients need education about how to *live* with their conditions, in that they are chronic.

Previous studies have shown that information and communication technologies can address these gaps, improving not only self-management and health care effectiveness but also social and emotional support. An extensive review of eHealth apps for cardiovascular disease [14] found promising results in clinical trials on hypertension and hyperlipidemia; another review [15] found that eHealth interventions reduce blood pressure and increase the likelihood of blood pressure control. Other reviews [16,17] found positive outcomes in 29 of 32 studies of chronic condition interventions delivered via computer and mobile phone, with more impact coming from multiservice programs [18]. Internet-based interventions have proven effective in reducing pain [19,20]. Finally, a review of eHealth programs for diabetes concluded that there is clear potential for benefit, although studies have generally been poorly designed or underpowered [21].

Need for a Trial

This paper reports on the study design and methods of a trial of ElderTree (ET), a web-based health intervention designed to improve quality of life and socioemotional outcomes among older adults with MCCs. One of several eHealth systems collectively known as CHESS (Comprehensive Health Enhancement Support System), ET is an information and support platform developed by our Agency for Healthcare Research and Quality Center of Excellence in Active Aging to help older adults remain independent. ET was previously tested in a randomized controlled trial (RCT) involving 390 older adults in 5 Wisconsin counties (urban, suburban, and rural) who were followed up during the 12 months of the intervention [22].

As reported in a paper submitted for publication and under review, the results of the intention-to-treat RCT showed that study arm interacted with amount of primary care use to predict mental quality of life, social support (both received and provided), and depression, such that for participants with 3 or more primary care visits in the 6 months before baseline, those in the ET group performed significantly better than those in the control group. In addition, positive results among ET participants for functional independence, as measured by independent activities of daily living, approached significance.

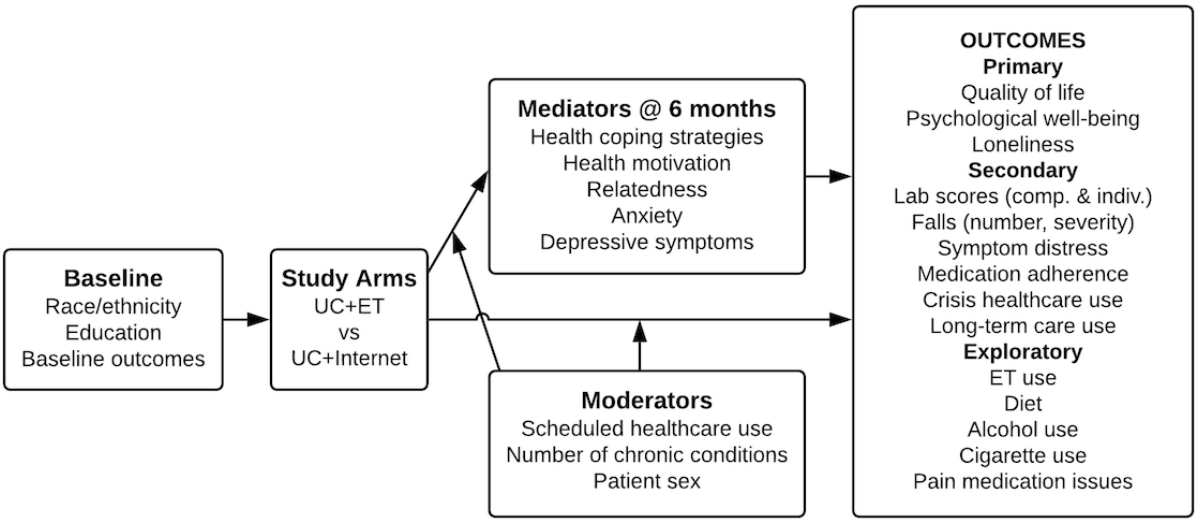
The results of the RCT suggest that ET may be more effective among patients dealing with MCCs, given that primary care use is relatively high among such patients, and that a system such as ET may be most effective if integrated into primary care. The study described in this protocol seeks to build on those findings, examining effects among patients in primary care with MCCs rather than a general older population, focusing not only

on patient-centered outcomes such as quality of life but also on laboratory scores and levels of crisis-related health care use.

Choice of Comparators

Participants recruited from primary care clinics have been randomized to receive either (1) usual care (UC) plus a touchscreen laptop delivering the ET intervention (UC+ET) or (2) a touchscreen laptop delivering internet access and links to high-quality medical information websites but not to ET (UC+internet) for 12 months. This comparison controls for the effects of access to the laptop and the internet, isolating the specific effects of access to ET. The overarching goal of the study is to test the effects of ET on patient outcomes, including the examination of mediating processes and subgroup differences (moderation). Figure 1 shows the logic diagram.

Figure 1. Study logic diagram. ET: ElderTree; UC: usual care.



Study Objectives

Primary Objective

The primary objective is to determine whether patients assigned to UC+ET (vs those assigned to UC+internet) will have greater improvements over time in quality of life and psychological well-being and greater reductions over time in loneliness. Quality of life is a multifaceted variable encompassing global assessments of health and quality of life as well as physical, mental, emotional, and social dimensions. Psychological well-being encompasses feelings of meaningfulness, social connectedness, engagement, and optimism.

Secondary Objectives

There are several key secondary objectives. One is to determine whether patients assigned to UC+ET, versus UC+internet, will have greater improvements in composite and individual health scores (see the *Measures* section). Other secondary objectives are to determine whether patients assigned to UC+ET will have greater reductions in the number and severity of falls, greater improvements in symptom distress, greater improvements in medication adherence, and greater reductions in crisis health care use and long-term care use.

Exploratory

We plan to explore the effects of study arm on improvements over time in patients' diet, alcohol use, cigarette use, and pain medication issues (eg, hoarding). Within the UC+ET arm, we will describe the amount and types of ET use (ie, services used) and examine the associations between these variables and the primary outcomes.

Mediation

We will investigate whether the effects of study arm on change from baseline to endpoint in primary and secondary outcomes (Figure 1) are mediated by midpoint (6-month) changes in health coping strategies, health-related motivation, feelings of relatedness, and levels of anxiety and depressive symptoms.

Moderation

We will investigate whether the effects of study arm on change from baseline to endpoint in primary and secondary outcomes (Figure 1) are moderated by participant sex (ie, women show more benefits than men), scheduled health care use (those with higher levels of primary, specialist, physical and occupational therapy, chiropractor, and counseling visits show more benefits), and number of chronic conditions (those with more conditions show more benefits).

Trial Design

The ET trial is a randomized controlled design with 2 parallel groups with a 1:1 allocation.

Methods

Sample Size and Study Setting

A total of 346 older adult patients with at least 3 of 5 targeted high-risk chronic conditions (hypertension, hyperlipidemia, diabetes, osteoarthritis, and BMI ≥30 kg/m^2) have been recruited

from primary care clinics within the University of Wisconsin–Madison Department of Family Medicine and General Internal Medicine system (UW Health).

Eligibility Criteria

Eligible patients (1) are aged 65 years or older; (2) have been treated in the clinic for at least the previous 18 months (to have baseline laboratory data on all measures) with no plans to leave during the study period; (3) have 3 or more of the following 5 chronic conditions: hypertension, hyperlipidemia, diabetes, arthritis, and BMI ≥30 kg/m^2; (4) report no current psychotic disorder that would prevent participation; (5) have no acute medical problem requiring immediate hospitalization; (6) do not have a visual or motor impairment that prevents them from using a computer; (7) are able to read and sign the consent form in English; (8) are willing to share health-related study data (eg, laboratory scores, health care utilization); (9) allow researchers to share information with the patient's primary care physician; and (10) do not have moderate or advanced dementia. In addition to 3 or more of the 5 conditions mentioned earlier, patients may have any of the following conditions: chronic kidney disease, chronic pain, chronic obstructive pulmonary disease, congestive heart failure, arrhythmia or atrial fibrillation, pulmonary heart or vascular disease, anxiety, and depression. We will document and describe eligible people who choose not to participate.

Intervention Groups

Patients in both conditions are continuing with their UC provided by primary care and internal medicine clinics in the UW system. Participants receive the intervention for 12 months and are followed up 6 months later for a total on-study period of 18 months.

All participants are offered a study laptop, whether or not they have one. A computer they already own may be older and out of date, so using the study laptop is better for both participant and technical support. In addition, the laptop can be a dedicated computer for the study so that participants are not sharing the study device with others in the household.

Control Condition: UC+Internet

In addition to UC, patients in the control condition receive internet service and a laptop computer, provided by the study group if desired, as well as training for 12 months. General health information websites published by the Cleveland Clinic, National Institute on Aging, American Academy of Family Physicians, and Mayo Clinic are loaded on the computer for easy access. These sites are vetted for quality by our research team. We expect the UC+internet intervention to be relatively ineffective because information alone is unlikely to have a significant effect on health behaviors [23-26]. Instead, access to the device, the internet, and the sites will function both as an attention control and as a way to isolate the specific effects of access to ET. In summary, this study is designed with an attention control rather than a pure control comparison.

Experimental Condition: UC+ET

Patients in the experimental condition receive ET access for 12 months in addition to their UC, as well as a laptop computer and internet, if desired. These patients do not receive the 4 health information websites placed on computers for the control condition patients, although they could seek them out.

ET Intervention

For more than 30 years, our Center has been developing and testing a suite of evolving eHealth systems built on principles of continuing care and self-management: long duration [27]; assertive outreach [28]; tracking [29]; prompts [30]; action planning [31]; problem solving [13]; self-tailoring [13]; peer, family, and clinical support [32]; case management [33]; and care coordination [34]. In randomized trials, these CHESS systems significantly improved asthma control [35]; quality of life and cost of care in patients with HIV [36]; quality of life and self-efficacy in patients with breast cancer, including older adult women [37], compared with control [38] and internet [26] groups; risky drinking [39]; and caregiver burden, symptom distress, and median length of survival in patients with lung cancer [40].

Although ET is built on the CHESS experience, its interface and content are quite different from our systems serving other health concerns and populations. ET is designed specifically for older adults and with their input, featuring larger fonts, fewer options, appealing images and layouts, and uncluttered screens for easier comprehension, navigation, and usability [41].

System Overview

ET provides tools, motivation, and social support to help patients (1) manage their specific set of chronic conditions, (2) communicate with peers and research staff, and (3) improve communication with clinicians. This study is based on the earlier ET system, with a few new or enhanced services (weekly health tracking survey, clinician report, daily entertainment feature) and expanded health information resources. The design and navigation are based on the original ET system and the principles established in our earlier testing [41].

As stated earlier (see the *Need for a Trial* section), our original clinical trial found the greatest improvements associated with ET in psychosocial outcomes. To further these outcomes, we added a daily interactive entertainment feature (lighthearted polls, quizzes, games, and reflection prompts) as a means of boosting enjoyment of the site and engagement with other participants.

The weekly survey is an enhancement of a basic health tracking feature in the original version, and the related clinician report, both described below, is altogether new to ET. We used a clinician report in a lung cancer RCT comparing a CHESS system alone with CHESS+clinician report [42] and found that the addition improved (P<.001) symptom distress by over 100% (26.2% improvement with CHESS vs 53% in those with CHESS+clinician report: n=71 vs n=68, respectively).

Weekly Survey

Patients using ET are prompted to complete weekly check-ins, on which they rate their experience on 10 health indicators: sleep, nutrition, physical activity, cognition, balance, falls, mood, pain management, medication adherence, and quality of social interactions. At the completion of each check-in, ET commends positive results or, if struggle is detected, directs the

patient to helpful site information. The system may also recommend contacting the clinic if the algorithm detects a sudden or steep change or a problem that may not be severe but is not improving. In addition, for easy visual interpretation, ET displays a graph charting the patient's responses for each indicator over the last 3 months. The graph, showing health trends and current status, is also shared with the primary care clinic (the clinician report). In addition, ET offers the patient a printout to take to a primary care visit, in case the clinician has not viewed the report.

Clinician Report

MCCs can lead to rapid declines in health [2]. However, support for patients with MCCs usually consists of periodic, onsite contact with primary care clinicians, who may be unaware of and/or cannot respond as promptly as may be warranted to such changes. Moreover, patients may avoid "bothering" the doctor, foreclosing a source of help that might make a difference.

The clinician report shares timely information on patient general indicators and helps both patients and clinicians prepare for and make the most of primary care office visits. As a one-page graphic summary of the patient's health tracking data, the report can be viewed in a matter of seconds, avoiding a time burden for clinicians while allowing them to be better informed and provide treatment more responsively on the basis of patient needs.

One week before a participant's scheduled appointment, the clinician report is sent to the primary care doctor via email (password-protected PDF file) or fax. The mode of delivery has been chosen by each clinic based on what works best in their workflow. Typically, the recipient of the clinician report is the clinic manager or other administrator, who then forwards it to the clinician, either printing it out or via email. A hard copy of the clinician report is also mailed directly to the participant, as noted earlier, to take to the appointment.

In addition, every 2 months, the project manager prepares a clinician report summary that provides an overview for all patients at each clinic. The goal is to help clinicians identify patients who are reporting issues between appointments, such as missed medications or mood declines, particularly as patients continue to isolate due to COVID-19. This report is emailed to clinic managers to share with individual clinicians.

Theoretical Foundation

Similar to other CHESS systems, ET is consistent with Self-Determination Theory, which asserts that satisfying 3 fundamental psychological needs contributes to adaptive functioning: competence (feeling effective), social relatedness (feeling connected to others), and autonomy (feeling internally motivated rather than coerced) [43].

Interface and Features

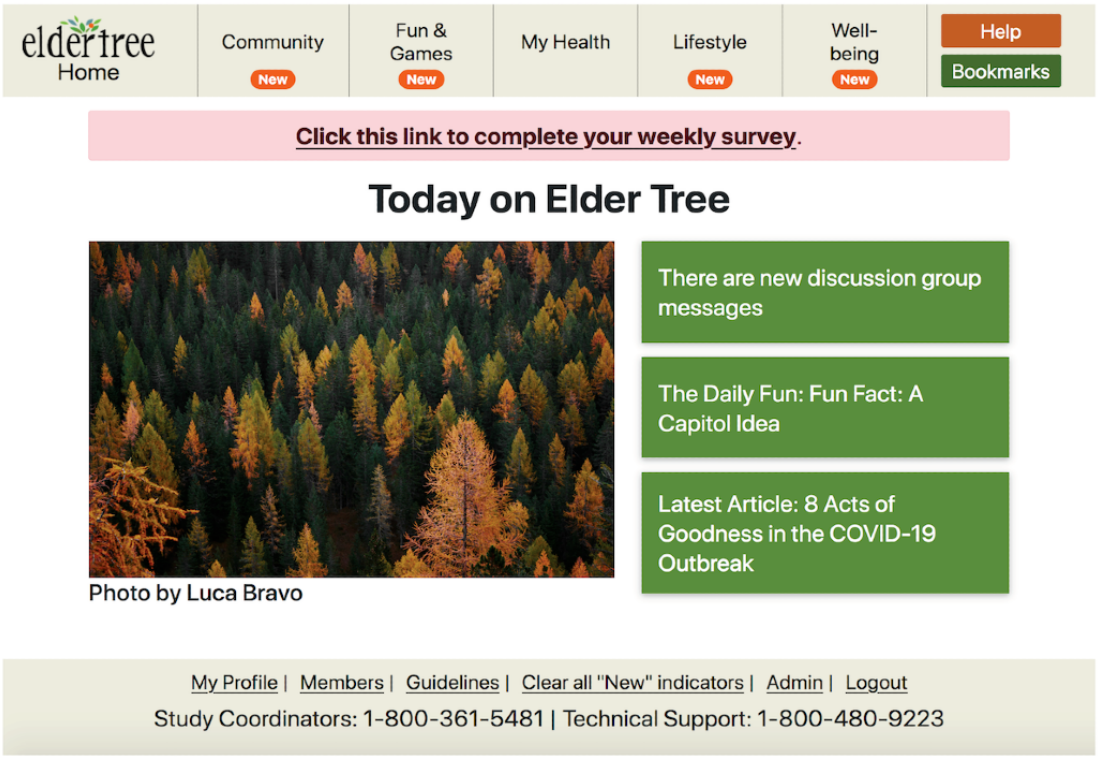
The key features of the site, aligned with how they relate to Self-Determination Theory, are described in Table 1. The ET system is based on the 3 components of the theory as shown, but we acknowledge that these are interrelated, potentially larger, latent constructs [44] and that services for one outcome likely affect other outcomes.

Figure 2 shows the ET home page, with its clear navigation to features listed in Table 1 and prompts customized to the individual user.

Table 1. Key features of the ElderTree eHealth intervention.

Aim of feature and ElderTree tab or element	Feature title or function	Description
Tools fostering health-related coping competence		
My Health	Health Library	Informational resources and materials, organized by health and wellness topic area
My Health	Weekly survey, clinician report	Tracking of 10 self-reported general health measures, graphed over time, displayed for patients, and sent to primary care clinicians
Community	Health Matters discussion board	Tips, experiences, and resources for managing multiple chronic conditions [45]
Tools fostering social relatedness and positive affect		
Community	Discussion Groups	Monitored online support and chat forums [46,47]
Community	Private Messages	Email-like function for private communication among users and research staff
Community	Bulletin Board	Local activities, continuously updated
Fun & Games	Laugh Out Loud, Social Games, Daily Fun	Interactive games, jokes, puzzles, polls, quizzes, videos, and trivia, refreshed daily
All areas	Comment functionality	Universal posting function to encourage engagement, support, and relationship building
Footer of every page	Members profiles	User-created interest and history profiles serving as introductions
Tools fostering health-related motivation		
Well-being	Daily Reflection	Journal function with prompts based on positive psychology principles
Opening screen, Community	Thought of the Day	Motivational and inspirational quotes
Well-being	Relaxation Exercises	Progressive relaxation, deep breathing, meditation, and mindfulness audio and video
Lifestyle	Lifestyle blog	Inspirational articles on topics such as travel, mind and body, and nature

Figure 2. ElderTree homepage view.



Measures

Table 2 lists the variables and measures for primary, secondary, and exploratory outcomes. Scales were selected to have good psychometric properties with similar populations. Patient-reported outcome measures, including any modifications to validated scales, are described following the table.

Table 2. Study outcomes, variables, and measures.

Category and variable	Measure name and description	Number of items	Source
Primary outcomes			
Quality of life	PROMIS[a] Global Health	10	Patient
Psychological well-being	Psychological Flourishing Scale	8	Patient
Loneliness	UCLA Loneliness Scale	8	Patient
Secondary outcomes			
Composite and individual laboratory scores	Z scores: mm Hg, mg/dL, glycated hemoglobin (HbA_{1c}), Visual Analog Scale pain, BMI deviation from normal range	6	EHR[b]
Falls	Number/severity in past 3 months	2	Patient
Symptom distress	General Symptom Distress Scale, Bayliss Disease Burden Scale	21	Patient
Medication adherence	Based on Brief Medication Questionnaire	8	Patient
Crisis health care use	Emergency room visits, urgent care visits, days/occurrences in hospital, 30-day readmissions	5	EHR, patient
Long-term care use	Nights in assisted living, nursing home	2	Patient
Exploratory outcomes			
Amount or type of ElderTree use	Automatically logged keystrokes	N/A[c]	System logs
Diet	Healthy foods and snacks (custom list)	7	Patient
Alcohol use	Alcohol Use Disorders Identification Test	8	Patient
Cigarette use	Cigarettes per day	1	Patient
Pain medication issues	Centers for Disease Control and Prevention pain medication survey (modified)	8	Patient

[a]PROMIS: Patient-Reported Outcomes Measurement Information System.

[b]EHR: electronic health record.

[c]N/A: not applicable.

Primary Outcomes

Quality of life is assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health measure [48,49]. For consistency with other measures (ie, to reduce respondent burden), the time frame has been modified to refer to the past 2 weeks. Psychological well-being is assessed using the Psychological Flourishing Scale [50]. The wording of items has been somewhat modified, including simplifying double-barreled items. For example, “I lead a purposeful and meaningful life” is shortened to “I lead a meaningful life.” Loneliness is measured using the 8 items from the UCLA Loneliness Scale with the highest factor loadings among older adults in the validation paper by Russell [51].

Secondary Outcomes

Health scores are obtained from the patient’s electronic health record (EHR). Composite health scores are the averaged Z scores of mm Hg for hypertension, mg/dL for hyperlipidemia, glycated hemoglobin (HbA_{1c}) for diabetes, deviation of BMI from the normal range of 18.5-24.9 kg/m^2, and Visual Analog Scale [52] pain ratings. Each of these variables will also be examined separately. Falls are assessed with 2 items asking how often the participant had fallen in the past 3 months and how many of the falls required medical attention. A fall is defined in the survey as “the body going to the ground without being pushed.” Symptom distress is assessed using a combined list of symptoms and chronic conditions from the General Symptom Distress Scale [53] and Bayliss Disease Burden Scale [54], assessing the severity of distress for each over the past 2 weeks (0=do not have this, 1=not very distressing, and 5=extremely distressing). Medication adherence is assessed with 8 items, 6 based on the Brief Medication Questionnaire by Svarstad et al [55]. We simplified response options so that participants rate how often they had specific issues with medication (1=never and 5=always). On the basis of patients’ experiences, we added 2 original items, “Feels like I no longer need it” and “Feels like I don’t need the full dose.” Patients also report on crisis health care (number of urgent care visits, emergency room visits, and hospitalizations, plus the number of days of each hospitalization, with the latter 2 items used to calculate the number of 30-day hospital readmissions). In addition, patients report on the use of long-term care (number of nights spent in assisted living facilities and nursing homes) over the past 3 months.

Exploratory Outcomes

Participants rate 7 items about their diet, indicating how often (1=never and 5=every day) they consumed healthy (eg, vegetables) and unhealthy (eg, processed or sugary) foods. They

reported on problem drinking using items 3 to 10 of the Alcohol Use Disorders Identification Test [56] and number of cigarettes smoked per day. They report on pain medication issues using a modified, 8-item version of the Centers for Disease Control Pain Medication Survey [57]. ET usage data are collected automatically, including when a patient accesses ET, services used, and duration of use.

Mediators

Anxiety is assessed using the Generalized Anxiety Disorder (GAD-7) scale [58]. Depressive symptoms are assessed using the Patient Health Questionnaire Depression Scale (PHQ-8) [59]. The response options for all items in both scales are frequency (1=not at all and 4=nearly every day) in the past 2 weeks. Health coping strategies are assessed using 10 items from the Ways of Coping Scale [60]. Relatedness is assessed with the McTavish Bonding Scale [61] plus the 3 items from the short form of the PROMIS emotional support scale [62]. For all 9 items, patients indicate the frequency of particular types of support (eg, someone you can count on to listen to you when you need to talk; 1=never and 5=always). Health motivations are assessed with 2 items from the autonomous motivation subscale and 2 from the external regulation subscale of the Treatment Self-Regulation Questionnaire [63].

Moderators

Patients report on their scheduled health care use by indicating the number of visits to primary care, specialists, physical and occupational therapists, chiropractors, and counseling. For a number of chronic conditions, they check off applicable items from a list of 27 conditions [64] and write in additional diagnoses if necessary. Participants also indicate their sex.

Covariates

Patients rate their comfort using technology (0=do not know what this is, 1=very uncomfortable, and 5=very comfortable) for 6 communication technologies (eg, computer). For physical issues with technology, they use a checklist to indicate issues with 5 items each for a computer or tablet and a smartphone (eg, vision, hand pain, or tremors). To gauge emotional well-being, patients check a list of 15 possible life stressors from the Social Readjustment Rating Scale [65]. Participants also report their ethnicity and race, education, income level, health insurance type (checklist including Medicare, Medicaid, ObamaCare, military, private insurance, other person's insurance, no insurance, and other), whether they have a significant other, their housing type (own home, rent, live in someone else's home, assisted living, residential care, nursing home, and other), and whether they live alone or with someone else.

Timeline

Recruitment was conducted from January 2018 to December 2019; the intervention period will end in June 2021. Table 3 shows the timeline by year of the study; Year 1 began on April 1, 2017, and Year 5 will end on March 31, 2022. Patients will be tracked for 12 months with access to the interventions plus 6 months for follow-up for a total of 18 months.

Table 3. Timeline of project activities.

Activity	Timeline
Clinicians set thresholds and comment on content	Year 1, months 1-3
Adapt ElderTree; prepare laptops and study materials	Year 1, months 1-9
Finalize outcome surveys	Year 1, months 4-9
Prepare clinics for ElderTree study	Year 1, months 4-9
Receive institutional review board approval	Year 1, months 7-9
Recruit, pretest, and randomize patients	Year 1, month 10, to year 3, month 9
Refresh ElderTree content	Year 1, month 10, to year 5, month 3
Collect quantitative and qualitative data	Year 1, month 10, to year 5, month 6
Clean and prepare data	Year 1, month 10, to year 5, month 6
Analyze results	Year 3, month 6, to year 5, month 12
Publish	Year 3, month 12, to year 5, month 12

Power Analyses for Primary Outcomes

We focus on the effect of Cohen *d*=0.50 on the primary outcome of patients' perceptions of their health-related quality of life, given recommendations that this is the minimally important difference for quality-of-life measures in clinical trials [66]. Our other primary outcomes are loneliness and psychological well-being. Here, effect sizes tend to be smaller. For example, a prior web-based intervention for rural women with chronic diseases showed an effect of Cohen *d*=0.29 on loneliness among those who scored above the median on baseline loneliness, depression, and stress [67]. Given that our intervention is substantially longer (12 months vs 22 weeks) and has more components specifically designed to address social connectedness, we expect somewhat larger effects; however, we do not expect to reach Cohen *d*=0.50. Balancing the need to be adequately powered with the need to focus on meaningful impacts, we have powered the study to detect a main effect of Cohen *d*=0.35 for our primary outcomes. Adequate power to detect a between-subjects effect of Cohen *d*=0.35 with a 4-time-point repeated measures multivariate analysis of variance ($1-\beta=.80$; $\alpha=.05$) will require a final sample of 262 patients

(130 per arm) [68-73]. On the basis of our prior trial of ET, we assumed 20.5% attrition and thus arrived at the recruitment goal of 330 patients.

Recruitment

The UW Clinical Research Data Service (CRDS) identified from clinic records those patients meeting the inclusion criteria. Potential UW Health participants received an opt-in letter from the university's Office of Clinical Trials. The letter described the study and included a postage-paid return invitation for further contact with the study team.

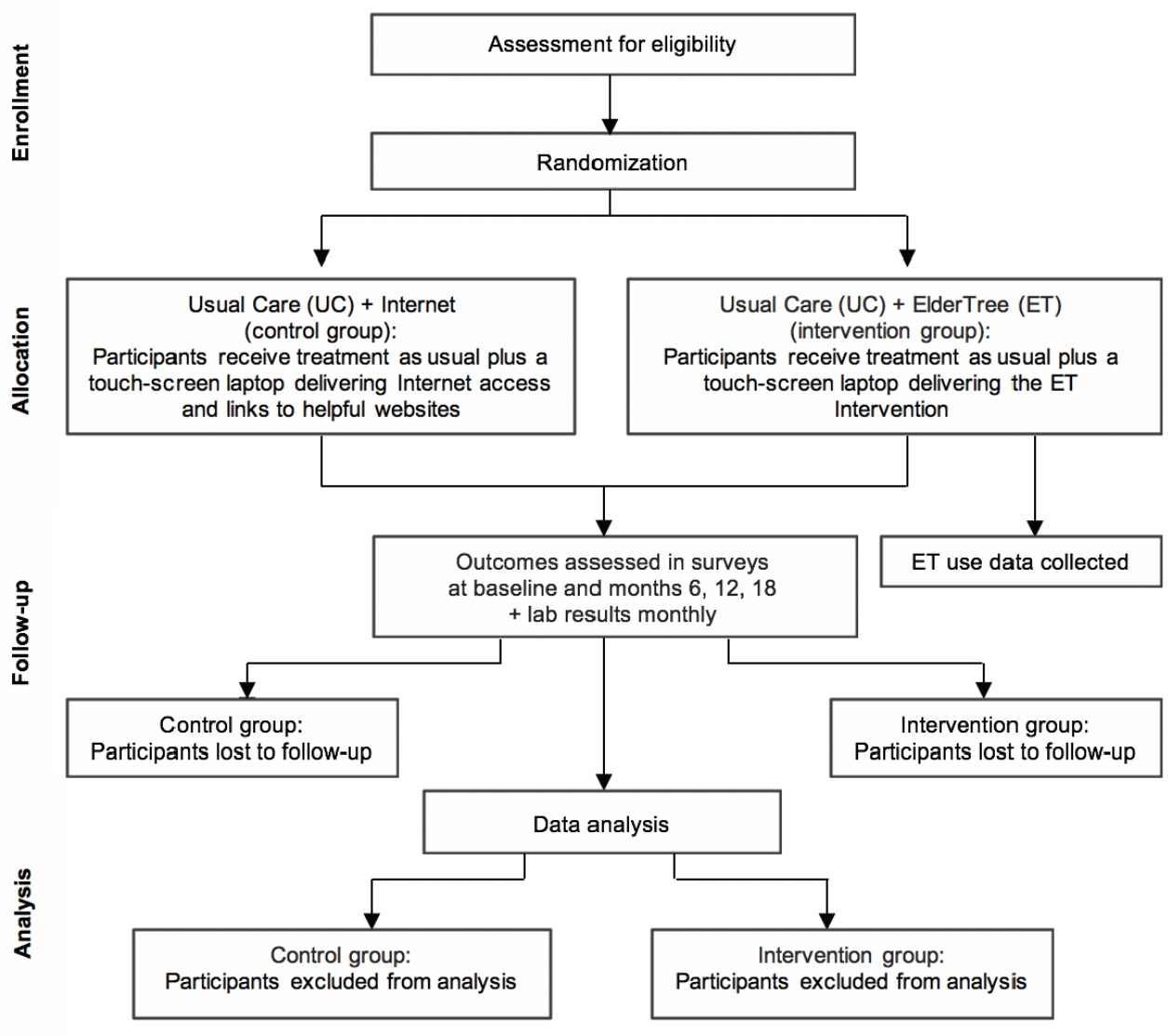
Study staff called potential participants who opted in to provide a detailed study overview, including benefits and potential risks of participation. If interested in the study, patients were asked additional questions regarding eligibility that were not addressed in the clinic record.

Patients who verbally confirmed they wanted to be in the study and met the screening criteria were mailed the baseline survey and received a home visit from a member of the research team, at which time written consent was obtained, completed baseline was collected, and randomization was determined.

Randomization

The project manager used a computer-generated allocation sequence to randomize patients on a 1:1 ratio to the experimental (UC+ET) or control (UC+internet) group, stratified by sex, clinic site, and number of chronic conditions (3-5 vs 6+). When baseline assessment and consent were complete, the research staff conducted equipment setup and training based on group assignment provided in a sealed opaque envelope. Once the assignment was made, participants could not be blinded to their condition, given that those in the ET arm are asked to participate in the site for the duration of the intervention and those in the control arm are not. The researcher doing the training also could not be blinded to the condition after assignment. Figure 3 shows the flow of participants through the trial.

Figure 3. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.



Data Sources and Collection

EHRs

Health care use, laboratory scores, and chronic conditions are gathered from EHRs. The UW CRDS pulls participant EHR data and shares the data with the study team via Research Electronic Data Capture (REDCap).

Patient Surveys

Patient-reported measures are gathered via participant surveys at months 0, 6, and 12 and an 18-month follow-up; demographics were gathered only at baseline. Each participant survey is expected to take 20 to 30 min. Surveys are mailed to participants with a stamped return envelope. Survey data are entered into REDCap. Participants are paid US $10 for each completed survey.

ET System Data

ET use data are automatically collected in time-stamped log files by subjects' ET code number, including when ET is accessed, services used, duration of use, pages viewed, messages posted versus received, and content of messages.

Qualitative Interviews

In-depth phone interviews will be conducted with random samples of participants assigned to the ET condition (not the attention control) early in the intervention period (1-4 months), mid-study (5-6 months), and at end of study (10-12 months). In addition, participants from racial or ethnic minorities will be interviewed. Our goal is 10 to 12 participants in each of these 4 groups (early, mid, and end of study, and minorities). Patients will be asked about barriers to use and the challenges and benefits of ET. Early and midpoint interviews help identify issues (eg, confusion, technical challenges) to be addressed with the ET group as a whole. End-of-study interviews shed light on the barriers, benefits, and contexts of ET use to inform future work. Interviews are expected to last 30 to 60 min and are based on a standard set of questions, although clarification questions may vary. We will seek a mix of men versus women, number of chronic conditions, and clinic sites. Potential participants will be contacted by ET system messaging or by phone. All interviews will be transcribed for more detailed coding, including quantitative tagging of key concepts.

Retention

Retention is promoted by providing ready access to support for patients' use of the technologies and by actively following up with patients to encourage them to return surveys. If a survey is not returned within 2 weeks, a research team member calls to check that the survey was received and encourages the patient to complete and return it in the addressed stamped envelope. The date and time of the phone call are recorded in REDCap, along with information gathered during the conversation and whether the researcher talked to the participant directly or left a message. If we cannot reach the participant, another copy of the survey is sent with a personal note asking them to complete it or call our toll-free number if they have questions or are no longer interested. In the prior ET study, survey response rates were 90.5% at 6 months and 79.5% at 12 months. If patients drop out, we do not use their EHR data beyond their dropout point.

Data Management

To mitigate the risk of breaches of patient confidentiality, all subjects are assigned a unique code number. All contact information and survey data are housed electronically in REDCap. Survey data are double-entered by 2 different individuals to ensure accuracy. Paper-based files are stored in a locked room in locked file cabinets and can be accessed only by authorized personnel. Participant EHR data are shared by the UW CRDS with the study team via REDCap. The database administrator provides access to study data at appropriate levels for various members of the research team. Members of the research team are able to view deidentified individual and clinic-level aggregations of variables.

Statistical Methods

Statistical Assumptions

Parametric test assumptions such as normality, linearity, homoscedasticity or homogeneity of variance, and missing data patterns will be assessed as follows.

Predictor Assumptions

Successful randomization of participants will be tested based on sex, clinic site, number of chronic conditions, and demographics, including all planned covariates (see the logic diagram in Figure 1). If randomization fails for any of these variables, it will be added as a covariate to subsequent analyses. We will assess whether there are main effects of clinic site or interactions with study arm (ie, whether data can be pooled across sites). If data cannot be pooled across sites, the clinic site will be addressed either by multilevel modeling or by treating the clinic site as a moderator, depending on the analyses being run.

Outcome Assumptions

Normality, linearity, and homoscedasticity or homogeneity of variance for outcome data will be assessed using descriptive statistics and graphical representations. Data transformation, linear mixed models (LMMs), or nonparametric tests will be used to deal with the assumption failures of outcome data.

Missing Data

In previous work with older adults using ET, we kept missing data on core interview items to about 2%; we expect similar rates in this study. In primary care, data are not likely to be missing at random (ie, the probability that data are missing relates to what the data would have been had the data been observed). We will conduct a sensitivity analysis on missing data using logistic regression to examine whether dropout at follow-up is associated with observed or assigned factors, covariates, or outcomes at baseline [74]. If missing data affect power or are significantly not missing at random, LMMs or multiple imputation will be used [75].

Effectiveness of UC+ET Versus UC+Internet

Given that we expect our primary outcomes to be highly correlated, we plan to assess the effectiveness of UC+ET versus

UC+internet on improving quality of life, psychological well-being, and loneliness using a repeated measures multivariate analysis of covariance (MANCOVA). If the continuous secondary outcomes (health or laboratory scores, symptom distress, and medication adherence) are highly correlated, they will be assessed using repeated measures MANCOVA. If not, we will run 3 separate repeated measures analyses of covariance (ANCOVAs). Secondary outcomes with count data (falls, symptom distress, medication adherence, crisis health care use, and long-term care use) will be assessed using repeated measures generalized linear mixed modeling (GLMM) with Poisson regression. Continuous exploratory outcomes (diet and problem drinking) will be assessed using repeated measures ANCOVAs or repeated measures MANCOVAs, depending on the level of correlation between these outcomes. Count exploratory outcomes (cigarettes per day and pain medication issues) will be assessed using repeated measures GLMM with Poisson regression.

ET Use

Within the UC+ET arm, we will conduct exploratory analyses on amount and type of ET use to describe patterns of use and test the effect of ET use on primary outcomes using LMMs.

Moderation

Moderators (scheduled health care use, number of chronic conditions, and sex) will be tested separately to determine whether study arm effects on the 3 primary and 2 of the secondary outcomes (falls and symptom distress) differ because of any of our hypothesized moderators. The same methods described earlier will be used with the addition of a moderator. For continuous moderators, LMM and GLMM are used instead of general linear models.

Mediation

The effect of study arm on mediators will first be tested using a repeated measures MANCOVA for anxiety and depressive symptoms and repeated measures ANCOVAs for health coping strategies, health-related motivations, and relatedness. Structural equation modeling will then be used to test mediation on primary and secondary outcomes examining those mediators that were significantly (P<.05) affected by study arm. Similarly, the effect of mediation will be tested only on outcomes that were significantly (P<.05) affected by study arm. All models will be tested as follows: study arm predicting outcome at 12 months mediated by mediator at 6 months, using linear regression for continuous outcomes, Poisson regression for count outcomes, or Zero-Altered Poisson regression for zero-inflated count data.

Type 1 Error

In cases where multiple tests relate to a single theoretical question, the Holm-Bonferroni method will be used to counteract the problem of multiple comparisons. For example, Holm-Bonferroni P value adjustments will be made to the 5 separate tests of individual health scores (mm Hg, mg/dL, HbA_{1c}, BMI, and pain) when examining if patients assigned to UC+ET have greater improvements in individual health scores than patients assigned to UC+internet.

Qualitative Analysis

A coding scheme of key themes will be constructed based on the research questions (perceived benefits, barriers to use) and examination of the data. Once reliability is established with 2 independent coders (minimum Krippendorff α of .80 per category), manifest expressions of benefits and barriers will be coded. More subtle themes, particularly regarding meanings and contexts of use, will be tagged for deeper qualitative analysis using NVivo (QSR International).

Trial Registration and Funding

This study has been funded by the National Heart Lung and Blood Institute, National Institutes of Health (NIH), United States Department of Health and Human Services (grant number 1R01HL134146-01A1); received ethical approval from the University of Wisconsin Health Sciences Institutional Review Board (reference number 2017-0849) on September 11, 2017; and is registered at ClinicalTrials.gov (NCT03387735).

Results

Recruitment was completed with 346 participants (target=330). Data collection is under way and to be completed in June 2021. The results will be communicated through publications and presentations.

Discussion

Changing Health Care Delivery

ET is conceived as an integrated, multiservice eHealth innovation aimed at changing in the following ways how care is delivered to patients coping with MCCs.

Single Disease Versus Multiple Diseases

Although information and communication technologies have shown promise in managing chronic conditions, most address a single disease (eg, tracking blood glucose for patients with diabetes). In contrast, ET offers interventions targeting behaviors that impact nearly all chronic conditions, such as social support, tracking of general health behaviors (eg, sleep, medication management), and relaxation and physical exercise resources (Table 1).

Single Intervention Versus Multiple Interventions

Many health care apps rely on a single tool, such as social networks. Despite having similar objectives, however, individuals benefit differently from various training and support. ET offers patients a broad choice of web-based training and support options, including tracking of health status and medication adherence, peer support groups and private messaging, web-based activities to promote social connection with other ET users, daily journaling with positive psychology prompts, guided relaxation audio, exercise videos for seniors with health conditions, a dynamic collection of quality health information, social and web-based games for pleasure and distraction, and data sharing with clinicians.

Complex Versus Simple

Many computer-based systems make extensive use of text and are complicated to navigate, and systems on smartphones are often challenging for older adults because of vision problems or tremors. ET's web-based design is based on extensive feedback from older adults and best-practice design principles for this population (eg, uncluttered screens, large type, good contrast) [76] to ease the user experience.

Clinic Based and Periodic Versus Just-in-Time and Anytime or Anywhere

Most tracking and support offered in traditional health care is built around periodic onsite contact with physicians. Unfortunately, this model is at odds with addressing problems and questions as soon as they occur, and it fosters a reluctance to contact a doctor when earlier help could make a difference. ET provides patients with anytime or anywhere access, frequent assessments, and customized, protected interventions for just-in-time support.

Productivity-Based Yet Expensive Versus Evidence-Based Yet Lower Cost

Productivity and cost pressures limit the clinician's time with patients [77,78]. In contrast, ET is an inexpensive and consistent yet customizable system that provides many evidence-based components of chronic care management.

Sustaining Use

A critical issue with any eHealth system is attrition. For example, studies have reported that approximately 25% of users abandon a health app after a single use [79], the average retention rate is just 29% after 90 days [80], and almost half of a diverse (age, race or ethnicity, and income) national sample of app users reported abandoning an app [81]. Activity trackers (eg, Fitbit) and other wearable sensors show similar drop-offs [82,83]. The engagement problem is even higher for older adults [81,84].

Our earlier RCT of ET found high and sustained engagement compared with reports for other health apps [79-83]. In months 1 to 6, 88.3% (174/197) of all participants used ET for a mean of 44.84 days. Nevertheless, in just 4 months, pages viewed dropped by 53%. Interviews with older adult participants found 2 main reasons: (1) the small but myriad hassles of access (going to and turning on the computer, remembering and entering a password, opening a service, etc) and (2) physical limitations such as arthritis and impaired vision.

Overcoming such barriers to sustained, in-depth use is a critical challenge. The ET system reported in this paper includes features designed to ease use (eg, large fonts and clear navigation) and promote engagement (eg, discussion prompts, new content daily, interactive games), and amount and type of ET use are among our exploratory outcomes. One of our latest projects, an Agency for Healthcare Research and Quality–funded study in its initial design phase, will involve converting ET to a voice-activated system, using technologies such as Google Hub Max to further improve accessibility and ease of use.

Impact on Public Health

The ET intervention is designed to simultaneously address hypertension, hyperlipidemia, diabetes, obesity, and arthritis, as well as underlying behavioral components. ET may also be used for almost any conditions that co-occur as MCCs. If our hypotheses about the benefits of ET are supported, this could point to a shift from care that is place based, focused on medical management, and periodic to nearly continuous care that is focused on helping patients manage their own conditions via a system built on proven principles of easy, effective behavioral interventions. The benefits to both quality of life and cost of health care are potentially broad and lasting.

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Authors' Contributions

DG is a coprincipal investigator (co-PI) of the study and one of the primary authors of the manuscript. MM is a coinvestigator of the study and one of the primary authors of the manuscript. DJ contributed to website development and is one of the primary authors of the manuscript. JM is the co-PI of the study. RB is a coinvestigator of the study. GL is the project manager for the study and contributed to the initial draft of the manuscript. KR is the study implementation coordinator and contributed to the initial draft of the manuscript. OC provides statistical and analytical support to this study and contributed to the *Statistical Methods* section. DG oversaw the design, development, and pilot testing of the website. DS is a coinvestigator who also participated in the writing of the manuscript. All authors contributed to the design of the study and have approved the manuscript.

Conflicts of Interest

DG has a small shareholder interest in CHESS Health, a corporation that develops health care technology for patients and family members struggling with addiction. The authors have no other disclosures to report.

Multimedia Appendix 1

Peer Review from Funding Agency.
[PDF File (Adobe PDF File), 185 KB - resprot_v10i2e25175_app1.pdf]

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Abbreviations

ANCOVA: analysis of covariance
CHESS: Comprehensive Health Enhancement Support System
CRDS: Clinical Research Data Service
EHR: electronic health record
ET: ElderTree
GLMM: generalized linear mixed model
LMM: linear mixed model
MANCOVA: multivariate analysis of covariance
MCCs: multiple chronic conditions
NIH: National Institutes of Health
PROMIS: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial

REDCap: Research Electronic Data Capture
UC: usual care
UC+ET: usual care+ET access (experimental condition)
UC+internet: usual care+internet access but no ET (control condition)
UW: University of Wisconsin–Madison

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Protocol

A Theory-Based mHealth Intervention (Getting Off) for Methamphetamine-Using Men Who Have Sex With Men: Protocol for a Randomized Controlled Trial

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Abstract

Background: Methamphetamine (meth) use among men who have sex with men (MSM) is associated with increased HIV prevalence and transmission and substandard advancement along the HIV prevention and care continuum. Given the growth of mobile health (mHealth) technologies, it is no longer necessary to limit meth treatment options to physical, brick-and-mortar sites, and administration using generic, nontailored content.

Objective: In a 2-arm randomized controlled trial (RCT; N=300), we aim to evaluate the use of an mHealth intervention (Getting Off) to assess the impact and noninferiority of a cross-platform app (developed from a manualized meth treatment intervention) to help MSM reduce meth use and HIV sexual risk behaviors and improve their advancement along the HIV prevention and care continuum (HIV testing, pre-exposure prophylaxis uptake and persistence, and antiretroviral therapy uptake and adherence).

Methods: Participants will be randomized into 2 arms: arm A, with immediate access to the app (immediate delivery: n=150), or arm B, with delayed access to the app after a 30-day period (delayed delivery: n=150). Participants in both arms will use the same Getting Off app and will have 30 days to complete the 24 sessions. Participants will be assessed at the 1-, 2- (delayed delivery arm only), 3-, 6-, and 9-month timepoints to determine observed treatment effects and will be compared with a historical matched sample of participants (n=~600) who received the brick-and-mortar group-based Getting Off intervention.

Results: Recruitment began in January 2019 for phase 1, the formative phase. In January and February 2019, 4 focus groups (N=36) were formed to provide input on the adaptation of the group-based manual intervention to a mobile app. Data collection for phase 2, the RCT, is expected to be completed in January 2023. The final results are anticipated in April 2023.

Conclusions: By creating a culturally responsive mobile app, Getting Off aims to reduce meth use and improve sexual health outcomes among meth-using MSM. The Getting Off app could have significant public health impact by greatly expanding access to effective, affordable, private, culturally competent, and highly scalable meth treatment for MSM.

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KEYWORDS

HIV; AIDS; methamphetamine; mHealth; mobile app; ART; mobile phone

Introduction

Background

Men who have sex with men (MSM) have elevated rates of methamphetamine (meth) use relative to non-MSM [1-3], as meth use is deeply integrated into the sexual identities and sexual behaviors of MSM in the United States [3-7] and permeates the venues most often associated with high-risk sexual behaviors among MSM [8-10]. Use of meth by MSM before or during sex is associated with decreased behavioral inhibition and increased engagement in HIV risk behaviors [11-14], including condomless anal intercourse (CAI) [15-22] with serodiscordant or HIV status unknown sexual partners [23-25].

HIV prevalence is significantly higher among MSM who use meth [14,25-29] and increases in concert with the intensity of meth use [30]. Meth use has thus been identified by the Centers for Disease Control and Prevention (CDC) as a driving force of the HIV epidemic among MSM in the United States [13]. Meth use is associated with poor antiretroviral therapy (ART) adherence and outcomes [31-34] and reduced adherence to HIV postexposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) among HIV-positive/-negative MSM, respectively [35]. Providing meth treatment to MSM is a public health imperative for addressing HIV/AIDS in the 21st century.

MSM use smartphones for sexual partner selection, sexual health information, and sexual identity expression at a higher rate than non-MSM [36-41], and they also use smartphone apps to facilitate GPS-based sexual partner selection (eg, Scruff, Grindr, and Jack'd) [42-44]. Such behaviors increase the odds of both meth use and HIV sexual risk behavior [45]. Young MSM report using such apps daily [37,39,46], and young, racial minority MSM are simultaneously both the group most at risk for meth use and HIV infection [47] as well as the group most likely to use smartphones [38,39,46]. MSM living in rural areas rely on internet resources and GPS-enabled smartphones to locate sexual partners [48]. High rates of smartphone use by young racial or ethnic minority and rural MSM dovetail cleanly with the current meth treatment and HIV risk reduction deficits evidenced in the United States health care system [38]. Psychosocial factors (eg, stigma) are the primary barriers discouraging MSM from accessing meth treatment [49,50], obstacles obviated through technology-based delivery. Given the severe personal and public health consequences of meth use, the ability to access treatment from a smartphone would eliminate embarrassment, homophobic prejudice, and/or any stigma associated with meth use and/or HIV sexual risk behaviors [50,51].

Providing theory-driven, MSM-specific meth treatment, which integrates HIV risk reduction programming, reminders about HIV testing, PrEP, PEP, and information about HIV care (including ART reminders), will address a range of HIV-related health deficits and address key priorities set by the National Institutes of Health HIV/AIDS research priorities and the National HIV/AIDS Strategy. Furthermore, the overall public health benefits could be tremendous, as meth use has also been associated with major physical harm [52], dental disease [53], psychological harm [15,54-56], and neurological damage [57]. The broader scientific community would benefit substantially from the knowledge that meth use and HIV sexual risk behaviors can successfully be reduced via remote intervention, and clinical practice could face a potential paradigm shift toward mobile content delivery for difficult-to-reach and/or stigmatized populations.

Given the growth of mobile technology, it is no longer reasonable or necessary to limit meth treatment to physical, brick-and-mortar sites. Only 1% of app-using MSM express a preference to participate in programs delivered in person, whereas 70% prefer content delivered via smartphones [36]. The Getting Off intervention is particularly well-situated for translation into a mobile app–driven format, as it has already been adapted to be carried out in community settings with peer counselors and does not require delivery via masters' level cognitive behavioral therapy (CBT) clinicians [4,58].

Mobile apps are available for download and use 24 hours a day, 7 days a week, making it easier to attempt treatment and access information in a contextualized and need-based manner; such immediacy cannot be achieved at a brick-and-mortar facility. In addition, the adaptation of a group-based intervention to a self-directed and individualized format provides the opportunity for novel delivery modalities such as gamifying formerly group-based intervention activities; insights and information will be conveyed to participants through activities such as sorting, matching, and interactive board games.

Objectives

The overall goal of this research study is to (1) adapt the Getting Off meth treatment intervention from a physical, brick-and-mortar facility to computerized delivery; a counselor-delivered intervention to self-directed; and a group-based to an individualized format and (2) assess the impact and noninferiority of the Getting Off app. The final Getting Off app will provide meth-using MSM and service providers with a culturally competent, free-to-own, cross-platform mobile health (mHealth) smartphone app that can be broadly disseminated.

Methods

Research Aims

The project builds upon the established efficacy of our manualized meth treatment intervention, *Getting Off*: *A Behavioral Treatment Intervention for Gay and Bisexual Male Methamphetamine Users*, and the highly promising findings from our successful stage 1 proof-of-concept study to complete translation of Getting Off into a cross-platform (iOS and Android) mHealth smartphone app and to assess the app's efficacy *and* noninferiority in a scientifically rigorous randomized trial. The stage 2 development of the cross-platform Getting Off app will be based on user feedback from the feasibility pilot test, current literature on app preferences among MSM, and state-of-the-art technology. The app will be an interactive presentation of the Getting Off manual. Health content, behavioral self-assessments, *homework* assignments, and multimedia content will be integrated in a walk-through (ie, step-by-step) manner, where the consumer will be presented dynamic content, all under the guidance of a culturally

competent, user-friendly, and attractive interface. The app could broadly disseminate culturally competent meth use and HIV risk reduction content to large numbers of demographically and geographically diverse users who otherwise could not access such services, particularly racial or ethnic minority MSM and MSM living in rural areas [38,47,59].

The aims of the research include the following:

- Primary aim 1: Refine and enhance the first 8 sessions of the Getting Off meth-use treatment intervention developed in stage 1 based on feasibility pilot test user feedback.
  - Approach: Integrate findings from stage 1, and refine or enhance the first 8 sessions with the technology team and input from our community advisory board.
- Primary aim 2: Conduct formative research to develop the remaining 16 sessions of the Getting Off meth-use treatment intervention into a cross-platform computerized mobile app targeted to reduce meth use and HIV sexual risk behaviors and increase advancement along the HIV prevention or care continuum.
  - Approach: Design and develop the complete app by guiding technology team revisions using focus group and community advisory board feedback; conduct a usability pilot study to assess the feasibility, acceptability, and preliminary effects of the Getting Off app; and refine app iterations through community input.
- Primary aim 3: Conduct a randomized controlled trial (RCT) to evaluate reductions in meth use and HIV sexual risk behaviors (eg, CAI, engagement in sex work, and sex while feeling the effects of alcohol or drugs) and increase advancement along the HIV prevention (repeat HIV testing, PEP or PrEP linkage and uptake, PEP adherence, and PrEP adherence and persistence) or care continuum (linkage to HIV care, ART adherence, and virological suppression).
  - Approach 3a: A 2-arm RCT to determine intervention effects through comparison of the immediate delivery (ID; n=150) and delayed delivery (DD; n=150) arms
    - Aim 3a hypothesis: Exposure to the Getting Off app will produce significant reductions in meth use and HIV sexual risk behaviors as well as increased odds of advancement along the HIV prevention or care continuum.
  - Approach 3b: An observed treatment effects analysis powered for prospective subgroup contrasts to compare longitudinal pre- or postdata from the pooled ID and DD arms (N=300)
    - Aim 3b hypothesis: Exposure to the Getting Off app will be associated with significant reductions in meth use and HIV sexual risk behaviors as well as increased odds of advancement along the HIV prevention or care continuum.
  - Approach 3c: A 2-arm historical matched comparison design to evaluate the outcomes of the Getting Off app (ID+DD; N=300) relative to a matched sample of participants who previously attended the brick-and-mortar group-based Getting Off intervention (N=~600; total N=900).
    - Aim 3c hypothesis: Reductions in meth use and HIV sexual risk behaviors as well as increased advancement along the HIV prevention or care continuum will be statistically noninferior to those observed in the brick-and-mortar group-based Getting Off intervention.
- Secondary aim 1: Determine the impact of structural- (eg, housing insecurity, food scarcity, educational attainment, and access to health care) and individual-level (eg, homophobia, stigma, and discrimination) factors as moderators of intervention outcomes.

Ethics Statement

All study procedures were approved by the Western Institutional Review Board (IRB Study #1248891; IRB Tracking #20182737). The study was registered as a clinical trial (Clinical Trials #NCT03884946). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Study Procedures

Aim 1

App refinement of the first 8 sessions addressed the areas identified through the feasibility pilot test. The research and app development teams designed and developed a cross-platform mobile app using a cross-platform framework (eg, Ionic) that will permit downloading the app on both the iOS and Android platforms. The cross-platform framework approach promotes extensive code reusability between the 2 platforms and ensures a consistent user experience. The app will be for the latest versions of iOS and Android operating systems and will include backward compatibility for one operating system version of each.

Aim 2

The research team conducted formative research to translate the remaining 16 sessions from the group-based manual-driven intervention to a computerized app, conducted alpha-phase postdevelopment bug testing, conducted beta-phase usability pilot testing, and refined the app according to alpha- and beta-phase testing.

Four focus groups (N=36) provided input on the development of the Getting Off app: (1) out-of-treatment, meth-using MSM (n=10); (2) meth-using MSM who are currently in outpatient treatment in the Getting Off program (n=10); (3) prior meth-using MSM with a minimum of 1 year recovery who have completed a minimum of 18 out of 24 sessions (75%) of the brick-and-mortar Getting Off program (n=6); and (4) prior meth-using MSM with a minimum of 1 year of recovery who have had no previous experience or knowledge of the Getting Off intervention (n=10). The focus groups were structured to provide guidance on translating Getting Off into an app that is responsive to culture (eg, sexuality, HIV prevention or care

including PrEP uptake, adherence and persistence, ART adherence, and viral load suppression) and meth treatment needs. Additional input was obtained through the ongoing community advisory board and usability pilot testing.

Following app development, alpha-phase testing has uncovered and removed unwanted bugs. Beta-phase usability pilot testing will be conducted with members of the target population (N=30) to test the feasibility and acceptability of the Getting Off app. Furthermore, pilot testing will be used to ensure the functionality of the app (ie, that the app is user-friendly, and all features function appropriately). Inclusion criteria for the pilot test were as follows: (1) self-identified MSM, (2) prior meth user but no meth use in the past 365 days, (3) aged between 18 and 65 years, and (4) able and willing to provide informed consent. The behavioral assessments will be consistent with those of the RCT. Although the group-based Getting Off intervention is delivered over 8 weeks (24 sessions at 3 groups per week), it is expected that it will take far less time to progress through the self-directed app, and because of the interactive features, participants may choose to replay treatment modules multiple times in the 30-day period. Behavioral assessments will be conducted at baseline and at the 1-month follow-up. In addition, at the 1-month follow-up visit, an open-ended, in-person, qualitative user experience exit interview will be collected to collect feedback on the app, including the perceived benefits, concerns, and suggestions for improvements. Qualitative interviews will be digitally recorded and analyzed using the same methodology as the focus groups.

Aim 3

Following screening, informed consent, and baseline assessments, participants will be randomized into 1 of 2 arms: arm A, immediate access to the Getting Off app (ID), or arm B, participants will have access to the Getting Off app after a delayed 30-day period (DD). Participants in both arms will receive the same Getting Off app and will be given 30 days to complete the 24 sessions. The randomized 2-arm repeated measures design will assess participants at 1, 2- (DD arm only), 3-, 6-, and 9-months after randomization to determine longitudinal intervention effects, observed treatment effects, and a historical comparison with a matched sample of participants who attended the brick-and-mortar group-based Getting Off intervention (Figures 1 and 2). The study will use an *intent-to-treat* design; participants will be assessed regardless of participation or retention.

Figure 1. Schematic of study design. MSM: men who have sex with men; RCT: randomized controlled trial.

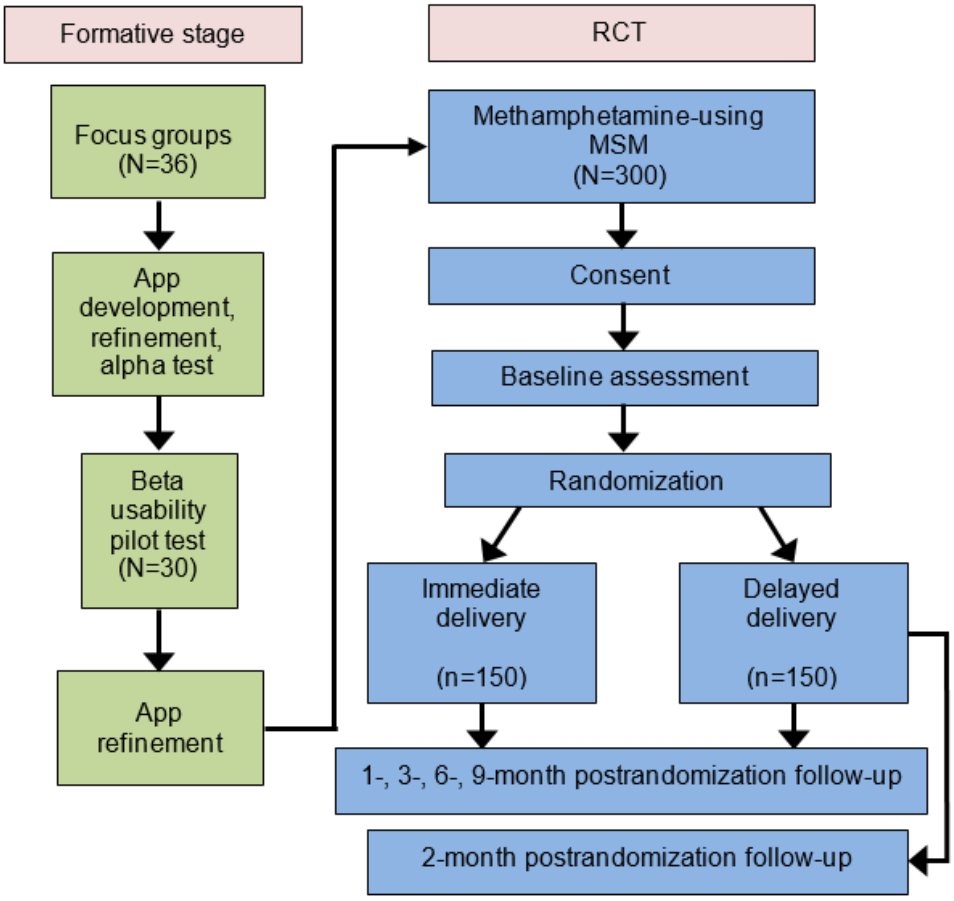
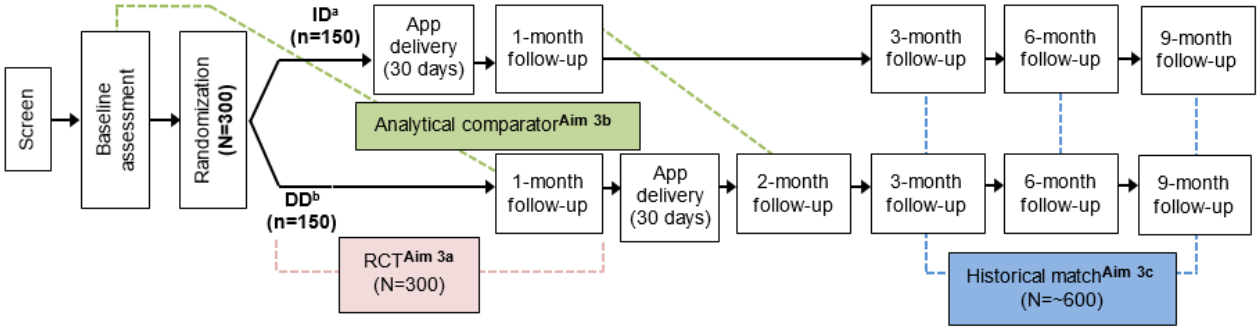


Figure 2. Randomized controlled trial design. DD: delayed delivery; ID: immediate delivery.



Sample

To ensure comparability of outcomes with those of the group-based Getting Off intervention manual, inclusion criteria must mirror that of the brick-and-mortar treatment site: (1) self-identified MSM, (2) any meth use in the past 365 days, (3) aged between 18 and 65 years, and (4) able and willing to provide informed consent. Both HIV-positive and HIV-negative participants will be eligible.

Recruitment

To ensure a steady stream of diverse participants, 4 recruitment strategies will be used: (1) online recruitment: banner ads or digital flyers will be placed on gay websites, apps, and social media sites that specifically target MSM, such as Scruff, Adelante, Craigslist, Adam4Adam, Jack'd, and Grindr; established relationships with web-based venues that cater to MSM will enable a successful and robust internet-based recruitment strategy. (2) Street- and venue-based outreach: a semistructured time-space sampling methodology will be used to conduct street- and venue-based outreach identified through the community advisory board and ongoing community mapping as locations where meth-using MSM congregate. (3) Poster advertisement: posters that introduce the study will be posted to inform potential participants who to contact for further information regarding the research study. (4) Long-chain referral sampling: the participants of this study will be asked to recruit potential new participants. The participants of this study participants will receive US $2 when they bring a potential participant to the site and US $18 if an eligible participant is enrolled. Potential participants who inquire about the study will be scheduled for intake within 24-48 hours. These strategies have previously been used to recruit similar samples in prior studies.

Randomization

Following informed consent and completion of the baseline assessment, participants will be randomized to either the ID or DD arm through a computerized variable-balanced procedure. Recent work with substance-dependent (predominantly meth) MSM revealed treatment outcomes to be associated with participant substance use histories and sociodemographics [60]. A variable-balanced procedure will thus provide a multivariate balance among the characteristics known or expected to influence outcomes. The randomization procedure will balance across age (<34 years or ≥34 years), race or ethnicity (White and all other race or ethnicities), HIV serostatus (+ or −), and stages of change (SOC; contemplation or preparation and action or maintenance) [61].

Study Arms

The study intervention will be delivered via the identical cross-platform Getting Off mobile app for participants in both arms. Postrandomization participants will download the app onto their phone or tablets. Those randomized into the ID arm will immediately be given a unique user passcode to access the intervention content, whereas those randomized into the DD arm receive their unique user passcode 30 days after randomization (Figure 2).

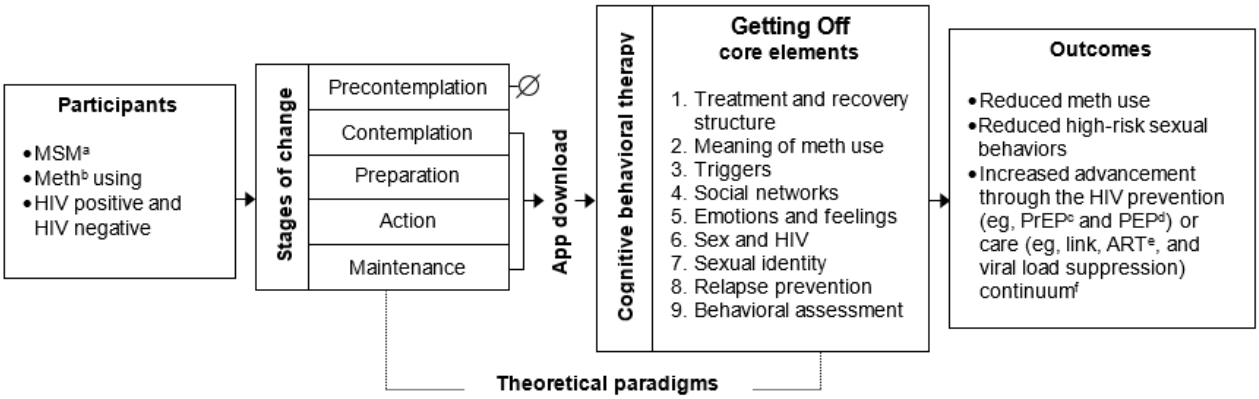
Theoretical Foundations: Mechanism of Behavioral Change

The SOC model [62-67] conceives of behavior change as a 5-stage process, ranging from not yet considering a particular behavior (ie, precontemplation) through ongoing, long-term maintenance of that same behavior (Figure 3). An individual moves through the stages as they become aware of the need for change, prepare for change, and implement change. Most individuals are in the *action* stage by the time they seek treatment at a brick-and-mortar facility. In contrast, due to the privacy and availability of a computerized intervention, the Getting Off app would be of interest and value to any meth-using MSM who has moved beyond the precontemplation stage, allowing for broader dissemination, earlier interruption of meth use and HIV sexual risk behaviors, and increased opportunities for advancement through the HIV prevention or care continuum, maximizing potential public health impacts.

The computerized Getting Off app, like the group-based intervention before it, will be guided by CBT and will use a broad set of psychological and educational techniques to provide meth-using MSM with critical knowledge about their meth use, teaching skills to initiate abstinence and to return to abstinence should relapse occur [68]. The theoretical principles of CBT have been widely integrated into most interventions for substance use disorders in the United States (including Alcoholics Anonymous) [69] and have shown efficacy for reducing both cocaine and meth use [70-74]. The CBT model in Getting Off provides education on internal and external triggers, stages of recovery from meth use, and identification of emotional states that can signal relapse. The CBT model also teaches cognitive skills such as thought stopping, craving management, relapse analysis, and adoption of healthy lifestyle behaviors. Figure 3 displays the conceptual model of behavior

change. The far-left components in the model include the participant profile, the SOC related to meth use that would encourage a MSM to download the Getting Off app, and the core elements of the Getting Off app. Outcomes include reductions in meth use and HIV sexual risk behaviors and increased advancement through the HIV prevention or care continuum.

Figure 3. Mechanism of behavior change. ART: antiretroviral therapy; meth: methamphetamine; HIV prevention continuum (HIV testing and pre-exposure prophylaxis/postexposure prophylaxis uptake) and HIV care continuum (link, antiretroviral therapy adherence, and virological suppression); MSM: men who have sex with men; PEP: postexposure prophylaxis; PrEP: pre-exposure prophylaxis.



Measures

All data will be collected on an Audio Computer-Assisted Self-Interview administered via the Qualtrics system. All materials will be stored in Qualtrics' Health Insurance Portability and Accountability Act-compliant (secure and encrypted) cloud-based databases. Data from historical comparators will be sampled from participants enrolled in the brick-and-mortar Getting Off intervention beginning in 2012, as research indicates that 2012 is when up to 95% of meth-using MSM in Friends Community Center reported owning their own cellphone [75]. The following subheadings (*Diagnostic Mental Health and Substance Use Disorder*; *Stages of Change*; *Sociodemographics, Familiar, Legal, and Health Status*; *Substance Use*; *Meth Use and Sexual Risks*; and *Biological Markers*) describe the measures used to address the study's specific aims.

Diagnostic Mental Health and Substance Use Disorder

Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Methamphetamine Use Disorder contains the DSM-5 diagnostic items necessary to determine mild, moderate, or severe meth use disorder. This information will determine the app's utility for consumers at various levels of meth use. It will be administered only at baseline.

Stages of Change

The University of Rhode Island Change Assessment (URICA) is a brief, self-administered inventory used to assess the participant's current position regarding readiness for change (eg, precontemplation, contemplation, and action) [66]. In nontreatment seeking MSM, the participant's motivation or readiness for change may be an important predictor of response to the computerized intervention app. The URICA will be helpful in characterizing participants' SOC [76]. It will be administered at all time points.

Sociodemographics, Familiar, Legal, and Health Status

Admission or follow-up form collects demographic information, housing status, food security, educational attainment, alcohol and other drug use history, family and social history, legal status, HIV status, location on the HIV prevention or care continuum, experiences with stigma and/or discrimination, and general and mental health status. The full form will be administered at baseline, and an abbreviated version (ie, a version that excludes all "lifetime recalls" and sociodemographic characteristics) will be administered at all follow-up time points.

Substance Use

Substance use frequency is a brief assessment, developed by the principal investigator that assesses substance use, injection drug use, and injection protocols in the past 30 days. It will be administered at all time points.

Meth Use and Sexual Risks

Behavioral Questionnaire-Amphetamine (BQA)-abbreviated version gathers information on HIV-related drug and sexual risk behaviors, assesses self-efficacy for sexual behavior change, collects detailed information on discrete sexual behaviors (with primary or nonprimary partners and whether or not the behavior occurred under the influence of meth and/or other substances), and collects episodic data about participants' most recent sexual encounters [77,78]. Although the heterogeneous nature of the material included in the BQA prevents estimation of omnibus reliability coefficients, the assessment has compared favorably in tests against similar instruments and has been validated for use in these and similar populations [70,77-79]. It will be administered at all time points.

Biological Markers

Urine drug screen: urine samples will be collected, monitored, and analyzed using a 5-panel Food and Drug Administration–approved urine test cup [80]. The test cup screens for metabolites of the following drugs of use at the noted cut-off levels: amphetamines (1000 ng/mL), cocaine (300

ng/mL), meths (500 ng/mL), opiates (300 ng/mL), and tetrahydrocannabinol (50 ng/mL). Urine sample validity checks will be provided by temperature and adulterant monitoring strips built into the customized test cup. Criteria for validity will be indicated by the temperature of the sample (eg, above 92 degrees Fahrenheit and below 98 degrees Fahrenheit) and the presence of normal ranges of creatinine; pH; specific gravity; and nitrates, pyridinium chlorochromate, and bleach provided by the adulterant strip. Results are coded qualitatively (above or below the threshold) and serve as the primary indicator of recent drug use. It will be administered at all time points.

Rapid HIV antibody test: HIV-negative and status unknown participants will receive a rapid point-of-care fingerstick HIV-antibody blood test [81] at 3-month intervals, as recommended by the CDC for high-risk individuals [82]. Participants who show documentation of HIV-positive serostatus will not be given an HIV antibody test.

Sexually transmitted infection (STI) testing: participants will be tested for *Neisseria gonorrhoeae (N. gonorrhea)* and Chlamydia in the urethra via urine sample. Pharyngeal and rectal swabs will be taken for *N. gonorrhea* and Chlamydia, and syphilis will be tested by serum red plasma reagin and confirmed by fluorescent treponemal antibody absorption testing. Positive STI results will be reported per state guidelines and will be immediately referred to care. Prior studies found high rates of undiagnosed STIs among out-of-treatment, meth-using MSM [29,83], which also serve as a marker of HIV sexual risk behaviors.

Virologic control for HIV-positive participants: as indicated by an undetectable HIV-1 level on the COBAS AmpliPrep/COBAS TaqMan HIV test kit [84], which has a threshold for undetectability set at ≤20 copies/mL, will be performed by Foundation Laboratory. It will be conducted at each 3-month assessment.

Dried blood spot (DBS) for HIV-negative participants who report PrEP uptake: a blood sample will be collected and a DBS analysis for intraerythrocytic tenofovir-diphosphate will be performed. It will be conducted at each 3-month assessment.

Health study locator form: the locator form asks participants to give consent for follow-up and to provide names; addresses; email and internet site profiles, particularly social network sites; and phone numbers of 3 relatives or friends who can reach the participant. Information is also collected on where (libraries, clubs, and bars) and with whom the participant associates (ie, social network). This will be administered at baseline, each follow-up time point, and on the off months of each follow-up time point, that is, on the months when a follow-up assessment is not being conducted.

Statistical Analysis

All primary outcomes are operationalized and assessed in at least two discrete ways, increasing accuracy of measurements, reducing concerns of fully missing data, and allowing for posthoc comparisons of concurrent validity across assessment modalities (Table 1 shows all outcome operationalizations). Descriptive statistics will be calculated and provided for all outcomes, with specific metrics chosen based on the distributional properties of each variable (eg, counts and percentages for nominal variables, means and standard deviations for parametric continuous variables, and ranges and medians for nonparametric continuous variables). All statistical analyses will be carried out using Stata 16SE [85], although the analytical methods described are amenable to most contemporary analytical programs.

Table 1. Instruments, targets, variable operationalizations, and minimum detectable effects (1−β=.80; α=.05, 2-tailed).

Instrument	Target	Variable operationalizations			Power-minimum detectable effects		
		Dichotomous	Count	Continuous	Model 1—randomized controlled trial (primary aim 3a; n=150 and n=150)	Model 2—Tx[a] effects (primary aim 3b; N=300)	Model 3—Matched comparison (primary aim 3c; N=300/N=~600)
DSM-5[b] (Meth[c])	Diagnosis of meth use disorder	Presence or absence of meth use disorder	Number of diagnostic criteria endorsed	N/A[d]	Potential statistical controls; exploratory subgroup analyses	N/A	N/A
URICA[e]	Stage of change or readiness for change	Above or below "Action" stage	N/A	URICA scores	Potential statistical controls; exploratory subgroup analyses	N/A	N/A
Admissions and follow-up form	Sociodemographics; HIV status and Tx history, barriers, and facilitators	Sexual identity; HIV status; linked or unlinked; housing insecurity	Prior drug treatment episodes; symptomology	Age; income	Potential statistical controls; HIV-related subgroup analyses; barrier or facilitator moderator analyses	N/A	N/A
Admissions and follow-up form	HIV prevention or care continuum[f]	HIV test; PrEP[g] uptake; advance along HIV prevention or care continuum	Number of HIV prevention or care continua steps completed	N/A	• Di[h]: OR[i]=1.97 • Cu[j]: IRR[k]=1.51	• Di: OR=1.61 • Cu: IRR=1.35	• Di: OR=1.52 • Cu: IRR=1.30
Biomarker tests (urinalysis, viral load, dried blood spot, HIV/STI[l])	Meth use, HIV prevention/care continuum outcomes, sexual risk behavior	Incident STI or incident HIV	Log reductions in HIV VL; DBS analysis of PrEP	Treatment effectiveness score	Variable, dependent on biomarker.	Variable, dependent on biomarker.	Variable, dependent on biomarker.
Substance use frequency	Meth use	Use or nonuse	Days of use	N/A	• Di: OR=0.48 • Cu: IRR=0.85	• Di: OR=0.59 • Cu: IRR=0.89	• Di: OR=0.62 • Cu: IRR=0.90
Behavioral Questionnaire-Amphetamine	HIV sexual risk behavior	CAI[m]	Number of CAI episodes	HIV sexual risk scale	• Di: OR=0.52 • Cu: IRR=0.78 • Co[n]: f^{2o}=0.03	• Di: OR=0.63 • Cu: IRR=0.85 • Co: f^2=0.01	• Di: OR=0.66 • Cu: IRR=0.87 • Co: f^2=0.01
Locator	Contact information	N/A	N/A	N/A	N/A	N/A	N/A

[a]Tx: treatment.

[b]DSM: Diagnostic and Statistical Manual of Mental Disorders-5.

[c]meth: methamphetamine.

[d]NA: not applicable.

[e]URICA: University of Rhode Island Change Assessment.

[f]HIV prevention continuum (HIV testing and pre-exposure prophylaxis or postexposure prophylaxis uptake) and HIV care continuum (link, antiretroviral therapy adherence, and virological suppression).

[g]PrEP: pre-exposure prophylaxis.

[h]Di: dichotomous variable.

[i]OR: odds ratio; estimated 95% CIs are not reported due to the lack of concrete variance estimates to apply to the estimated mean.

[j]Cu: count variable.

[k]IRR: incident rate ratio.

[l]STI: sexually transmitted infection.

[m]CAI: condomless anal intercourse; this includes both receptive and insertive anal intercourse and will be assessed by partner type (eg, main, casual, and exchange).

[n]Co: continuous variable.

[o]f^2: multiple linear regression effect size estimation.

Diagnostic (ie, DSM-5), psychosocial (eg, URICA), barriers and facilitators (eg, housing insecurity, lack of transportation), and/or sociodemographic variables will be tested for significant association with study outcomes (ie, advancement through the HIV prevention or care continuum, meth use, and HIV sexual risk behaviors), with specific tests of association chosen based on the distributional properties of the outcome variables in question. All variables demonstrating significant statistical association with one or more of the study outcomes will be included as statistical covariates in all multivariate outcome analyses associated with primary aims 3a, 3b, and 3c and will additionally be included in exploratory subgroup analyses to test for moderating effects on treatment response and/or contingent effects among subsets of participants. Primary outcome analyses for primary aims 3a, 3b, and 3c will be carried out using mixed effects generalized linear model (GLM) equations.

Advancement through the HIV prevention or care continuum will be assessed at all time points throughout the study and will be operationalized dichotomously (ie, yes or no achievement of one of the steps on either the HIV prevention or care continuum; eg, viral suppression) and as a counted variable (eg, consecutive DBS results indicating successful PrEP adherence). Power calculations related to advancement through either continuum will assume a 30% probability of achievement of at least one of the steps on either the HIV prevention or care continuum (equivalent to approximately 1:2 odds of advancement). Meth use outcomes will be assessed repeatedly (ie, at all time points) and will be operationalized dichotomously (eg, meth-metabolite-free urine sample) as a counted variable (ie, number of meth-metabolite-free urine samples provided) and as a continuous variable (ie, treatment effectiveness score [86] [total number of meth-metabolite-free samples divided by total samples possible]). Power calculations related to meth use outcomes assumed an 80% probability of meth use during the preintervention period for participants in the DD arm (equivalent to 4:1 odds of use).

HIV sexual risk behavior outcomes will be assessed at all time points throughout the study and will be operationalized dichotomously (eg, incident STI via biomarker testing) as a counted variable (eg, number of days or times engaged in CAI in the past 30 days) and as a continuous variable (eg, an HIV risk severity index generated from multiple factor-analyzed items). Power calculations for engagement in HIV sexual risk behaviors assume a 65% probability of engagement during the preintervention period for participants in the DD arm (equivalent to approximately 2:1 odds of engagement).

Multivariable inferential analyses of dichotomous outcomes will take the form of GLMs employing the Bernoulli family and logit link function; counted outcomes will be analyzed with GLMs employing the Poisson-log or negative binomial link functions, as distributional patterns dictate (note: if after the participant data collection period ends the data evidence an overrepresentation of zeros or an overdispersion of variance, zero-inflated Poisson and/or negative binomial analyses may be substituted). Continuous outcomes will be analyzed using GLMs employing the identity link and Gaussian family functions and assume a single covariate unless otherwise stated (note: iteratively reweighted, bootstrapped, or jackknifed estimation procedures may be used in Gaussian models if sensitivity analyses indicate an undue influence from outliers). Mixed effects GLM models are considered the best linear unbiased estimators for repeated measures data employing nonparametric and/or limited dependent variables. All power calculations are premised on tests of association across 2 time points (eg, baseline with app completion and app completion with brick-and-mortar program completion), providing the most conservative estimate of minimum detectable effect size estimations. All power calculations assume $\alpha \leq .05$ (2-tailed) and $1-\beta=.80$.

Results

Recruitment began in January 2019 for phase 1, the formative phase. In January and February 2019, 4 separate focus groups (N=36) were conducted to provide input on the adaptation of the Getting Off group-based manual intervention to a cross-platform, computerized mobile app–based intervention. The data collection for phase 2, the RCT, is expected to be completed in January 2023. The final results are anticipated in April 2023.

Discussion

The Getting Off app is designed to expand access to effective, affordable, private, culturally competent, and highly scalable meth treatment for MSM. MSM experience higher rates of meth use relative to non-MSM, as meth use is deeply integrated into the sexual identities and sexual behaviors among MSM. Use of meth by this population, before or during sex, is associated with decreased behavioral inhibition and increased engagement in HIV risk behaviors. Given the growth of mobile technology, it is no longer reasonable to limit meth treatment options to physical sites, clustered in urban areas and administered using generic, nontailored content. A cross-platform mHealth smartphone app is well suited for engaging MSM because apps are easily accessible, widely used, private, portable, and inexpensive.

There are limitations to the Getting Off study. Given that the study procedures are entirely virtual and that the intervention is app based, enrollment is limited to those that can afford a modern smartphone with an active monthly data plan, as the study does not provide smartphones to participants. However, given that smartphone use is ubiquitous among this population, it is expected that this will not be a major impediment to enrollment. In addition, the study will be conducted in a west coast metropolitan city, and therefore, findings may not be

representative of meth-using MSM in other regions of the United States or globally. Finally, the sample may be biased toward MSM who are more likely to enroll in a research study; thus, it may not reflect meth-using MSM that do not self-select to participate in a clinical trial.

The Getting Off app aims to reduce meth use and improve HIV prevention and care continuum outcomes among MSM by providing a culturally competent, user-friendly, and attractive interface that promotes reduced drug use and engagement in high-risk sexual behaviors. The Getting Off mobile app is highly scalable, and if successful, it can be made publicly accessible through the Apple App Store for iOS platforms or Google Play Store for Android platforms for widespread distribution. Given that meth use has also been associated with negative physical and mental health consequences [14,45,50-53], the overall public health benefits from an efficacious meth treatment app could be tremendous.

Acknowledgments

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Conflicts of Interest

The authors were involved in the app development process and will be involved in the evaluation of the app. The authors have no financial interests in the app.

Multimedia Appendix 1
Peer review report by the NIH Center for Scientific Review.
[PDF File (Adobe PDF File), 163 KB - resprot_v10i2e22572_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
BQA: Behavioral Questionnaire-Amphetamine
CAI: condomless anal intercourse
CBT: cognitive behavioral therapy
CDC: Centers for Disease Control and Prevention
DBS: dried blood spot
DD: delayed delivery
DSM: Diagnostic and Statistical Manual of Mental Disorders
GLM: generalized linear model
ID: immediate delivery
IRB: Institutional Review Board
meth: methamphetamine
mHealth: mobile health
MSM: men who have sex with men
PEP: postexposure prophylaxis
PrEP: pre-exposure prophylaxis
SOC: stages of change
STI: sexually transmitted infection
URICA: University of Rhode Island Change Assessment

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Protocol

A Digital Health Intervention (SweetGoals) for Young Adults With Type 1 Diabetes: Protocol for a Factorial Randomized Trial

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Abstract

Background: Many young adults with type 1 diabetes (T1D) struggle with the complex daily demands of adherence to their medical regimen and fail to achieve target range glycemic control. Few interventions, however, have been developed specifically for this age group.

Objective: In this randomized trial, we will provide a mobile app (SweetGoals) to all participants as a "core" intervention. The app prompts participants to upload data from their diabetes devices weekly to a device-agnostic uploader (Glooko), automatically retrieves uploaded data, assesses daily and weekly self-management goals, and generates feedback messages about goal attainment. Further, the trial will test two unique intervention components: (1) incentives to promote consistent daily adherence to goals, and (2) web health coaching to teach effective problem solving focused on personalized barriers to self-management. We will use a novel digital direct-to-patient recruitment method and intervention delivery model that transcends the clinic.

Methods: A 2x2 factorial randomized trial will be conducted with 300 young adults ages 19-25 with type 1 diabetes and (Hb)A_{1c} ≥ 8.0%. All participants will receive the SweetGoals app that tracks and provides feedback about two adherence targets: (a) daily glucose monitoring; and (b) mealtime behaviors. Participants will be randomized to the factorial combination of incentives and health coaching. The intervention will last 6 months. The primary outcome will be reduction in A_{1c}. Secondary outcomes include self-regulation mechanisms in longitudinal mediation models and engagement metrics as a predictor of outcomes. Participants will complete 6- and 12-month follow-up assessments. We hypothesize greater sustained A_{1c} improvements in participants who receive coaching and who receive incentives compared to those who do not receive those components.

Results: Data collection is expected to be complete by February 2025. Analyses of primary and secondary outcomes are expected by December 2025.

Conclusions: Successful completion of these aims will support dissemination and effectiveness studies of this intervention that seeks to improve glycemic control in this high-risk and understudied population of young adults with T1D.

Trial Registration: ClinicalTrials.gov NCT04646473; https://clinicaltrials.gov/ct2/show/NCT04646473

International Registered Report Identifier (IRRID): PRR1-10.2196/27109

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KEYWORDS

type 1 diabetes; mhealth; incentives; health coaching; young adults

Introduction

Type 1 Diabetes in Young Adults

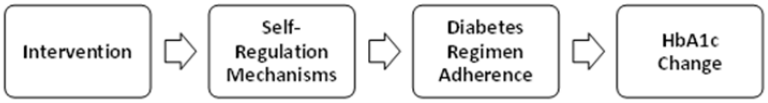
The incidence of type 1 diabetes (T1D) is rising [1], and T1D results in significant economic costs in the United States, with yearly medical expenditures estimated at approximately $7 billion with an additional $7 billion in lost wages [2]. T1D also significantly increases mortality, especially among those with above target hemoglobin A_{1c} (HbA_{1c}) levels [3]. Young adults are a population at unique risk, with only 14% of young adults aged 18 to 25 years meeting the target HbA_{1c} goal (HbA_{1c}≤7%) versus 30% of those over 30 years [4]. One in 4 young adults aged 18 to 35 years already have one or more medical complications related to their T1D, most commonly renal problems reflecting micro- or macroalbuminuria and/or retinopathy [5]. Furthermore, young adulthood is a critical developmental period when adult habits are formed as patients transition from parental involvement with diabetes management to independence in self-management of their T1D [6,7].

Despite the unique clinical needs of patients in this age group, few interventions have been tested for this high-risk population. A 2017 systematic review found 18 intervention studies for young adults with T1D [8]. Across studies, the most common intervention strategy (13/18, 72%) targeted engaging young adults with clinical services, an important goal, but unfortunately one that did not routinely result in improved glycemic control in most trials. Only 67% (12/18) of studies reported HbA_{1c} outcomes and, of these, only 2 were randomized, both showing no impact on HbA_{1c}. Since this review, several protocols and intervention development studies have been published [9,10]; several reported the results of uncontrolled studies with none showing impact on HbA_{1c} to date [11-13] and one showing significant effects on HbA_{1c} for continuous glucose monitor (CGM) use versus blood glucose meters [14]. These results highlight a major gap in and need for more rigorous research on effective ways to improve glycemic outcomes among young adults with T1D.

Intervention Model

The proposed intervention model offers a multipronged self-regulation approach for targeting glycemic control that is tailored for young adults. The goal of the selected intervention components is to improve self-regulatory mechanisms [15] including self-monitoring, goal setting, self-efficacy about diabetes management, and problem-solving skills. These self-regulatory mechanisms promote improved T1D regimen adherence and HbA_{1c} [16-20]. The conceptual model in Figure 1 highlights the role of self-regulation as an intervention target leading to improved outcomes. To target self-regulation among youth with T1D, we developed a multicomponent intervention that includes (1) weekly diabetes device data upload and data review designed to promote healthy self-monitoring and goal-setting habits for diabetes management and provide feedback about goal attainment, (2) web-based human coaching to deliver motivational interviewing exercises and teach a structured problem-solving method, and (3) motivational incentives to enhance adherence.

Figure 1. Conceptual model of intervention effects on hemoglobin A_{1c}.



A series of prior iterative studies developed and tested this intervention approach, including a randomized trial comparing a similar intervention to usual care for adolescents aged 13 to 17 years. Intervention youth had significantly lower HbA_{1c} levels at the end of the 6-month intervention (d=.45), and this effect was fully maintained indicating no weakening of the intervention effect at the 12-month follow-up (d=.44) [21]. Our new study adapted this earlier intervention to enhance both efficacy and disseminability. The primary modification to increase efficacy involves expanding the goal target from glucose checking to encompass the additional key self-management behavior of carbohydrate counting. Enhancements to promote dissemination (and scalability) include (1) modifying goals to encompass the full spectrum of diabetes devices, (2) automating the goal setting and feedback components via an app, and (3) recruiting young adults via social media. In addition, this study uses a factorial design to test the independent effects of incentives to promote consistent daily adherence to goals and web health coaching to teach effective problem solving focused on personalized barriers to self-management, providing better understanding of the intervention mechanisms.

Incentives to Promote Self-Management

Incentives may be an effective tool for increasing self-management behavior. Because interventions that support self-monitoring of diabetes management have shown limited effects on HbA_{1c}, incentives are designed to enhance the impact of the intervention on HbA_{1c}. Consistent with behavior economic theory [22], most daily adherence behaviors necessary to manage T1D do not result in immediate positive experiences. The benefits from consistent, daily adherence accrue over weeks, months, years, and decades of life. The use of immediate incentives for adherence is one way to increase the value of such behaviors in the present, providing an immediate reason to adhere. In the SweetGoals intervention, incentives target improvement in specific self-management behaviors, and such improvement is expected to improve glycemic control. Three studies [23-25] using incentives for glucose checks have shown significant positive effects, as have our prior studies [21,26,27].

Health Coaching to Improve Self-Regulation

This study will also test the impact of a coaching intervention focused on enhancing motivation and teaching problem-solving skills to promote long-term outcomes. There is evidence that motivational interviewing and instruction in problem-solving

skills can improve medical adherence including in T1D [28-35]. Health coaches will teach these skills in brief web-based sessions in the context of device data review focused on actionable self-management targets. The curriculum begins with motivational exercises to guide selection of concerns that become the target of the problem-solving sessions. The health coach also facilitates engagement with self-monitoring and goal-setting habits using the Glooko data visualization platform and the SweetGoals app goal feedback, consistent with the supportive accountability model [36]. Providing such support increases the efficacy of digital interventions [37-42], and delivery by bachelor's level coaches can be as effective as professional clinicians across diverse clinical targets [43,44]. The supportive accountability model emphasizes the key role that social presence (human coach) plays in setting clear expectations regarding adherence to the steps necessary to achieve a positive outcome (eg, glucose monitoring) and in supporting goal attainment via progress monitoring and feedback [36]. Our pilot results strongly support the long-term sustained efficacy of this coaching approach combined with incentives [21], but those results cannot inform the need for both of these distinct interventions. This new study will replicate those earlier results in a novel population of young adults and test the separate impact of incentives, coaching, and their interaction.

Methods

Participants

We will enroll 300 young adults with T1D, aged 19 to 25 years (target 50% female) who have HbA_{1c}≥8%. Young adults must use a Glooko compatible glucometer or CGM and may use either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII). See Textbox 1 for detailed inclusion and exclusion criteria.

Textbox 1. Inclusion and exclusion criteria for the SweetGoals study.

Inclusion criteria:

- Diagnosis of type 1 diabetes for longer than 18 months
- HbA_{1c} ≥8.0%
- Report a visit with physician managing type 1 diabetes within the previous 6 months
- Participants must use a glucometer or continuous glucose monitor compatible with Glooko

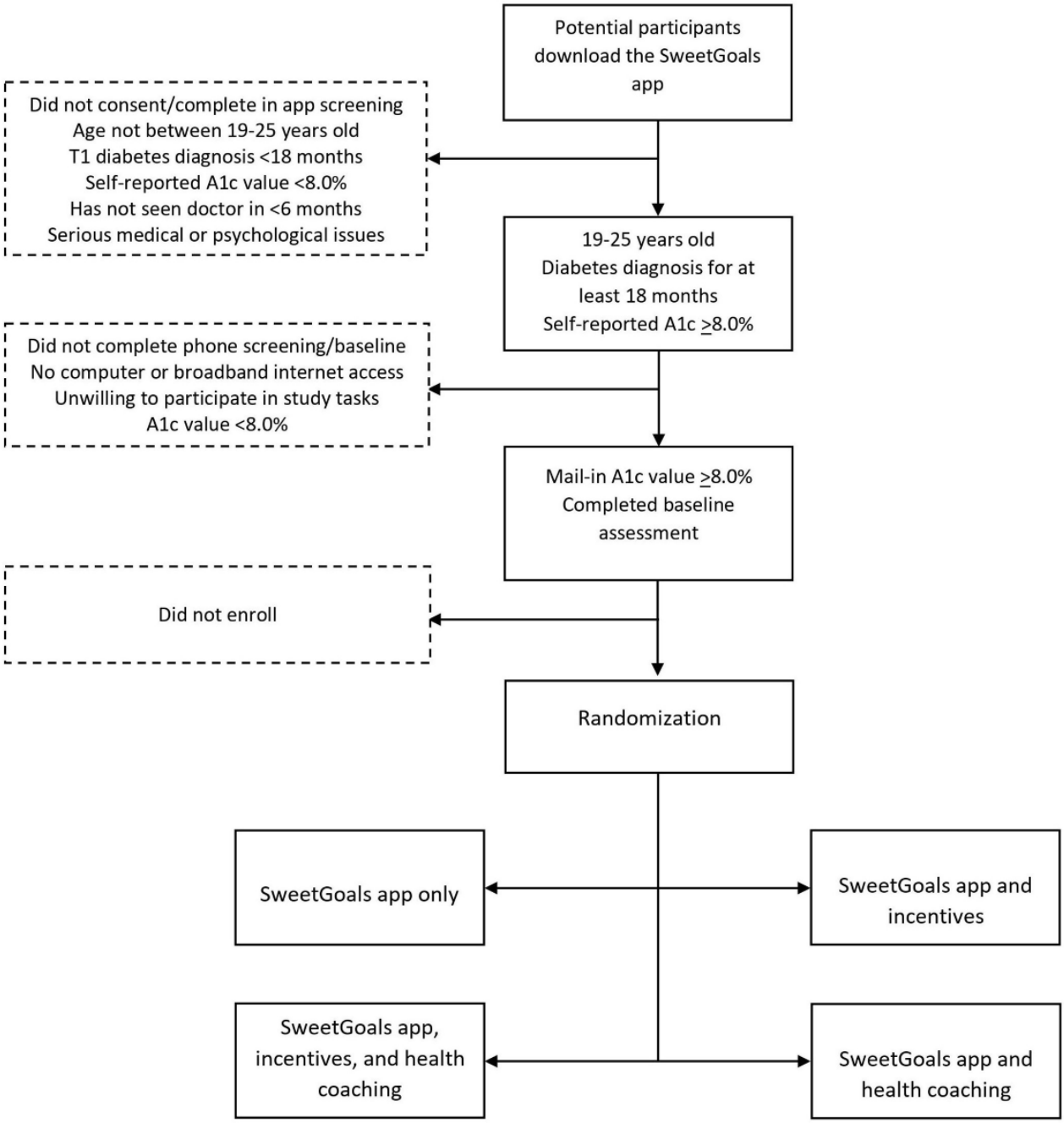
Exclusion criteria:

- Pregnancy or breastfeeding
- Severe medical illness that would preclude participation (eg, cystic fibrosis, developmental disability, severe cognitive impairment)
- Psychiatric illness that would preclude participation
- Diabetes diagnosis other than type 1 diabetes (type 2 diabetes, maturity onset diabetes of the young)
- Use of any medications known to impact glycemic control (oral or injectable corticosteroids, beta-blockers, antipsychotic medications such as risperidone)
- History of known hemoglobinopathy, anemia, or transfusion (which could alter the validity of HbA_{1c} measurement)
- Already being engaged in a psychological intervention targeting diabetes adherence

Recruitment

Participants will be recruited using Facebook, Instagram, and Google ads. Best practices for ethical recruitment using social media platforms will be followed [45,46]. Breaks will occur between ad runs to reduce ad fatigue. The ads will prompt potential participants to download the SweetGoals app. Once they confirm that they are in the target age range, they will complete the study consent in the app. Consenting participants will complete a brief survey via the app to confirm eligibility. Research staff will follow up to complete the screening process, confirming device compatibility with Glooko and arranging for completion of the HbA_{1c} test via postal mail. Once eligibility is confirmed (mail-in HbA_{1c}≥8%), staff will help participants create their Glooko accounts and install the Glooko uploader and Glooko smartphone app via phone or a web video chat. Staff will then complete the randomization as described below. Figure 2 displays the screening, recruitment, and randomization process.

Figure 2. Screening, recruitment, and randomization process.



Procedure

A fully powered 2×2 randomized factorial experiment (see Table 1) will be used to evaluate specific intervention components in terms of HbA_{1c} outcomes. Factorial designs are a highly efficient experimental approach for answering questions about the utility of multiple intervention components and their combinations. Data from these designs can be used to test the main effect of each intervention component as well as their interaction [47,48]. All participants will receive the SweetGoals app. Those assigned to the incentive group will receive incentives for meeting glucose monitoring and mealtime targets. Those assigned to the coaching group will receive web coaching in problem-solving skills focused on achieving better self-management and glycemic control. If assigned to incentives, participants will receive incentives weekly for 3 months, with gradually fading frequency over the next 3 months. If assigned to coaching, participants will meet with the coach weekly via web video for 3 months, with the frequency of those meetings also fading gradually over the next 3 months. The intervention period lasts for 6 months. Follow-up assessments will be completed at 6 months and 12 months after baseline.

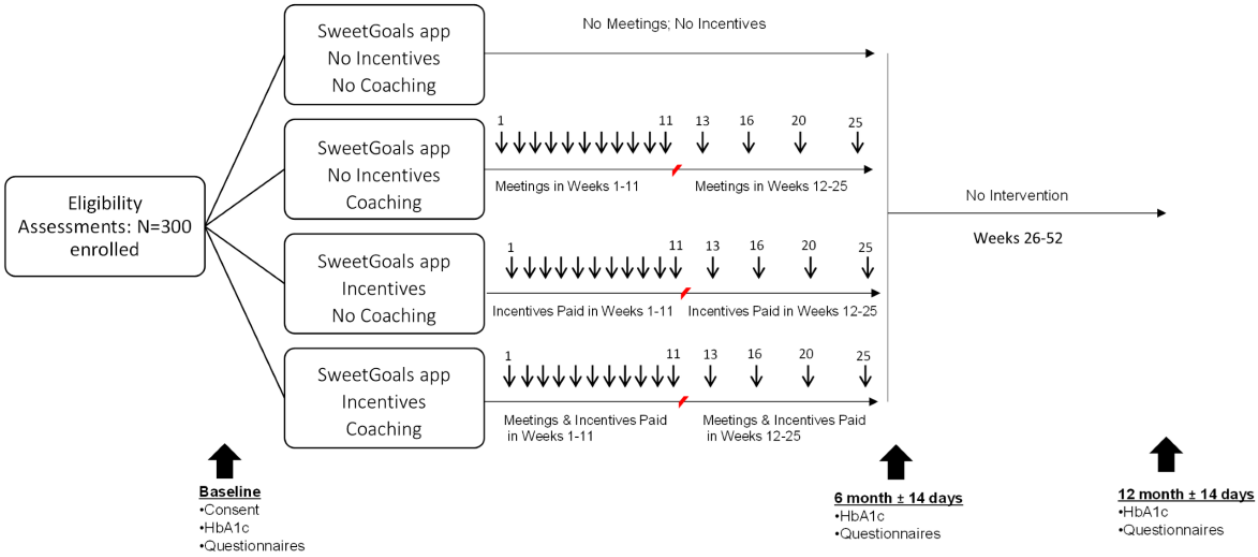
Table 1. Experimental conditions of the 2×2 factorial design.

Experimental condition	SweetGoals app	Incentives	Web coaching
1	Yes	No	No
2	Yes	No	Yes
3	Yes	Yes	No
4	Yes	Yes	Yes

Each component will take on 2 levels: yes or no. Note that the factorial design in Table 1 is not a 4-arm trial with each condition compared with a control or to each other. Instead, our interest is in tests of standard analysis of variance main effects and interactions [49]. These involve comparison of outcome means across multiple experimental conditions. For example, the main effect of the incentives component will be tested by comparing the mean of the outcome variable across the 2 conditions in which incentives will be delivered (ie, those in conditions 3 and 4; n=150 before attrition) versus the 2 conditions in which incentives will not be delivered (ie, those in conditions 1 and 2; n=150 before attrition). Hence, this main effect will be tested by comparing half of the sample (those offered incentives) versus the other half (those not offered incentives) in terms of the primary outcome. In this factorial experiment, each effect (including the interaction between the 2 components) will be estimated based on data from all 4 conditions (ie, the full sample) [48,50,51].

Figure 3 shows the study design. An online minimization program (MinimPy) will be used to assign participants [52]. Minimization assures similarity across intervention groups on multiple key covariates [52]. Differences between conditions will be minimized on gender, age, ethnicity (minority vs White), CSII versus MDI, CGM use, and HbA_{1c}. Follow-ups will occur at 6 months and 12 months. Compensation will be $25 for the baseline assessment, $50 for each follow-up assessment, and a supplement of $50 for completing both follow-ups. This study was approved by the Committee for the Protection of Human Subjects at Dartmouth College and is registered at ClinicalTrials.gov [NCT04646473].

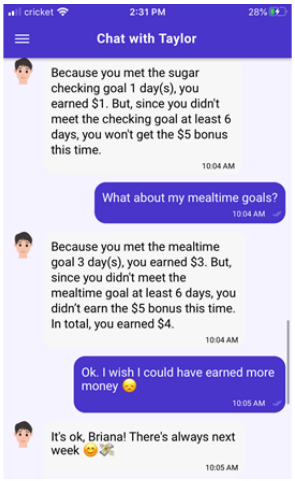
Figure 3. Study design.



SweetGoals App Core Intervention

All participants will receive SweetGoals, an app that sends messages about self-management goals, goal adherence, and encouragement about adherence in the upcoming week. Participants will receive messages on Sunday reminding them to upload their data and feedback detailing their goal achievement on Monday. They will also receive educational materials in a second message most weeks (eg, links to information about self-management of T1D). The app is programmed in MobileCoach [53-55], an open-source app platform that has the functionality to integrate our goal-tracking algorithms and provide messages that prompt device uploads and provide automated feedback. MobileCoach sends messages written by the research team in the style of Facebook Messenger or WhatsApp from a digital coach who communicates with the app user to provide scripted feedback about goals as shown in Figure 4. Participants select from a random sample of 4 coaches offered from a bank of 12 coaches of diverse gender and race/ethnicity. The participant (Briana in Figure 4) can answer the digital coach (Taylor in Figure 4) using predefined responses.

Figure 4. SweetGoals dialogue with digital coach Taylor.



Daily and Weekly Self-Management Goals

The SweetGoals app will automatically download the participant's device data each Sunday at midnight using the Glooko application programming interface. The app will use the device data to provide feedback each Monday about goals that target glucose monitoring and mealtime behaviors tailored by device as shown in Table 2. The glucose monitoring goal for participants who use a glucometer only (no CGM) is ≥5 checks, each ≥2 hours from another check. Additional checks—regardless of spacing—are encouraged based on clinical needs (eg, hypoglycemia). This same criterion was used successfully in prior studies [21,26,27]. For participants who use CGM, we conservatively define adequate daily CGM wear time as 80% of expected values each day. We selected this daily glucose monitoring goal to provide clinically meaningful data to the participant but also allow for legitimate disconnect time (sports, leisure activities) and sensor changes.

Table 2. Goals based on devices used.

Glucose monitoring device	Insulin delivery method	Glucose monitoring goal	Mealtime goal
Glucometer	MDI[a]	SMBG[b]	Enter in Glooko Mobile
Glucometer	CSII[c]	SMBG	Enter in pump
CGM[d]	MDI	CGM wear time	Enter in Glooko Mobile
CGM	CSII	CGM wear time	Enter in pump

[a]MDI: multiple daily injections.

[b]SMBG: self-monitored blood glucose.

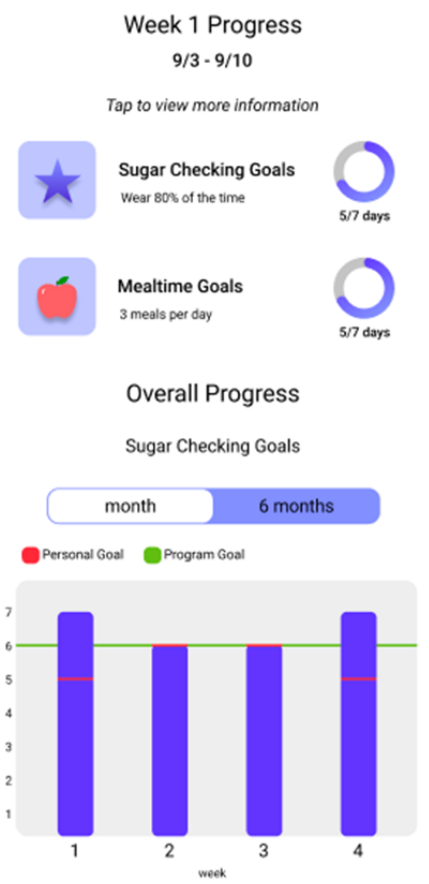
[c]CSII: continuous subcutaneous insulin infusion.

[d]CGM: continuous glucose monitor.

The mealtime goal for participants who use a glucometer only (no CGM) is to check their glucose before they enter their carbs. Those who use MDI will enter their carb counts in the Glooko app. Participants who use CSII will enter their carb value in their pump. A glucose check must be documented within 30 minutes of the carb entry, an evidence-based criterion [56] that should occur at least 3 times per day according to clinical practice guidelines [57]. An algorithm based on the type of devices used will evaluate whether the mealtime goal was met. The daily mealtime target is 3 properly timed paired glucose levels and carb count values.

The weekly goal for all participants is to meet the daily goal on 6 or more days per week. Each week, participants will also be asked to set personal goals for the next week for the number of days they think they can meet each daily goal, to help participants build motivation to gradually increase their self-management behaviors. Each week, participants will receive feedback messages and graphical reports about goals met (see Figure 5 for an example of a participant who uses a CGM). The app will send reminders to upload device data and set personal goals.

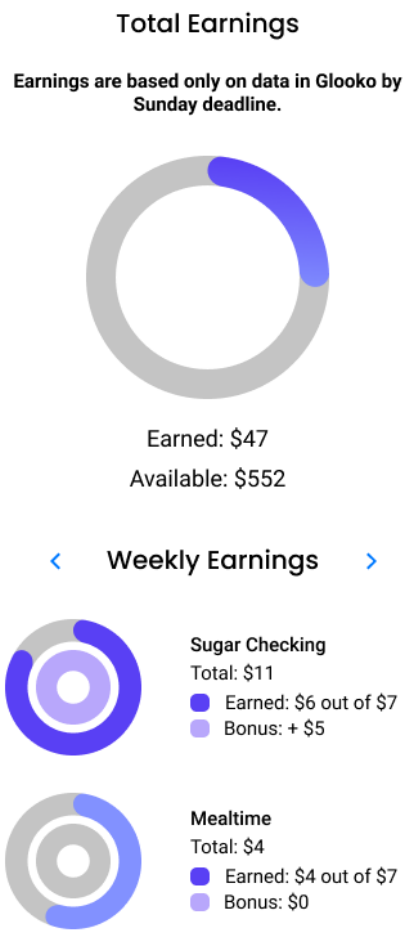
Figure 5. SweetGoals goal feedback graphs—continuous glucose monitor user.



Incentives Component

Participants assigned to the incentive group will earn $1 per day for meeting each daily goal (glucose monitoring, mealtime behaviors) and will receive a $5 bonus for meeting the weekly target of 6 or more days per week meeting each goal, for a total of $24 maximum per week (approximately $3.50 per day). The maximum earnings for all goals are $600 across 25 weeks. The app will provide messages and graphical reports about incentives (see Figure 6). Incentives accrue weekly throughout the 25 weeks but are paid weekly from weeks 1 to 11, with payments fading in frequency from weeks 12 to 25 (ie, paid at weeks 13, 16, 20, and 25). Fading of reinforcement delivery has been shown in human and animal research to engender resistance to extinction after reinforcers end, increasing the maintenance of behavior change beyond the intervention period [58-62]. For this reason, we have incorporated a lengthy (3-month) fading period to promote maintenance of improvements in daily self-management.

Figure 6. SweetGoals incentives feedback graphs.



This fading procedure is used to promote habit automaticity and long-lasting improvements in adherence and HbA_{1c}. We have successfully used this fading paradigm in our prior studies, which resulted in no weakening of intervention effects on HbA_{1c} up to 6 months after the end of the intervention.

Web Health Coaching Component

Participants assigned to the coaching group will receive 16 web health coaching sessions by a bachelor's level health coach. Weekly coaching sessions occur from weeks 1 to 11, and then fade over the second half of the intervention with 4 sessions held during weeks 12 to 25 (weeks 13, 16, 20, and 25). Coaches will use their own chat interface in SweetGoals and text messages to communicate with participants. Coaches will also remind participants of meetings, offer encouragement, and respond to any messages the participant sends. In each meeting, coaches will review weekly glucose monitoring and mealtime goals and incentives earned in the context of diabetes device data reviewed using the Glooko website. Motivational exercises are completed in the first few meetings to develop rapport and allow the young adult to explore and reflect on their self-management strengths and challenges [63]. The young adult will work together with the coach to identify barriers to adherence. Coaches will also teach a structured problem-solving method to the young adult [64].

During the second half of the intervention, as coaching sessions are spaced at increasing intervals, participants are encouraged to review their diabetes data weekly on the Glooko website or app and complete the problem-solving steps on their own to address self-management concerns. Success and challenges with independent problem solving are reviewed at coaching sessions during the fading period. Throughout the intervention, if the young adults experience challenges meeting glucose monitoring or mealtime goals, coaches encourage them to use the problem-solving steps to develop a plan to improve adherence. As they gain more success meeting those goals, they are encouraged to select new goals regarding glucose levels and problem solve potential barriers to achieving those goals. Participants are always encouraged to reach out to their providers with any concerns about the insulin regimen, hypoglycemia, or hyperglycemia as coaching does not address medical management of diabetes. The structure of the problem-solving method is constant across participants; however, the content is highly personalized based on the unique challenges faced by each young adult.

Coaches receive training in communication skills consistent with a motivational interviewing approach [65]. Importantly, motivational interviewing has been identified as an effective approach for improving diabetes outcomes clinical trials

[35,66,67]. Coaches are also trained in providing instruction and support in problem-solving [64,68]. Training involves didactic material and extensive role play practice.

Diabetes Care

Participants in all conditions will receive ongoing diabetes treatment from their current medical provider. Study staff will not provide medical care or intervention. The project includes an endocrinologist who will monitor device data regularly in Glooko, and research staff will encourage participants to follow-up with their medical provider as necessary.

Measures

Measures will be collected at baseline, 6 months (end of intervention), and 12 months unless otherwise noted. Assessments will not be blinded. All measures will be completed by participants online via the app or LimeSurvey or are objective measures (eg, device downloads, HbA_{1c} tests, or recorded directly via the app).

Demographic Characteristics

At baseline, demographics will be collected (eg, age, sex, race/ethnicity, insurance type). We will assess socioeconomic status using a single item measure appropriate for young adults [69]. We will assess diabetes indicators (eg, duration of diabetes, device use, past 12-month frequency of severe hypoglycemic events defined as episodes of documented or presumed low blood glucose that resulted in seizure or loss of consciousness [70] and hospitalization for diabetic ketoacidosis). Additionally, we will ask if the participant has been suspected of having a COVID-19 infection.

Primary Outcome

The primary outcome will be HbA_{1c} assessed using a Clinical Laboratory Improvement Amendments–waived nonfasting whole blood HbA_{1c} test (AccuBase A_{1c} test kit by DTI Laboratories) mailed to the participant (with a postpaid return envelope) at each assessment. Samples are stable at room temperature for 21 days after collection, and results are available within 48 hours of receipt. AccuBase is FDA-cleared and uses capillary tube collection. Lab testing uses high-performance liquid chromatography, including abnormal hemoglobin screening. This method has been used effectively in a large national web-based study [71].

Secondary Outcomes

Secondary outcomes will include key self-regulation constructs including adherence, self-efficacy, and problem solving. Adherence to glucose monitoring and mealtime behaviors will be assessed during the 30 days prior to each assessment by calculating the percentage of days meeting each goal from device data. Diabetes management self-efficacy and outcome expectations will be assessed using the 10-item Self-Efficacy for Diabetes Management scale [72] that has shown strong relations with adherence among young adults with T1D [16]. Problem-solving skills will be assessed using the 10-item version of the Social Problem-Solving Inventory–Revised (α=.85) [73,74]. To assess symptoms of diabetes distress (a moderator), the 28-item T1-Diabetes Distress scale (α=.91) [75,76] will be used. Additionally, behavioral and emotional problems will be assessed with the 34-item version of the Counseling Center Assessment of Psychology Symptoms (α=.91 with all items), with the suicidality and desire to harm others items removed [77]. Self-regulation will be assessed using a brief self-regulation scale [78], a 12-item measure. Body awareness will be measured with the Body Awareness Questionnaire (18 items; α=.82) [79]. Hypoglycemia awareness will be measured by a single item [80]. Baseline levels of technology experience will be measured using the Technology Readiness Index (16 items) [81] and a novel measure based on Venkatesh et al [82] which asks about experience with specific types of technologies. We will also assess past 30-day substance use frequency (tobacco, alcohol, cannabis, other drugs) with items adapted from the 2018 Monitoring the Future survey [83], the National Survey on Drug Use and Health [84], and the Tobacco, Alcohol, Prescription medication, and other Substance use tool [85].

Implementation, Satisfaction, and App Metrics

For participants who receive human coaching, satisfaction with the human health coach will be assessed at the beginning, during, and the end of the program with the Session Alliance Inventory (α=.94) [86] and an adaption of the Working Alliance Inventory [87,88]. Satisfaction with the SweetGoals digital coach will be assessed at the beginning, during, and at the end of the program with the Session Alliance Inventory [86] and (at the end of the 6-month intervention period only) an adaption of the Working Alliance Inventory [87,88]. We will assess usability of the app components with items from the Usefulness, Satisfaction, and Ease of Use questionnaire (α=.98) [89] and overall app satisfaction with items adapted from Wixom & Todd [90] 3 times (early, midway, and at the end of the 6-month intervention period). In addition, the app will collect engagement metrics including the percentage of messages from digital coaches responded to within 24 hours of receipt and the mean length of the delay between when messages are sent by the app and accessed by the participant. These data will be used to explore objective app engagement and whether satisfaction and app engagement were better when receiving incentives or coaching.

Health Coaching Fidelity

Coaches will complete a detailed checklist after each meeting. In addition, fidelity coding of one randomly selected session for each participant will be completed [91]. Undergraduate coders will complete an extensive training protocol in the rating system. Coders will double code a randomly selected subset (25%) of sessions, and reliability will be tracked on an ongoing basis to ensure reliability of more than 80%.

Statistical Analysis

All subjects, once randomized, will be included in the intent-to-treat sample. We will strive to collect all primary and secondary outcomes even if a participant does not engage in assigned interventions. Data will be stored in the Research Electronic Data Capture, MobileCoach, and a secure Dartmouth server.

Missing Data

As in any study, missing values may occur due to dropout (anticipated to be less than 20% by the end of 12 months), inability to reach a participant for follow-up, item nonresponse, or gaps in or missing device data. The proposed structural equation modeling (SEM) and linear mixed effects models (LMMs) use all available data and are robust to outcome data that are missing at random.

Primary Outcome Analyses

The primary aim is to test the main effects of incentives and coaching on HbA_{1c}. We will also test the interaction between components (eg, the synergistic effect of adding one component to another). Two effect-coded indicators (see Collins [51] for detailed justification for using effect coding in the analysis of data from factorial designs) will be created, one for each component: the indicator for incentives (yes vs no) will differentiate between those offered incentives (coded +1; conditions 3 and 4 in Table 1) and those who were not (coded –1; conditions 1 and 2 in Table 1); the indicator for coaching (yes vs no) will differentiate between those offered coaching (coded +1; conditions 2 and 4 in Table 1) and those who were not (coded –1; conditions 1 and 3 in Table 1). To assess the impact of each component on HbA_{1c} over time (baseline, 6 months after, and 12 months after), an LMM will be fit. The model will include fixed effects for time, two component indicators, the component × component interaction, two component × time interactions, and the component × component × time interaction as fixed effects. The LMM will also include random effects for the intercept and time to account for within-person correlation. Based on this LMM, we will test the hypothesis that the yes level of each component (vs no) results in lower HbA_{1c} over time via the component × time interaction parameters.

We calculated the power for testing effects on HbA_{1c} based on the following assumptions: (1) models will include baseline HbA_{1c}; (2) a within-person correlation between baseline HbA_{1c} and HbA_{1c} at each follow-up assessment of 0.6 (based on our pilot study); and (3) a standard deviation for HbA_{1c} of 1.2, based on our pilot data. Table 3 shows detectable main effects and interactions in terms of Cohen *d* [92] and HbA_{1c} mean differences. Given n=240 to n=270 (based on 80% to 90% retention), we will be able to detect small effect sizes (Cohen *d*=0.27 to *d*=0.29) with 80% power.

Table 3. Aim 1 power for main effects and interaction between components.

Retention %	N	Power %	2-sided *P* value	Cohen *d*	HbA_{1c} difference %
90	270	80	.05	0.27	0.32
85	255	80	.05	0.28	0.33
80	240	80	.05	0.29	0.35

Secondary Outcome Analyses

Secondary analyses will evaluate change in 4 potential mechanisms of action of incentives and coaching (and their interaction) on HbA_{1c} at 6 months: glucose monitoring adherence, mealtime adherence, self-efficacy, and problem solving. We will follow the methods recently outlined for conducting mediation analysis in a factorial design with multiple mediators [93]. The mediation model will be tested using SEM with full maximum likelihood estimation, as outlined by MacKinnon et al [94]. The models will test effects of (1) each component and their interaction on the 4 mediators assessed at 6 months, (2) each mediator on HbA_{1c} at 12 months, and (3) each component and their interaction on HbA_{1c} at 12 months. Models will control for baseline levels of HbA_{1c} and the mediators. This model will evaluate the indirect effect of each component on HbA_{1c} through each mechanism, thereby testing whether the effect of coaching and incentives on HbA_{1c} is through increasing each of the 4 potential mechanisms.

Exploratory Analyses

Informed by the approach of Yardley et al [95], these analyses aim to determine whether app engagement and use metrics predict improvements on HbA_{1c} outcomes. We will first examine how engagement metrics differ between those receiving incentives versus no incentives and coaching versus no coaching. Use metrics will include the percentage of messages responded to within 24 hours of receipt and the mean length of the delay between when messages are sent and accessed. In LMM models predicting HbA_{1c}, we will adjust for one or both components if we find significant component effects on engagement metrics. Effects of engagement metrics on HbA_{1c} outcomes are of interest in terms of future refinement and development of the SweetGoals app, suggesting critical app features that may be important to retain in future interventions or features that appear to have less impact and may need to be improved upon in future research [95].

Results

We anticipate recruiting 300 young adults in a 36-month period (approximately 8 per month). The anticipated date of enrollment of the first participant is February 2021. We expect that data collection will be complete by February 2025. We expect to complete analyses of the primary and secondary outcomes by December 2025.

Discussion

Design Innovations

This study focuses on investigating the utility of two intervention components, seeking to optimize an intervention for improving glycemic outcomes among young adults with T1D. Innovations include recruiting participants with T1D into an intervention

via social media and intervention delivery via an app plus coaching and incentives both delivered remotely, strategies that may be vital to reaching the targeted, understudied, and underserved population of young adults. In addition, this is the first intervention designed to target adherence via incentives among patients using diverse glucose measurement methods (glucometer, CGM) and methods of insulin delivery (MDI, CSII). This trial also makes innovative use of existing diabetes device technology by integrating a diverse array of devices with an app to automate tracking of and feedback on daily adherence habits. This digital and web-based model is designed to be broadly applicable across the range of health conditions in which patients struggle with self-management.

Design Considerations

The study design was informed by research evidence across multiple domains. For example, the focus on young adults was based on evidence suggesting they are at unique risk for above target HbA_{1c} levels and that periods of above target HbA_{1c} levels during these years have a long-lasting negative impact on health [96]. We chose to focus on early young adulthood (ages 19 to 25 years) due to their higher risk for above target HbA_{1c} [97] and possible developmental differences across the later 20s and early 30s. Further, we chose to target young adults outside the traditional clinic setting directly via social media, empowering them to address their diabetes self-management. Many young adults are less compliant with obtaining regular medical care [98], which suggests it may be important to offer services to young adults with T1D outside the endocrinology setting to problem solve their barriers to clinical care and encourage them to schedule regular visits with their provider. This proposed model focuses on directly engaging participants rather than targeting changes in provider behavior. As such, it offers a practical outreach approach that could be deployed nationally and adopted by medical practices, health systems, or insurers outside of office visits to engage young adults with T1D in working together with their provider and managing their own health.

Intervention Targets

There were several decisions made in relation to our choice of particular adherence behaviors to target. Key to effectively using incentives to change behavior is the identification of specific, objectively verifiable, targets. Research on diabetes has long identified self-monitored blood glucose (SMBG) as a fundamental adherence behavior related to better glycemic control [99], and our pilot research focused on increasing SMBG. However, the increasing use of CGM (approximately 25% in the T1D Exchange sample [97]) led us to develop a strategy to include all participants with above target HbA_{1c}, using any combination of diabetes devices. This choice required us to identify a key adherence behavior necessary for CGM use to have a positive impact on glycemic control. Research suggests that CGM wear time is the analog to SMBG that positively impacts glycemic control [100]. Of note, high wear time is defined as providing 80% of expected glucose values each day, based on a review of CGM studies and the recent international consensus statement [101]. By selecting targets that allow the inclusion of participants using all current glucose monitoring devices, we have greatly increased the intervention generalizability.

There are many other self-management behaviors in addition to glucose monitoring necessary to achieve below target HbA_{1c} levels, and these primarily reflect timely and accurate insulin dosing. In selecting additional specific, objectively verifiable targets related to insulin dosing we needed to address multiple challenges. Some of these include the different regimens and rules associated with use of MDI versus CSII, highly individualized insulin dosing regimens across participants, and diverse circumstances under which the dosing rules should be altered (eg, when ill, due to exercise, due to nutritional factors other than simply the number of carbs consumed). It is also not possible to objectively verify for a patient who uses MDI the timing and amount of insulin delivered. For these reasons, we opted to focus on mealtime behaviors involving a glucose value less than 30 minutes prior to an entered carb value, a pair of behaviors that are fundamental to accurate insulin dosing and that are required of all participants regardless of method of insulin dosing.

Ideally, mealtime adherence reflects 3 steps: a properly timed glucose check, entry of the number of carbs consumed, and correct insulin dosing. There are few data regarding carb counting among young adults who do not use CSII. However, research has investigated adherence among young adults using CSII [56,102-106]. Overall, adherence is highly variable across individuals, and days on which a mealtime bolus occurs more than 3 times are significantly correlated with HbA_{1c} [103,105,107,108]. Participants who complete these first two steps (glucose check and carb entry) are likely to deliver a bolus, as supported by research showing that the sequence of a properly timed glucose check and a carb entry without a bolus occurred less than 1% of the time [56].

In selecting adherence targets, we also considered targeting individual glucose levels or time in the target glucose range. Unfortunately, for participants who do not use CGM, these data are sparse and potentially not representative of daily fluctuation in glucose levels. Our selected mealtime behaviors are more actionable and are key adherence behaviors for participants using CGM, even when hybrid closed-loop systems are in widespread use [109-114]. Further, access to such systems is often allowed only for participants showing adherence and moderate HbA_{1c} elevations. For example, in the recent closed-loop study with patients with above target HbA_{1c} levels, participants with HbA_{1c}>10% were excluded and participants were required to show use of CGM for at least 12 days and use of the bolus calculator for at least 75% of meal boluses over 2 weeks prior to randomization [115]. Finally, discontinuation rates for such systems may be high [116], suggesting the continued need for solutions to improve outcomes for participants using diverse treatment regimens.

Inclusion of Incentive Component

Some research on the use of incentives to promote health behavior related to diabetes have not shown significant benefits. For example, a scoping review [117] reported that using incentives for health behavior related to type 2 diabetes showed

limited efficacy. The review highlights several critical issues related to the design of incentive interventions that can result in poor outcomes. For example, ineffective incentive programs typically offer infrequent rewards provided long after the target behavior occurs. To be effective, incentives should be provided frequently and immediately after the targeted behavior. Ineffective programs often target one-time behaviors (eg, attending a clinic visit). Instead, incentives should target learning new, daily healthy habits. Consistent with best practices, our intervention uses immediate rewards, focuses on daily health behaviors, incorporates behavioral economic principles of goal setting to engage commitment to behavior change, and provides frequent feedback.

Concern is sometimes expressed that incentives may undermine intrinsic motivation; however, the undermining effect of rewards on intrinsic motivation appears limited to simple tasks for which motivation is initially high [118]. When baseline levels of incentivized behaviors (and motivation) are low (as they generally are for health-related behaviors such as adherence among those with above target HbA_{1c}), there is no evidence for a negative impact on intrinsic motivation [119]. In fact, studies have shown that incentive interventions can increase intrinsic motivation [120] and engage deliberative cognitive processes related to self-regulation to offset automatic selection of unhealthy but reinforcing behaviors [121]. Incentives can also build sustained habits [122], and habits with high automaticity may be stronger predictors of health behavior than positive intentions [123,124].

Because concern is sometimes raised about the potential for dissemination of financial incentive interventions, this study will experimentally test the impact of the incentive component of SweetGoals. In recent years, use of incentive interventions has greatly expanded across the United States. These include deploying incentives for abstinence from substance use across 94 locations in the Veterans Affairs system [125], workplace wellness programs (offered by 80% of employers with more than 1100 employees) many of which include financial incentives or penalties for employees with chronic conditions [126], offering financial incentives specific to diabetes or prediabetes (type 2 diabetes) conducted in federally qualified health centers and large health systems (Kaiser Permanente, Cleveland Clinic) [127-131], and programs offering incentives for Medicaid enrollees with prediabetes for weight loss [132] and for enrollees with hypertension or diabetes who meet health targets [133]. These efforts show the increasing dissemination of the use of financial incentives to change health behaviors in the United States and highlight the need to enhance science-based guidance to inform such programs.

Conclusion

This study is designed to test the role of two evidence-based behavioral intervention components (incentives and health coaching) in supplementing a mobile health approach to improve glycemic outcomes among high-risk young adults with T1D who have above target HbA_{1c} levels. We will also test the effect of these intervention components on key self-regulatory mechanisms hypothesized to be impacted by these components, including two aspects of adherence (glucose monitoring and mealtime behaviors), plus self-efficacy and problem solving. Overall, results will provide critical data on enhancements to a digital intervention for T1D that are highly disseminable. They will also advance the field of theoretically driven interventions aimed at improving self-management and glycemic outcomes among high-risk young adults with elevated HbA_{1c} levels.

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Authors' Contributions

CS, TK, HX, IN, and FL were responsible for the study design. PS developed the SweetGoals app. CS, MA, SK, and BR developed the study protocol. CS, HX, and IN were responsible for the data analysis plan. CS and SK wrote the first draft. All authors were responsible for critical feedback and final revisions of the manuscript.

Conflicts of Interest

TK and PS are affiliated with the Center for Digital Health Interventions [134], a joint initiative of the Department of Management, Technology, and Economics at ETH Zurich and the Institute of Technology Management at the University of St. Gallen, which is funded in part by the Swiss health insurer CSS (Christian Social Health Insurance Company of Switzerland). TK is a founder of Pathmate Technologies, a university spin-off company that creates and delivers digital clinical pathways. Neither CSS nor Pathmate Technologies were involved in any way in this manuscript.

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Abbreviations

CGM: continuous glucose monitor
CSII: continuous subcutaneous insulin infusion
CSS: Christian Social Health Insurance Company of Switzerland
SEM: structural equation modeling
HbA_{1c}: hemoglobin A_{1c}
LMM: linear mixed effects model
MDI: multiple daily injections
SMBG: self-monitored blood glucose
T1D: type 1 diabetes

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Protocol

A Multimodal Mobile Sleep Intervention for Young Adults Engaged in Risky Drinking: Protocol for a Randomized Controlled Trial

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Abstract

Background: This paper describes the research protocol for a randomized controlled trial of a multimodal mobile sleep intervention for heavy-drinking young adults. Young adults report the highest rates of heavy, risky alcohol consumption and are a priority population for alcohol prevention and intervention efforts. Alcohol strategies that leverage other health concerns and use technology may offer an innovative solution. Poor sleep is common among young adults and is a risk factor for developing an alcohol use disorder. Moreover, young adults are interested in information to help them sleep better, and behavioral sleep interventions address alcohol use as a standard practice.

Objective: The primary aim of this study is to assess the effectiveness of a 2-week multimodal mobile sleep intervention for reducing drinks consumed per week among heavy-drinking young adults. We will explore the effects on alcohol-related consequences, assessing quantitative and qualitative sleep characteristics as secondary aims. The study's goals are to identify the optimal combination of sleep intervention components for improving drinking outcomes, the feasibility and acceptability of these components, and the potential mechanisms by which these components may promote alcohol behavior change.

Methods: Young adults (aged 18-25 years) who report recent heavy drinking will be randomly assigned to one of three conditions: mobile sleep hygiene advice (n=30), mobile sleep hygiene advice and sleep and alcohol diary self-monitoring (n=30), or mobile sleep hygiene advice, sleep and alcohol diary self-monitoring, and sleep and alcohol data feedback (n=60). For the feedback component, participants will complete two web-based sessions with a health coach during which they will receive summaries of their sleep and alcohol data, and the potential association between them along with brief advice tailored to their data. All participants will wear sleep and alcohol biosensors daily for 2 weeks for objective assessments of these outcomes.

Results: The study was funded by the National Institutes of Health in May 2018. Recruitment began in December 2018 and will be concluded in Spring 2021. As of February 4, 2021, we have enrolled 110 participants.

Conclusions: Ultimately, this research could result in an efficacious, low-cost intervention with broad population reach through the use of technology. In addition, this intervention may substantially impact public health by reducing alcohol use disorder risk at a crucial developmental stage.

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KEYWORDS

sleep; binge drinking; young adults; mHealth; biosensor; behavior therapy; mobile phone

Introduction

Background

Alcohol Use and Sleep Among Young People

Alcohol use disorder (AUD) onset peaks during young adulthood (ie, 18-25 years) [1]. Compared with older adults, young adults report more frequent and heavier alcohol use, which is linked to substantial negative consequences, including the risk of accidental injury, the primary cause of death among young adults [2-4]. Current alcohol interventions for young adults have modest effects [5-7], and young adults rarely self-identify for specialized alcohol treatment [8,9]. Thus, more work is needed to identify effective alcohol interventions and novel treatment engagement strategies to reduce this substantial public health burden.

A novel approach is to target poor sleep, a common complaint among young adults who drink heavily [10,11] and an AUD risk factor in young adulthood [12-18]. Sleep problems in young adults may be because of developmental sleep changes that begin with puberty and continue into young adulthood. During this developmental period, there is a need for more sleep [19] and a preference for later bed and wake times [20], which often conflict with school or work demands and social or cultural obligations [21]. To cope with these conflicts, adolescents and young adults may maintain shorter, more variable sleep schedules putting them at risk for sleep problems, excessive daytime sleepiness, and other negative consequences [21-23].

AUD risk is an important correlation and a potential consequence of poor sleep. In young adults, greater alcohol consumption and alcohol-related consequences are associated with shorter sleep duration, poorer sleep quality, and more delayed bed or wake times [10,11]. In addition, various sleep problems in adolescence predict earlier AUD onset and a greater risk of heavy drinking, alcohol-related consequences, and AUD in young adulthood [12,18,24]. Furthermore, poor sleep in young adults predicts a greater future risk of alcohol-related problems [14].

The nature of this sleep-alcohol association in young adults is not clear but is likely bidirectional. Heavy alcohol use may directly disrupt sleep [25-28]. Conversely, vulnerability to both poor sleep and heavy drinking may be because of mental health concerns [29]. Another possibility is that poor sleep may reduce control to resist drinking or alter reward sensitivity through adverse cognitive function effects [21]. In neuroimaging studies, healthy adolescents with poor sleep habits exhibited altered reward processing and reduced cognitive control compared with adolescents with good sleep patterns [21,30-32]; sleep-deprived adults also exhibited an altered reward processing [33-35]. It is also possible that poor sleep is associated with disrupted chronobiology that interrelates a host of neuroendocrine and physiological changes and alcohol misuse [36,37]. Regardless of the initial cause, poor sleep and heavy drinking likely become a negative feedback cycle that both interact and influence each other. Thus, an important hypothesis that warrants further investigation is whether improving sleep might reduce alcohol-related risks among young adults.

Sleep Interventions to Reduce Heavy Drinking

With the exception of our preliminary work [38] and a recent pilot study [39], sleep interventions for reducing drinking and alcohol-related risks have only been tested in older adults and focused on cognitive behavioral therapy for insomnia [40,41]. In older populations, poor sleep is a well-established alcohol relapse risk factor [42-45], but sleep interventions have yielded mixed results [28,42,46]. Among older adults, chronic AUDs may cause permanent sleep changes that are not amenable to sleep interventions [45]. Conversely, in young adults who drink heavily, sleep problems may be reversible because of other factors that are amenable to treatment (eg, poor sleep hygiene). Early intervention in young adults may prevent the establishment of persistent sleep problems and continuous heavy drinking.

Another potential advantage of sleep interventions is that heavy-drinking young adults are open to information to help them sleep better [47] and standard-of-care sleep interventions address alcohol use [48]. Specifically, individuals are advised to moderate alcohol use for better sleep and are informed of the sleep-disruptive effects of alcohol [48]. Thus, sleep interventions may provide a potential gateway for intervening in alcohol use and engaging heavy-drinking young adults in treatment. This novel engagement strategy could potentially benefit this population, as it does not rely on self-identification for alcohol treatment.

Objectives

Formative Research

To test poor sleep as a novel treatment target, we conducted the first preliminary test of a sleep intervention in 42 heavy-drinking young adults with sleep concerns [38]. We intentionally targeted sleep more broadly than the specific problem of insomnia. Poor sleep in young adults, especially college students, manifests in several ways, such as sleep deprivation or restriction, delayed sleep phase syndrome, or insomnia [49-51]. Young adults face unique pressures (eg, college life) and many report voluntarily altering their sleep schedules to meet them [49,52]. Our goal was to develop a sleep intervention that could engage and benefit a larger proportion of young adults who have sleep concerns and engage in risky drinking than just those with insomnia. We derived the sleep intervention from previous evidence-based interventions for improving sleep and drinking in young adults and formative work in this population [38,53]. The study,

advertised through social media, targeted heavy-drinking young adults with sleep concerns and generated high interest (ie, 400+ inquiries in 4 months). Eligible participants were randomly assigned to one of two 4-week web-based conditions: (1) a sleep intervention that included a brief alcohol intervention or (2) a general wellness active control intervention with minimal sleep and alcohol advice. Consistent with our hypotheses, greater sleep improvement predicted less drinking (regardless of participants' sleep concern level). However, contrary to expectations, participants in both conditions had medium-to-large improvements in alcohol and sleep outcomes. The effects on alcohol consumption were larger than those of typical brief alcohol intervention studies for young adults [5-7].

These results generated new hypotheses and directions for further sleep intervention refinement. The unexpected finding of comparable improvements across both conditions suggested that common elements may have contributed to the outcomes. Participants in both conditions received brief sleep hygiene advice and advice to moderate their drinking for improved sleep. This brief advice alone may have been sufficient to improve sleep and reduce drinking. In addition, participants in both conditions actively monitored their sleep and alcohol use. Sleep hygiene education is effective for improving sleep in young adults [50,54]. Similarly, self-monitoring (SM) can improve many health behaviors such as poor sleep and alcohol use [55-59], as it may help individuals learn more about their behavior, identify discrepancies between their goals and behavior, and acquire a greater sense of control over their behavior [60,61]. According to the Theory of Planned Behavior (TPB), perceived behavioral control is a factor that can increase intentions to change behavior [62]. To clarify whether sleep SM, including monitoring of drinking, is an effective intervention component, a control condition that does not include SM is needed in a follow-up study.

Our qualitative research also yielded insights into ways to improve our intervention. Specifically, participants expressed in exit interviews a desire to receive (1) personalized feedback about their sleep data and the links with alcohol use and (2) health advice tailored to this data. Health feedback, another effective behavior change strategy in line with the TPB [62], may facilitate behavior awareness and goal setting; ongoing feedback may reinforce behavior change, increase motivation, and enhance self-efficacy [61]. Greater positive beliefs about the outcome of behavior change and greater confidence in one's ability to perform this behavior may increase behavior change intentions [62].

Current Protocol

To our knowledge, no studies have tested these 3 sleep intervention components in combination (ie, SM, evidence-based sleep intervention content, and personalized sleep or alcohol feedback) for alcohol prevention or early intervention. This approach, delivered through a mobile platform, aligns well with the help-seeking behaviors of heavy-drinking young adults and their comfort and facility with technology. Many young adults do not perceive a need for help with their drinking and are increasingly less likely to visit a health care provider [63,64]. Thus, other *on ramps* to alcohol preventive services are urgently needed. Young adults are concerned about sleep and health [47]. Therefore, it may be useful for this population to embed alcohol-related content within other health programs and connect alcohol use to health outcomes. Young adults are also the largest consumers of new health technology [65]. Within the last decade, there has also been an explosion in the importance of sleep [66-68] and technology options for improving it (eg, mobile apps, wearable sleep biosensors) [69,70]. This paper describes the rationale and design of a randomized controlled trial to develop and test a multimodal mobile sleep intervention to reduce alcohol use and alcohol-related consequences among young adults who engage in risky drinking.

Methods

Design

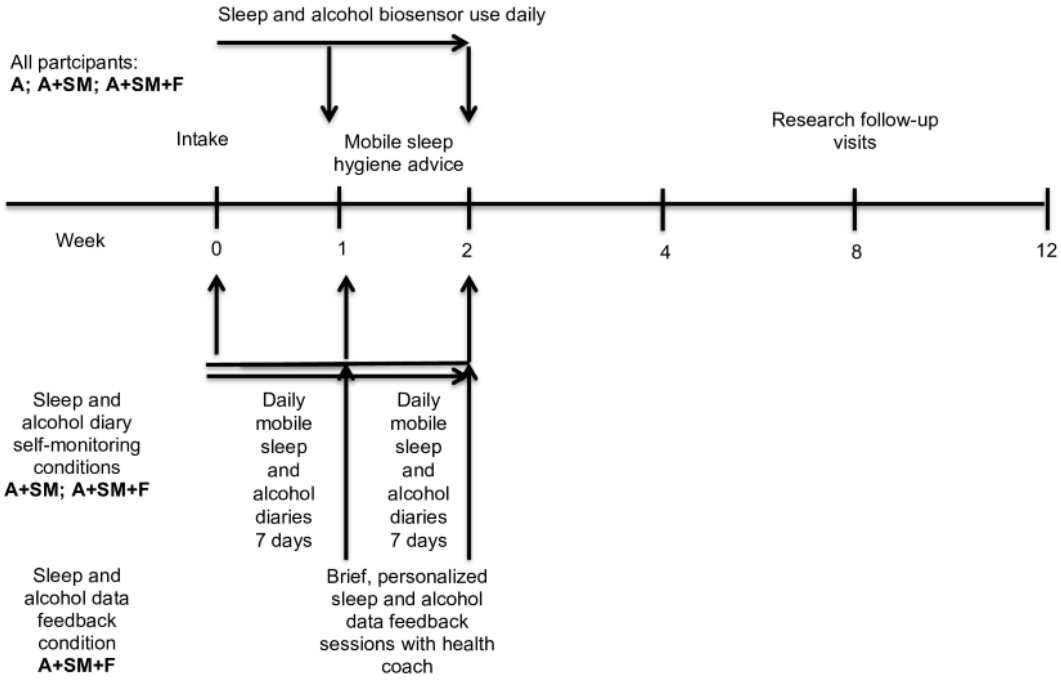
Heavy-drinking young adults aged 18 to 25 years (N=120) will be randomized using a 1:1:2 ratio to one of 3 conditions: (1) mobile sleep hygiene *advice* (*A*; n=30), (2) mobile sleep hygiene *advice* and sleep and alcohol diary *SM* (*A+SM*; n=30), or (3) mobile sleep hygiene *advice*, sleep and alcohol diary *SM*, and sleep and alcohol data *feedback* (*A+SM+F*; n=60); 5 pilot participants will first be tested in the A+SM+F condition to finalize the study procedures and refine the feedback reports. We added more participants to A+SM+F to have a larger sample to assess the variability of participants' sleep and alcohol data and the perceived acceptability and helpfulness of data feedback and advice tailored to this data for heavy-drinking young adults.

Our primary hypothesis is that combining all 3 intervention components (ie, A+SM+F) will yield the greatest reductions in alcohol consumption and alcohol-related consequences compared with combining advice with active SM (A+SM) or providing brief advice alone (A), in that order. We also anticipate that the 3-component intervention (A+SM+F) will rank best among participants and result in the largest improvements in quantitative and qualitative sleep outcomes. These hypotheses are based on our preliminary research findings and behavior change theory [62]. The 3-component intervention targets most behavior determinants, including perceived behavioral control, beliefs and attitudes about behavior, and motivation. We will explore whether sleep intervention promotes reductions in drinking through behavioral control changes and/or changes in attitudes or perceptions about alcohol.

Following intake, all participants will wear mobile sleep and alcohol biosensors daily for 2 weeks to measure sleep and alcohol outcomes. However, participants will not receive immediate feedback from these devices. A+SM and A+SM+F participants will also complete daily mobile sleep and alcohol diaries during the 2-week period but will not receive immediate feedback on this diary data. Once a week, all participants will receive brief mobile sleep hygiene advice using the program from our pilot study. In the A+SM+F condition, participants will also have brief sessions with a health coach once a week to review their sleep and alcohol diary and biosensor data and the potential bidirectional links between them, along with brief advice tailored to these data. Participants will receive an electronic copy of their health feedback after each session. All

participants will complete follow-ups at weeks 4, 8, and 12 (see Figure 1 for a single participant flowchart).

Figure 1. Single participant timeline.



Participants

Young adults will be included in the study if they (1) are aged between 18 and 25 years, (2) report ≥3 heavy-drinking occasions in the past 2 weeks (ie, ≥5 drinks on 1 occasion for men; ≥4 for women), (3) report sleep concerns, (4) are willing or able to complete daily mobile diaries and wear sleep or alcohol biosensors, (5) report Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) scores indicative of a risk of drinking harm (ie, ≥7 for men; ≥5 for women) [71], (5) are English speaking, and (6) have a smartphone for syncing biosensor data. An estimated 86% of young adults own a smartphone [72].

Young adults will be excluded if they (1) have a history of a sleep disorder or a severe alcohol use disorder (ie, severe alcohol withdrawal syndrome); (2) are currently enrolled in alcohol or sleep treatment; (3) report night or rotating shift work or travel beyond 2 time zones in the month before and/or plan to travel beyond 2 time zones during study participation; (4) exhibit current, severe psychiatric illness by history or examination; (5) have medical conditions contraindicated for the use of the ankle-worn alcohol biosensor (ie, circulation problems, neuropathy, deep vein thrombosis, leg ulcers, tendonitis, diabetes, pregnancy, history of swelling, nickel or other metal allergies, pacemaker, or any other implanted medical device); or (6) meet current Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V), substance use disorder criteria for substances other than marijuana or have a positive urine drug screen for opiates, cocaine, barbiturates, benzodiazepines, amphetamines, or phencyclidine. Marijuana use is very common among heavy-drinking young adults [73]; exclusion limits recruitment and external validity.

Procedures

Screening and Randomization

We will recruit most participants through web advertising or social media (eg, Facebook, Instagram, Snapchat), a method we have successfully used to recruit young adults and heavy drinkers [74,75]. We will also display notices around the local community. Interested individuals who contact investigators by telephone or email will be directed to a secure website link to complete a brief, 5-min prescreening survey. Digital advertisements will also direct volunteers to the prescreener. Before completing the prescreener, volunteers must provide informed consent. Following completion of the prescreener, research staff will contact potential participants and inform them of their initial eligibility status.

Individuals who meet initial screening criteria will complete an in-person intake to determine final study eligibility and receive US $30. Eligible participants will complete baseline questionnaires and be randomized to their condition. A statistician will create a randomization list that will be stratified by sex and implemented through REDcap, an electronic clinical trial management system, to ensure allocation concealment.

2-Week Treatment Phase

Immediately following randomization, participants will begin the 2-week intervention period that will vary by condition assignment (see Table 1 for a comparison of study conditions). At the end of week 2, all participants will complete an exit interview and a survey to assess the acceptability of the study intervention components they received.

Table 1. Intervention conditions.

Condition	Intervention components			
	Daily sleep and alcohol biosensor use	Mobile sleep hygiene advice (includes brief alcohol advice)	Daily sleep and alcohol diary self-monitoring	Personalized sleep and alcohol feedback sessions with a coach
A[a] (n=30)	✓[b]	✓	—[c]	—
A+SM[d] (n=30)	✓	✓	✓	—
A+SM+F[e] (n=60)	✓	✓	✓	✓

[a]A: advice.

[b]Intervention component present in intervention condition.

[c]Intervention component not present in intervention condition.

[d]SM: self-monitoring.

[e]F: feedback.

Biosensors

Participants in all conditions will wear sleep and alcohol biosensors daily for 14 days. The research coordinator will fit participants with biosensors at intake and then arrange brief weekly visits with participants to synchronize their devices to the study computer and download their data. To measure objective quantitative sleep characteristics, participants will wear a Philips Respironics Actiwatch Spectrum Plus actigraph device, a well-validated wrist-worn sleep biosensor that measures sleep or wake activity. Participants will be instructed to continuously wear the waterproof Actiwatch on their nondominant wrist and depress the event marker when ready to initiate sleep after getting into bed and immediately upon waking to indicate the end of the sleep episode. Actigraphy is a valid, reliable methodology to objectively estimate sleep based on measuring activity and inactivity and is sensitive to changes over time and interventions [76]. As an objective measure of alcohol use, participants will wear the secure continuous remote alcohol monitor (SCRAM) ankle bracelet from Alcohol Monitoring Systems, Inc. The SCRAM uses an electrochemical sensor to sample transdermal alcohol concentration (TAC) levels from sweat in the skin at regular intervals (ie, every 30 min) and store readings for later download [77]. SCRAM TAC readings are highly correlated with peak blood alcohol concentrations (BACs) and self-reported alcohol use [77]. The device is particularly effective at detecting heavy alcohol consumption (ie, ≥5 drinks) [77]. The SCRAM is water resistant (participants have to avoid swimming or baths) and can only be removed by cutting the strap. To encourage adherence, participants will be compensated for wearing the devices each day (US $2 per day for a total of US $28) and for returning them (US $10 per device for a total of US $20). Participants will also wear a new, wrist-worn transdermal alcohol biosensor, BACTrack Skyn, and will receive US $1 per day for wearing it (total US $14). Unlike the large SCRAM biosensor, which relies on active airflow, the smaller Skyn biosensor relies on passive airflow and permits more regular TAC sampling (ie, every 20 seconds) [78]. Preliminary evidence from controlled laboratory studies suggests that Skyn is sensitive to alcohol consumption changes [78].

Mobile Sleep Hygiene Advice

All participants will receive brief sleep hygiene advice via a mobile sleep program adapted from our pilot study. Module 1, which they will view on the day of the first biosensor data download (middle of week 1), focuses on behaviors that affect sleep (ie, exercise, eating, stimulant use, marijuana use, use of sleep aids, alcohol use, and sleep routines) and general recommendations for optimal sleep. Module 1 also contains a brief alcohol intervention content (ie, standard drink conventions and moderate drinking guidelines, how to calculate blood alcohol level and the effects at different levels, and normative information about young adults' drinking, controlled drinking strategies, effects of alcohol on sleep, and advice to moderate drinking for improved sleep). Module 2, which they will view on the day of the second biosensor data download, focuses on establishing a good sleep environment (ie, optimal lighting, temperature, noise, comfort, and stress levels). Both modules are approximately 10 min in length. Biosensor data are not viewed anywhere in this mobile sleep hygiene advice program; rather, they are saved for the health feedback coaching sessions discussed below and thus are only visible to participants in A+SM+F.

Mobile Sleep and Alcohol Diaries

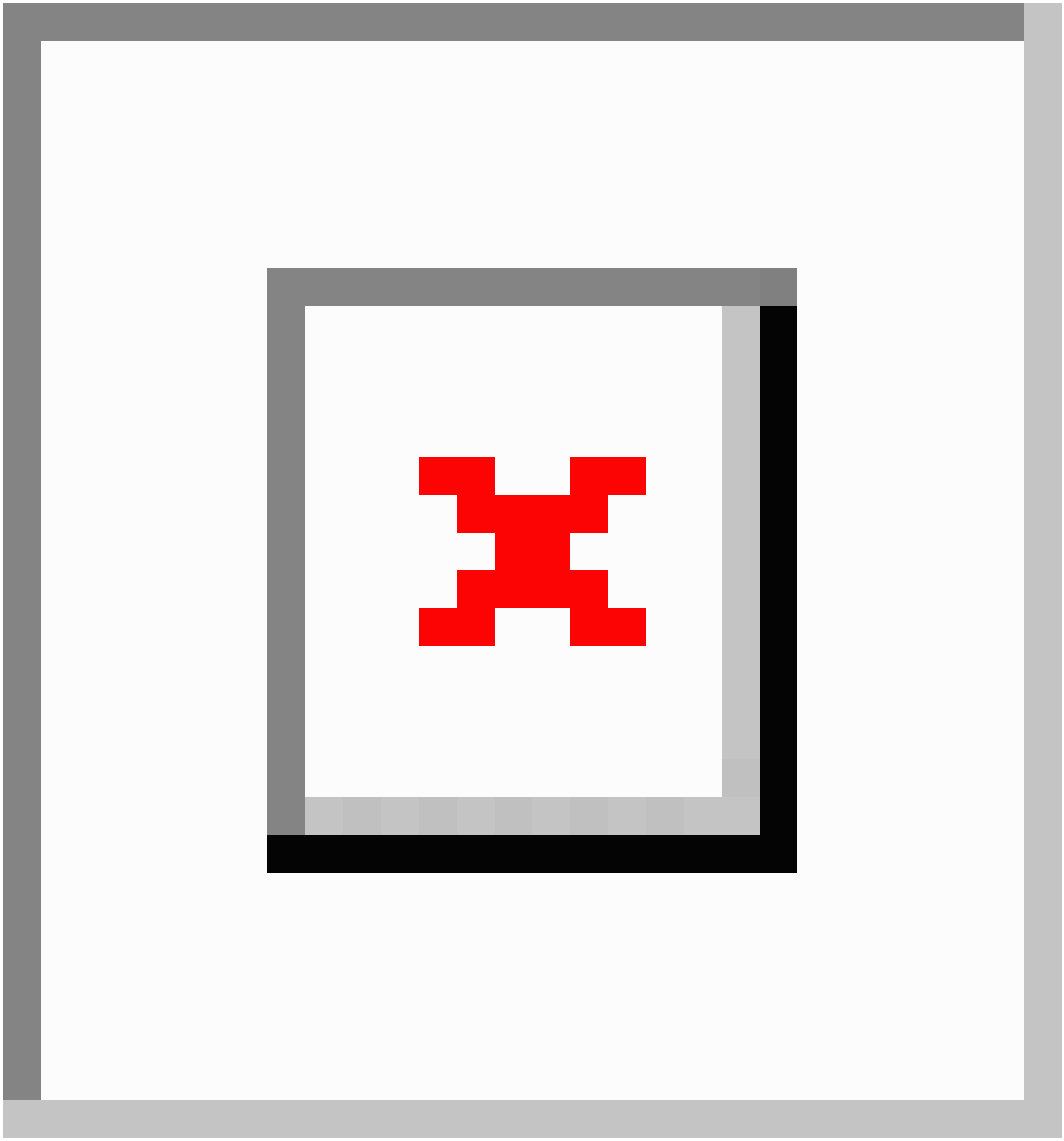
Participants in the A+SM and A+SM+F conditions will complete mobile diaries of their sleep and alcohol use daily for 14 days. Diaries will be programmed in Qualtrics and sent to participants each morning via text message. To encourage adherence, participants will be compensated for completing diaries (US $1 per day for a total of US $14).

Health Feedback Coaching Sessions

Participants in A+SM+F will have 2 weekly, brief sessions with a health coach to review their health data and receive brief health advice. Participants will receive the following information in handout form: (1) 7-day average quantitative sleep characteristics from the Actiwatch; (2) 7-day average of qualitative sleep diary ratings; (3) diary entries of alcohol consumption (ie, total drinks consumed, number of heavy-drinking occasions, maximum drinks on an occasion) and tobacco and marijuana use (ie, total occasions); (4) estimated BAC levels from the diaries and estimated TAC levels from the SCRAM; (5) average quantitative and qualitative sleep

characteristics on drinking occasions versus nondrinking occasions; (6) total occasions of alcohol, tobacco, and/or marijuana use on days following ≥7 hours of sleep compared with <7 hours of sleep (ie, the minimum recommendation for young adults); and (7) health recommendations for sleep (ie, optimal duration, timing, consistency, efficiency) and alcohol use for young adults (ie, moderate drinking guidelines). Participants will also receive the visual output data from the Actiwatch with their estimated BAC level superimposed over their sleep window for any drinking occasions that occurred close to bedtime (see Figure 2 for a sample feedback handout). Similarly, they will receive visual representations of their BAC and TAC data curves with their sleep window superimposed (Figure 2). These figures will enable participants to understand how long it takes alcohol to metabolize, how high alcohol levels may remain while they are sleeping and upon waking, and how their sleep quantitative and qualitative data may vary between drinking and nondrinking occasions (eg, wakefulness during sleep, perceived sleepiness upon waking). In accordance with motivational enhancement therapy for problem drinkers, the health coach will review the health feedback with participants and engage them in an open-ended, empathic, nonjudgmental discussion in an effort to enhance their motivation to change both behaviors [79]. The health coach will encourage a discussion of future plans regarding both behaviors, offer respectful advice to change risky sleep and drinking behaviors, and offer a menu of change strategies tailored to participants' responses and health data (eg, maintaining a regular sleep schedule, setting a minimum sleep duration threshold of 7-9 hours, using scheduled napping to reduce sleep deprivation effects, shifting alcohol use earlier in the evening, lowering peak BAC before bedtime, following moderate drinking guidelines, controlled drinking strategies).

Figure 2. Sample participant feedback. SCRAM: secure continuous remote alcohol monitor.



Follow-Up

At weeks 4, 8, and 12, participants will complete follow-up visits to assess potential changes in primary and secondary outcomes (see Table 2 for the schedule of assessments). Participants will be compensated for completing the week 4, 8, and 12 visits in escalating amounts to encourage adherence (ie, US $50, US $55, US $60).

Table 2. Schedule of assessments.

Variables and assessments	Intake	Diary	Alcohol and sleep biosensors	Weeks 1, 2, 4, 8, and 12
Eligibility				
Demographics	✓[a]	—[b]	—	—
DSM-V[c] diagnoses	✓	—	—	—
Urine drug screen and breath alcohol	✓	—	—	✓
AUDIT[d]	✓	—	—	—
Endorse sleep concerns	✓	—	—	—
Alcohol variables				
Timeline followback	✓	—	—	✓
Alcohol-related consequences	✓	—	—	4, 8, 12
SCRAM[e] and TAC[f] levels	—	—	✓	—
Alcohol diary	—	✓	—	—
Sleep variables				
PROMIS[g] sleep-related impairment	✓	—	—	4, 8, 12
PROMIS sleep disturbance	✓	—	—	4, 8, 12
Pittsburgh sleep diary	—	✓	—	—
Positive and negative affect	✓	—	—	4, 8, 12
Chronotype and morningness or eveningness	✓	—	—	—
Actiwatch: duration; bed time or wake time; min awake after sleep onset; sleep efficiency	—	—	✓	—
Mechanisms				
TPB[h] questionnaires; cognitive tasks	✓	—	—	4
Feasibility				
Adherence (diaries, biosensors, and tips)	—	✓	✓	✓
Acceptability				
Treatment evaluation survey; exit interview	—	—	—	2

[a]Variables or assessments administered at this time point.

[b]Variables or assessments not administered at this time point.

[c]DSM-V: Diagnostic and Statistical Manual of Mental Disorders, fifth edition.

[d]AUDIT: Alcohol Use Disorders Identification Test–consumption.

[e]SCRAM: secure continuous remote alcohol monitor.

[f]TAC: transdermal alcohol concentration.

[g]PROMIS: patient-reported outcomes measurement information system.

[h]TPB: Theory of Planned Behavior.

Variables and Measures

Eligibility

Interviews, questionnaires, and biosamples will be used to verify participant eligibility. These measures will include (1) a sociodemographic survey; (2) the Structured Clinical Interview for DSM-V [80] (ie, current and past substance use disorders, other current psychiatric diagnoses); (3) the Alcohol Use Disorders Identification Test, a reliable, valid alcohol use screener (at-risk drinking eligibility will be based on recommended AUDIT-C cut-off scores for young adults) [71]; (4) a single-item question to assess whether participants were concerned about their sleep using a dichotomous item (ie, yes or no) used in our previous research [38]; (5) a urine toxicology test kit for opiates, cocaine, barbiturates, amphetamines, benzodiazepines, or phencyclidine (JANT Pharmaceuticals); and (6) a breath alcohol concentration test using a hand-held breathalyzer unit—an Alcohol-Sensor III (Intoximeter Inc). Participants need to test negative to provide consent at intake and need to test <0.04% at subsequent in-person treatment and assessment visits.

Alcohol Variables

We will administer the Timeline Followback Interview, a standardized, validated, and reliable experimenter-administered interview to obtain daily reports of drinking that will be used to compute summary measures of alcohol use (ie, total drinks, drinks per day, drinks per drinking day) for the 30-day period before study enrollment and monthly following intake for a total of 4 months [81]. Calendar prompts and memory aids (eg, holidays) are used to facilitate accurate recall of substance use during the targeted period. Participants will complete the Young Adult Alcohol Consequences Questionnaire, a reliable, valid survey of 48 consequences of alcohol consumption predictive of drinking persistence among young adults [82]. We will derive estimates of participants' peak and average TAC levels from the SCRAM biosensor. Alcohol use episodes will be detected using the criteria developed by Barnett et al [83] and using software that processes the sensor data accordingly [84]. In the A+SM and A+SM+F conditions, participants will complete the Drinking Self-Monitoring Log, a standardized, validated methodology for measuring drinking on a daily or drink-by-drink basis [85]. Participants will record the total number of *standard drinks* consumed the preceding day, the type of beverages consumed, and the duration of alcohol consumption to allow for BAC level estimates. Diaries will also assess alcohol cravings and the drinking context.

Sleep and Sleep-Related Characteristics

We will use multiple assessments to characterize participants' quantitative and qualitative sleep characteristics and the potential consequences of their sleep. All participants will wear an Actiwatch. Actigraphy is a valid and reliable methodology used in research to objectively estimate sleep or wake activity. Validation studies provide evidence of its reliability and validity relative to well-validated ambulatory and laboratory sleep assessment methods (ie, polysomnography) [86-88]. We will derive the following quantitative sleep variables: sleep onset or offset (ie, bed or wake time), total sleep time (ie, sleep duration), sleep efficiency, and the number of minutes awake after sleep onset. Participants will complete 4 questionnaires: National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep-Related Impairment, a validated, reliable measure of perceived alertness, sleepiness, and tiredness during waking hours and functional impairments because of sleep problems [89]; NIH PROMIS Sleep Disturbance, a validated, reliable measure of perceived sleep quality or satisfaction and difficulty initiating or maintaining sleep [89]; the Munich Chronotype and Horne-Ostberg Morningness-Eveningness Questionnaires, both reliable, valid assessments of participants' chronotype and morning or evening preference [90]; and the Positive and Negative Affect Scale, a validated, reliable 20-item measure of positive and negative emotion and mood that yields 2 subscales—a positive and negative score [91]. Sleep improvement may cause mood changes that could affect alcohol outcomes. In the A+SM and A+SM+F conditions, participants will complete the Pittsburgh Sleep Diary, a well-validated assessment of daytime sleep-related behaviors and nocturnal sleep characteristics [92]. Participants will record daytime sleep-related behaviors and nocturnal sleep characteristics of the preceding day. Diaries will include questions about caffeine use and ratings of sleep quality, mood, and sleepiness upon waking.

Mechanisms of Sleep Intervention Component Effects

To evaluate potential intervention mechanisms, we will assess several TPB constructs based on a prior TPB growth model of risky drinking in young adults [93]. A possibility is that greater awareness of one's behaviors through active SM and/or feedback about the association between sleep and alcohol use may alter participants' beliefs and attitudes about drinking. The Behavioral Intentions Questionnaire includes 2 internally consistent items to assess intentions to engage in risky drinking [94]. Reliable and valid adapted versions of the Global Attitudes Scale [93,95,96] and Subjective Norms Questionnaire [95,97] will be used to assess participants' overall opinions about heavy alcohol consumption, perceptions of how others view their drinking, and their perceptions of typical drinking among their peers. A reliable and valid adapted version of the Drinking Refusal Self-Efficacy Questionnaire [93,98] and additional items suggested by Azjen [95] will assess participants' perceptions of being able to control or resist heavy drinking.

It is also possible that improving sleep might have direct effects on cognitive mechanisms linked to alcohol-related risks. We will also administer two computer tasks to test these potential intervention mechanisms. The Stop Signal Task is a reliable, valid computerized task that assesses self-control, specifically the ability to inhibit an inappropriate response. The ability to inhibit responding has been shown to be related to alcohol use and to be sensitive to changes in sleep [70,78]. In the Stop Signal Task, participants are instructed to respond when an *O* signal is present but refrain from responding when an *X* signal immediately follows it. They will complete 300 such trials over a 30-minute session (with a 1 minute break every 10 minutes) at intake and week four. The delay between the two signals (stop-signal delay, SSD) will be initially 200 milliseconds, then increased by 32 milliseconds after each successful trial (making the response inhibition more challenging) and decreased by 32 milliseconds after each unsuccessful trial. This titration should yield a mean success rate of 50% (SD 10%) over the session and estimate the critical SSD corresponding to exactly 50% success. This critical SSD minus the participant's average reaction time to the *O* signal (go reaction time) at that session defines the amount of additional time the participant required to inhibit the inappropriate response (stop-signal reaction time [SSRT]). Thus, a higher SSRT indicates worse inhibitory abilities. A titration increment of 32 milliseconds was chosen because it yielded the desired 50% (SD 10%) success rate among the 4 pilot participants. The N-Back Task, another reliable, valid computerized task, will be used to assess working memory. Performance is related to alcohol use and is sensitive to changes in sleep [77,91]. In the N-Back Task, participants are presented with a series of letters and instructed to respond when the letter matches the letter presented *N* stimuli before. A series of difficulty levels with *N* values ranging from 1 to 3 will be used. Both tasks will be administered at intake and week four.

Intervention Component Feasibility and Acceptability

We will evaluate participant use metrics to determine intervention component feasibility (ie, diary and biosensor adherence, use of sleep hygiene tips during treatment and follow-up). At week 2, all participants will complete an end-of-treatment evaluation form. We will also interview participants in A+SM+F to evaluate their reactions to and preferences for sleep or alcohol data monitoring and feedback.

Statistical Analyses

Statistical analyses will use an intent to treat approach and mixed models, both gold standards (along with multiple imputation) for handling outcome variable missing data in longitudinal studies. For the analyses of primary and secondary outcomes, a type I error of 5% (two-sided) will be used to test for statistical significance using SAS V9.4. Exploratory analyses will be adjusted for multiple testing using the Bonferroni correction. Data will be examined for conformity to the normal distribution, and transformation or nonparametric methods will be used if necessary.

The goal of the primary aim is to examine the effect of the intervention condition over time on total drinks consumed over weeks 4 to 12, controlling for baseline total drinks. For this analysis, we will evaluate changes in scores using a mixed model repeated measures analysis with condition and sex as between-subject factors and time as a within-subject factor. We will also test changes in secondary alcohol outcomes: drinks per day, drinks per drinking day, and alcohol-related consequences, controlling for the corresponding baseline measure alcohol outcomes, which we will adjust for multiple comparisons. Using all repeated measures on individuals in the context of a mixed model will allow us to assess temporal patterns of change over time and to use all available data on an individual. This approach therefore helps to avoid imputing missing data. The mixed model allows us to obtain unbiased and efficient estimates of change over time and between-group differences. Within the mixed model, our primary hypothesis is the change from baseline to end-point, and we will perform focused comparisons to assess these effects. A mixed model will account for the correlation between alcohol outcomes measured in the same individual. We will select the best-fitting variance-covariance structure using the Schwartz-Bayesian information criterion. Time will be considered as a categorical factor, but we will also evaluate whether alcohol outcomes change linearly by condition over time. We will evaluate the alcohol outcomes for normality assumptions. If an outcome is not normally distributed, we have several options, including applying transformations or utilizing alternative methods (eg, generalized linear mixed models, resampling, nonparametric tests). For drinking outcomes that may be best modeled as count data, we can use mixed models using Poisson and negative binomial generalized linear mixed models.

A secondary aim is to examine the effect of condition on sleep quality ratings over time, controlling for baseline ratings. We will use a mixed model repeated measures analysis as described above. We will also test changes in secondary sleep outcomes: ratings of sleep-related impairment and quantitative sleep outcomes (ie, duration, efficiency, number of minutes awake after sleep onset, bed or wake times), controlling for baseline responses. We will evaluate the sleep outcomes for normality assumptions. If an outcome is not normally distributed, we will apply transformations or utilize alternative methods.

Another secondary aim is to summarize participants' acceptability ratings of mobile sleep hygiene advice, sleep or alcohol diary SM, sleep or alcohol biosensor use, and personalized sleep or alcohol data feedback using descriptive statistics. We anticipate that the A+SM+F condition will yield the highest acceptability ratings for all 3 conditions. A review of participants' reactions to personalized feedback will provide insight into what types of feedback and tailored health tips are feasible and useful for heavy-drinking young adults.

As an exploratory aim, we will evaluate improvements in TPB constructs (ie, drinking intentions and attitudes, perceived drinking norms, perceived control over drinking, and cognitive task performance) over time as mechanisms of condition effects on total drinks at month 3. We will calculate individual slope change estimates for sleep quality and TPB constructs and then evaluate these slope estimates as potential mechanisms using the SAS macro outlined by Valeri and Vanderweele [99]. This method allows for independent variable X mediator interactions and is suitable for continuous and count outcomes (ie, total drinks). Given the smaller sample size for this exploratory research, we will evaluate correlations between sleep quality and TPB construct slope estimates rather than structural equation modeling to model potential complex pathways among conditions, TPB constructs, and drinking. We will also characterize the daily variations in the sleep diary and biosensor data and potential dynamic relationships between them and daily diary or biosensor drinking data using methods for longitudinally intensive data (eg, time-varying effects models) [100].

Sample size estimates were based on enrolling a sufficient number of participants to ensure adequate power to detect a clinically significant medium effect in total drinks consumed over time, controlling for total drinks consumed at baseline, among the three conditions, which is lower than the medium-to-large effect sizes for alcohol-related outcomes observed in our pilot study. Sample size estimates were obtained under the following assumptions: 80% power, a two-sided .05 significance level, medium effect size for the between-group difference (Cohen f=0.3; Cohen d=0.6 for the comparison of the personalized feedback condition with the other two conditions), one binary stratification variable (ie, sex), and 10% drop out. On the basis of these metrics, we estimated that a total sample size of 120 individuals would be required to complete the study.

Results

This project was funded by the NIH in May 2018, and data collection began in December 2018 following institutional review board (IRB) approval. In December 2018, IRB approval was obtained and data collection began. We first enrolled 5 pilot participants to finalize the study procedures. After completing the pilot, we enrolled 110 individuals in the randomized controlled trial. The completion rates for the 2-week intervention

phase (107/110, 97.3%) and 12-week follow-up (92/98, 94%) were high. Similarly, adherence to monitoring activities was high: diaries (819/882, 92.9% possible diaries) and nighttime Actiwatch use (1119/1176, 95.15% possible assessment points). Data collection for the final 10 participants is expected to be concluded in early 2021.

Discussion

Conclusions and Future Directions

We hypothesize that a multimodal, mobile sleep intervention will reduce drinking and alcohol-related harm in heavy-drinking young adults. We anticipate that sleep or alcohol diary SM and/or personalized feedback about sleep or alcohol data will be the most effective sleep intervention techniques for this purpose. We will use the results to finalize the sleep intervention for future testing. We will then evaluate this sleep intervention against standard alcohol interventions for young adults in a phase II randomized controlled trial. The rich database of objective and subjective sleep and alcohol data will enable us to explore relationships among these variables to inform our understanding of the role of sleep in young adult AUD risk.

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Conflicts of Interest

LF and KD registered the name and content of the Call it a Night web-based sleep program with the US Patent and Trademark Office. Unrelated to this work, SO reports the following: consultant or advisory board member for Alkermes, Amygdala, Indivior, Mitsubishi Tanabe, Opiant; a member of the American Society of Clinical Psychopharmacology Alcohol Clinical Trials Initiative supported by Alkermes, Amygdala Neurosciences, Arbor Pharmaceuticals, Dicerna, Ethypharm, Indivior, Lundbeck, Mitsubishi, and Otsuka; donated medications from Astra Zeneca, Novartis, and Pfizer; and Data Safety Monitoring Board member for the National Institute on Drug Abuse (Emmes Corporation). The remaining authors have no conflicts of interest to declare.

Multimedia Appendix 1
NIH grant peer-review documentation.
[PDF File (Adobe PDF File), 163 KB - resprot_v10i2e26557_app1.pdf]

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Abbreviations

AUD: alcohol use disorder
AUDIT-C: Alcohol Use Disorders Identification Test–Consumption
BAC: blood alcohol concentration
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, fifth edition

IRB: institutional review board
NIH: National Institutes of Health
PROMIS: Patient-Reported Outcomes Measurement Information System
SCRAM: secure continuous remote alcohol monitor
SM: self-monitoring
SSD: stop-signal delay
SSRT: stop-signal reaction time
TAC: transdermal alcohol concentration
TPB: Theory of Planned Behavior

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Protocol

The Impact of Nonpharmacological Interventions on Patient Experience, Opioid Use, and Health Care Utilization in Adult Cardiac Surgery Patients: Protocol for a Mixed Methods Study

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Abstract

Background: Despite pharmacological treatments, patients undergoing cardiac surgery experience severe anxiety and pain, which adversely affect outcomes. Previous work examining pediatric and nonsurgical adult patients has documented the effectiveness of inexpensive, nonpharmacological techniques to reduce anxiety and pain as well as health care costs and length of hospitalization. However, the impact of nonpharmacological interventions administered by a dedicated *comfort coach* has not been evaluated in an adult surgical setting.

Objective: This trial aims to assess whether nonpharmacological interventions administered by a trained *comfort coach* affect patient experience, opioid use, and health care utilization compared with usual care in adult cardiac surgery patients. This study has 3 specific aims: assess the effect of a *comfort coach* on patient experience, measure differences in inpatient and outpatient opioid use and postoperative health care utilization, and qualitatively evaluate the *comfort coach* intervention.

Methods: To address these aims, we will perform a prospective, randomized controlled trial of 154 adult cardiac surgery patients at Michigan Medicine. Opioid-naive patients undergoing first-time, elective cardiac surgery via sternotomy will be randomized to undergo targeted interventions from a *comfort coach* (intervention) versus usual care (control). The individualized *comfort*

coach interventions will be administered at 6 points: preoperative outpatient clinic, preoperative care unit on the day of surgery, extubation, chest tube removal, hospital discharge, and 30-day clinic follow-up. To address aim 1, we will examine the effect of a *comfort coach* on perioperative anxiety, self-reported pain, functional status, and patient satisfaction through validated surveys administered at preoperative outpatient clinic, discharge, 30-day follow-up, and 90-day follow-up. For aim 2, we will record inpatient opioid use and collect postdischarge opioid use and pain-related outcomes through an 11-item questionnaire administered at the 30-day follow-up. Hospital length of stay, readmission, number of days in an extended care facility, emergency room, urgent care, and an unplanned doctor's office visit will be recorded as the primary composite endpoint defined as total days spent at home within the first 30 days after surgery. For aim 3, we will perform semistructured interviews with patients in the intervention arm to understand the *comfort coach* intervention through a thematic analysis.

Results: This trial, funded by Blue Cross Blue Shield of Michigan Foundation in 2019, is presently enrolling patients with anticipated manuscript submissions from our primary aims targeted for the end of 2020.

Conclusions: Data generated from this mixed methods study will highlight effective nonpharmacological techniques and support a multidisciplinary approach to perioperative care during the adult cardiac surgery patient experience. This study's findings may serve as the foundation for a subsequent multicenter trial and broader dissemination of these techniques to other types of surgery.

Trial Registration: ClinicalTrials.gov NCT04051021; https://clinicaltrials.gov/ct2/show/NCT04051021

International Registered Report Identifier (IRRID): DERR1-10.2196/21350

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KEYWORDS

cardiac surgery; patient experience; nonpharmacological interventions; child life specialists; opioids; anxiety; stress; depression

Introduction

Nonpharmacological Interventions

Adults undergoing inpatient surgery commonly develop both severe perioperative anxiety [1-5] (28%-70% of patients) and postoperative pain (54%-74% with moderate-to-severe pain at discharge), [6,7] both of which may significantly affect patient outcomes [8-11]. Nonpharmacological interventions such as distraction techniques, guided imagery, music, and art have been found to be inexpensive complements to pharmacologic treatments, effectively reducing both anxiety and acute and chronic pain [12-14] in pediatric [15] and hospitalized nonsurgical adult patients [16-19] when administered routinely by a dedicated child life specialist *comfort coach*. However, the impact of nonpharmacological interventions and the role of a comfort coach in an adult surgical setting has not been evaluated.

Certified Child Life Specialists

Certified child life specialists are frontline health care professionals trained to provide psychosocial care to pediatric patients and families facing stressful medical experiences. Child life specialists conduct thorough assessments and build therapeutic relationships with patients and families to support them to cope and protect emotional safety. Individualized interventions include fostering healing environments, therapeutic play, nonpharmacological pain management, procedural preparation, diagnosis teaching, sibling support, medical play, and bereavement support. Child life specialists obtain a bachelor's degree with an emphasis on psychology, education, and human development. They complete comprehensive clinical training, pass a certification exam, and maintain certification through targeted continuing education [20].

Applications in the Pediatric Setting and Translation to the Adult Setting

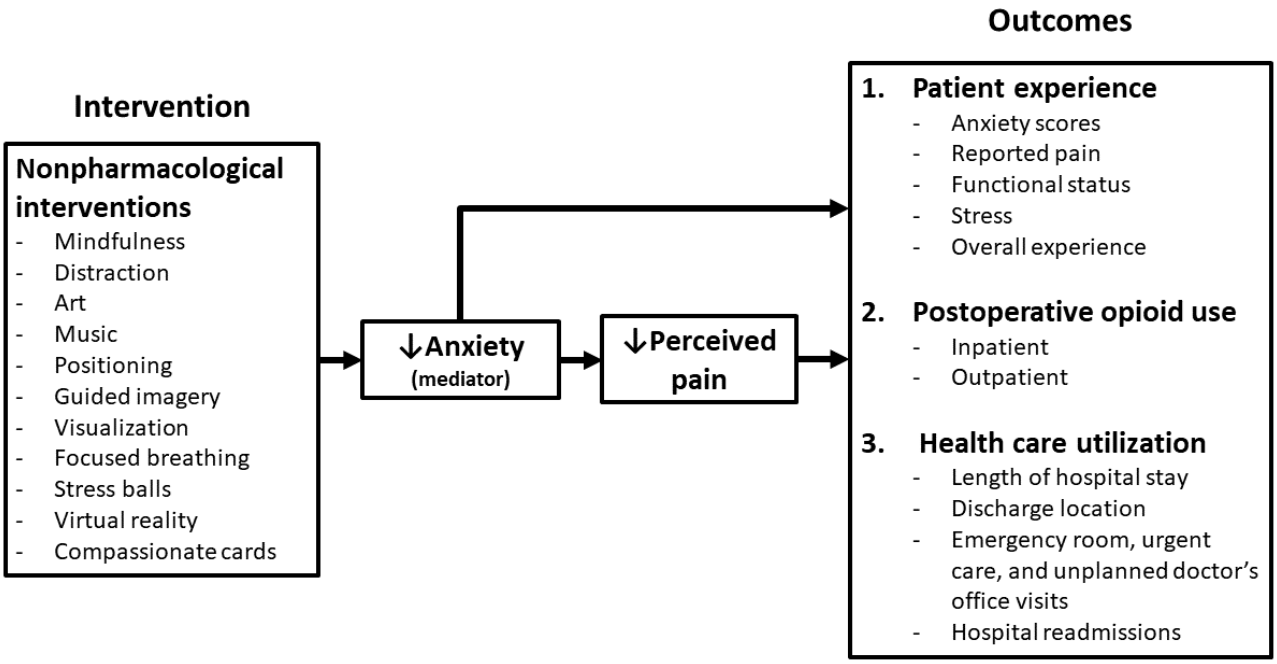
Child life specialists work with pediatric patients to teach individualized coping strategies to mitigate anxiety and manage both acute and chronic pain. Play is the universal language of all children, and play-based coping strategies foster expression and promote a sense of control and mastery. Nonpharmacological interventions effective in pediatric and adolescent patients include calm breathing techniques, distraction, guided imagery, art, muscle relaxation, music, environmental modification, and comfort positioning [20]. The child life specialist's role has resulted in reduced pain, anxiety, use of analgesics, and length of stay [16]. We often assume that adults can handle medical stressors and employ coping skills, but many adults do not have such skills established [21]. In addition, this has resulted in underestimating adult patients' pain effects [22] and often not addressing pain with known effective nonpharmacological interventions in combination with pain medication [13]. Building on the effectiveness and essential skills that have been dedicated to pediatric patients can facilitate opportunities for adult patients to reframe health care experiences and provide coaching through pain and anxiety, adding to their coping skills to support comfort. Applying child life strategies across the age span can further enhance the human experience of health care [23].

Conceptual Model

We propose that providing a dedicated, trained comfort coach administering nonpharmacological interventions will improve cardiac surgery outcomes, including anxiety, self-reported pain, opioid use, and health care utilization. Periprocedural nonpharmacological approaches are well established in pediatrics [24,25], especially for needle-related pain [26]. Nonpharmacological approaches to acute pain management are rooted in the *gate-control theory* [27,28]. This theory suggests that descending nerve impulses from the brain, including

thoughts, beliefs, emotions, and attention, can influence the ascending pain signal from tissue damage. In the context of surgery, anxiety may heighten pain, whereas attention focused on pleasant activity might decrease pain. In this context, many nonpharmacological interventions mitigate anxiety, which mediates pain perception, with both decreased anxiety and perception of pain affecting patient outcomes (Figure 1).

Figure 1. Conceptual model. This conceptual model demonstrates the hypothesized effect of nonpharmacological interventions on the outcomes in this study rooted in gate-control theory.



Rationale for the Study

Approximately 300,000 adults undergo cardiac surgery in the United States each year [29], with 90-day episode payments combined to exceed US $15 billion [30-32]. Cardiac surgery through a sternotomy has been shown to cause severe anxiety and pain that persist in spite of pharmacologic pain control with opioids [5,33,34], with up to 81% reporting some pain at 1 month [35] and up to 43% reporting persistent pain at 1 year [36]. Rates of persistent opioid use and long-term opioid dependence in cardiac surgery patients have increased 8-fold over the past 15 years, resulting in higher postoperative complication rates, prolonged hospital length of stay, and increased health care costs [37]. Moreover, opioid prescription sizes remain high, and overprescribing is common [38-47]. Whereas assessments of individual nonpharmacological interventions such as preoperative education [48,49], massage [50], and music [34] have demonstrated an improvement in self-reported pain scores after cardiac surgery, differences in opioid use have not been reported. Furthermore, individualized nonpharmacological interventions by a comfort coach have been shown to reduce the length of hospital stay [15,51] and health care costs [52,53] in pediatric patients, prompting the establishment of child life services as a *quality benchmark* and *indicator of excellence in pediatric care*, [15,54]. In contrast, these techniques have not been studied in adult cardiac surgery patients.

Data generated by this study may highlight effective techniques and support a multidisciplinary approach to nonpharmacological interventions to decrease pain, opioid use, anxiety, and health care utilization while increasing patient comfort and overall satisfaction during the adult cardiac surgery patient experience.

Methods

Overall Study Design

We will perform a prospective, double-armed, randomized, controlled trial of 154 cardiac surgical patients at a large academic center to assess whether nonpharmacological interventions by a trained comfort coach affect patient experience, opioid use, and health care utilization as compared with usual care. The individualized comfort coach interventions will be administered at 6 time-points: (1) at the preoperative clinic, (2) on the day of surgery, (3) at extubation, (4) at chest tube removal, (5) at hospital discharge, and (6) at the 30-day clinic follow-up.

This study has 3 specific aims: (1) assess the effect of a comfort coach on patient experience, (2) measure differences in inpatient and outpatient opioid use and postsurgical health care utilization, and (3) qualitatively evaluate the effectiveness of the comfort coach intervention. Toward aim 1, we will use validated survey metrics to capture anxiety and depression (preoperative clinic, discharge, 30-day follow-up, and 90-day follow-up), functional status (preoperative clinic and 30-day follow-up), surgery-related psychological stress (30-day follow-up), patient-reported in-hospital pain (discharge), and patient experience (30-day follow-up). Toward aim 2, we will compare inpatient and postdischarge opioid use and patient-reported outcomes, including pain scores and pain management practices between

groups. In addition, the composite primary endpoint of the study will be recorded as the total number of days spent at home out of the first 30 after surgery, incorporating hospital length of stay, readmissions, number of days in an extended care facility, emergency room, urgent care, and unplanned doctor visits. Aim 3 will include semistructured interviews of patients in the intervention group to understand the role, impact, and acceptability of a comfort coach.

All requirements for conducting human subjects research at the University of Michigan have been met. The study protocol has been reviewed, and the University of Michigan Institutional Review Board has approved this trial (quantitative, HUM00161399, and qualitative, HUM00170502). This clinical trial has been registered at ClinicalTrials.gov (NCT04051021).

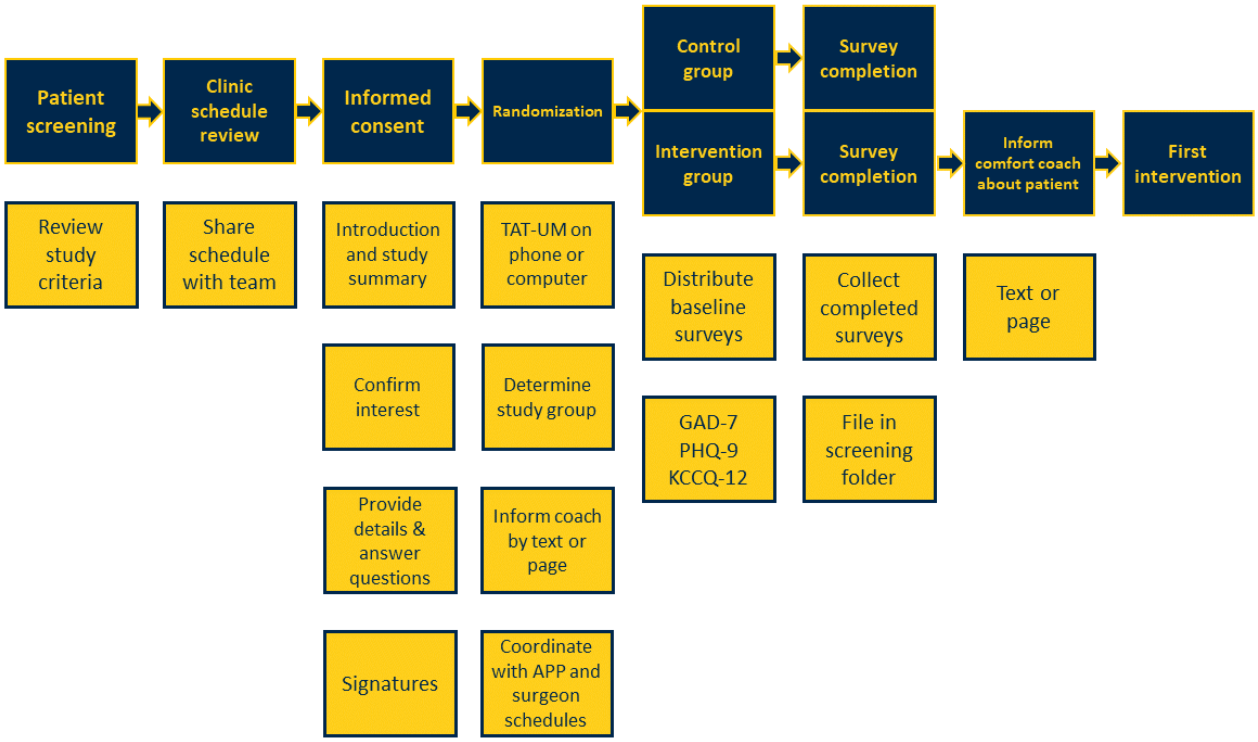
Patient Enrollment and Randomization

Cardiac surgical patients will be recruited from the Frankel Cardiovascular Center (FCVC) at Michigan Medicine. Opioid-naive patients undergoing first-time, elective cardiac surgery through a full median or miniature sternotomy beginning September 3, 2019, were screened for a targeted enrollment of 154 patients for randomization. Approximately 600 to 750 patients meeting these criteria underwent surgery at Michigan Medicine in 2017. Opioid-naive is defined as opioid-free at the time of preoperative clinic history and physical examination.

Patients lost to follow-up will be censored for data analysis, and missing individual intervention points will be dealt with by multiple imputations, as appropriate. We will compare the clinical and sociodemographic attributes of patients who decline participation and patients lost to follow-up with those of patients with complete follow-up to assess potential responder bias. We estimated a 20% rate of missingness, which was incorporated into our power calculation. On the basis of historical institutional data, we anticipated approaching 5 to 10 patients per week for potential enrollment, with an approximate 5 to 7 month enrollment period within a 12-month study period for completion of clinical follow-up, data analysis, and manuscript production. Although this timeline was affected by the COVID-19 pandemic forcing a pause in enrollment between March 14th and the time of writing, we were 93.5% (144/154) enrolled at the time of pausing and remained optimistic about completing enrollment within our 12-month study period. We used block randomization with randomly variable block sizes generated with Stata 15 software (StataCorp LLC, College Station, TX) and computer randomization occurred with the treatment assignment tool (Treatment Assignment Tool-University of Michigan [TATUM]) from the Michigan Institute for Clinical and Health Research.

Patients were approached, participated in the informed consent process, and were enrolled during the preoperative history and physical appointment, typically after being seen by a member of the advanced practice team. The study coordinator approached potential subjects either in exam rooms or in the clinic waiting room to describe the study and offer participation. Interested patients engaged with the study coordinator and gave informed consent, at which point the coordinator randomized and assigned a sequential subject identification number to each study patient using TATUM (Figure 2).

Figure 2. Preoperative clinic value stream map. Blue blocks with maize writing indicate the main steps in the clinic process, whereas maize blocks with blue writing summarize tasks performed by the study coordinator. APP: advanced practice providers; GAD-7: Generalized Anxiety Disorder 7-item scale; KCCQ-12: Kansas City Cardiomyopathy Questionnaire 12-item short-form; PHQ-9: Patient Health Questionnaire-9; TATUM: Treatment Assignment Tool-University of Michigan.



The Comfort Coach Approach and Interventions

In this trial, the *comfort coach* is a trained Certified Child Life Specialist who provides therapeutic interventions that have been shown to reduce anxiety and pain medication use while increasing patient and family satisfaction [15]. Child life specialists use evidence-based nonpharmacological pain management techniques such as preparing patients for painful encounters, comforting and reassuring them, coping strategies such as distraction, and offering positive reinforcement to support patients undergoing painful procedures [55]. These interventions focus on improving patient experience, validating emotions, and offering an individualized approach with the goal of reducing pain and anxiety. Focused breathing and guided imagery with targeted relaxation and pain management outcomes will support patient choice and engagement to encourage sustainable coping skills.

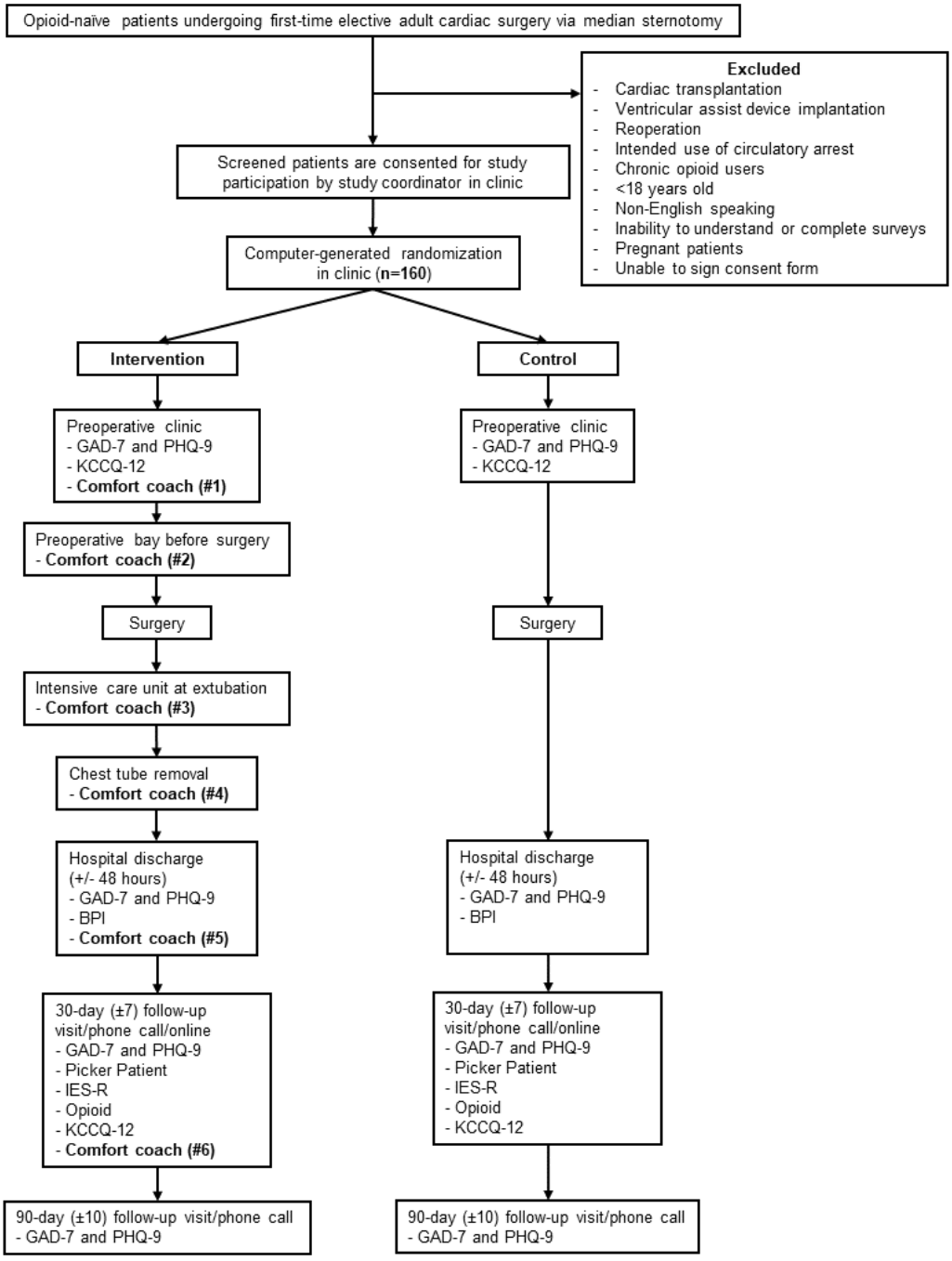
Child life specialists are trained in lifespan development and family systems theories, specifically addressing pain and anxiety through individualized comfort techniques. Though they are trained specifically in pediatrics, these coping strategies translate across ages. Adults routinely express the desire for distraction techniques, guided imagery, and preparation procedures during procedural care [16,23]. Moreover, adults may benefit, similar to pediatric patients, from nonpharmacological interventions when undergoing cardiac surgery. Whereas adults may have more experience with anxiety and pain management than children, new perioperative experiences have the potential to raise anxiety levels that can be mitigated by simple comfort strategies. Thus, child life specialists are ideally equipped to address perioperative anxiety and painful situations in both children and adults. We performed an 11-patient feasibility study in patients who underwent open cardiac surgery at Michigan Medicine using certified child life specialists, which demonstrated that nonpharmacological comfort coach interventions were feasible.

In this study, patients randomized to the intervention group will meet the comfort coach in the preoperative clinic (#1), where the coach will perform an introductory emotional, medical, and psychosocial needs assessment to consider the impact of surgery on the patient. The comfort coach will also introduce a *comfort menu* (Multimedia Appendix 1) [56-63] for pain management. After the preoperative clinic visit, the comfort coach will see the patient 5 additional times: at the preoperative bay immediately before surgery (#2), at extubation in the intensive care unit (#3), at chest tube removal (#4), at discharge (#5), and at the 30-day clinic follow-up visit (#6). These points of intervention were defined through feedback provided during our initial 11-patient feasibility study. During these intervention points, patients will receive the comfort menu and choose individualized interventions, including guided imagery, guided visualization, focused breathing, distraction techniques, music, art, mindfulness, and patient positioning. Supplies used during comfort coach interventions commonly include music playlists, compassion cards, stress balls, iPad activities, and virtual reality goggles. Additional activities are listed in the comfort menu in Multimedia Appendix 1.

Study Overview and Pretrial CONSORT (Consolidated Standards of Reporting Trials) Flow Diagram

Screening, enrollment, randomization, and study design are summarized in Figure 3.

Figure 3. Clinical trial CONSORT (Consolidated Standards of Reporting Trials) diagram. Patient population and clinical trial flow diagram. The timing of each *comfort coach* intervention touchpoint is indicated, and each touchpoint is numbered. BPI: Brief Pain Inventory; GAD-7: Generalized Anxiety Disorder 7-item scale; IES-R: Impact of Events Scale-Revised; KCCQ-12: Kansas City Cardiomyopathy Questionnaire 12-item short-form; PHQ-9: Patient Health Questionnaire-9.



Aim 1: Assess the Effect of a Comfort Coach on Patient Experience

To address this aim, we will examine the effect of the comfort coach on perioperative anxiety, self-reported pain, functional status, and patient satisfaction. We will use the Generalized Anxiety Disorder 7-item scale (GAD-7) [56] anxiety assessment and Patient Health Questionnaire-9 (PHQ-9) [57] depression scale at 4 points: preoperative clinic visit, discharge, and at 30- and 90-day follow-up. The Kansas City Cardiomyopathy Questionnaire short-form (KCCQ-12) [58,59] will be administered at the preoperative clinic visit and 30-day follow-up to evaluate functional status. The Impact of Events Scale-Revised (IES-R) [60] will measure event-related psychological stress at 30-day follow-up, and the Picker Patient Experience Questionnaire [61] will be administered at the 30-day follow-up. The Brief Pain Inventory [62,63] will be administered at discharge to assess in-hospital pain. We hypothesize that patients who receive a comfort coach report a better hospital experience, improved functional recovery, and lower levels of depression, anxiety, stress, and pain.

Outcome Measures for Aim 1

Outcome measures for aim 1 exclusively consist of validated measures for anxiety, depression, stress, pain, and patient satisfaction (Textbox 1). These validated tools were adapted to better evaluate differences in pharmacological and nonpharmacological treatments and their corresponding effects and are included in the Multimedia Appendix 1.

Textbox 1. Evaluative surveys and questionnaires.

Generalized Anxiety Disorder 7-item Scale

- A 7-item validated questionnaire to assess and potentially diagnose generalized anxiety disorder [56].

Patient Health Questionnaire

- A 9-item validated questionnaire which generates a total score out of 27 used to diagnose 5 different degrees of depressive disorders [57].

Impact of Events Scale-Revised

- A 22-item validated scale used to measure event-related stress with the potential to indicate clinical suspicion or diagnosis of posttraumatic stress disorder [60].

Picker Patient Experience Questionnaire

- A 15-item questionnaire designed to capture the patient's inpatient experience [61].

Brief Pain Inventory

- Short-form 9-question inventory assessing patient pain location, severity, relief, and activity level [62,63].

Postoperative Opioid and Pain Management Questionnaire

- An 11-item questionnaire developed at Michigan Medicine for collecting data on opioids prescribed, opioids used, pain scores, opioid storage and disposal practices, and assessment of opioid education.

Kansas City Cardiomyopathy Questionnaire

- A 12-item questionnaire assessing the impact of heart failure on the patient's daily activities and lifestyle [58,59].

The survey and questionnaire instruments were used as part of specific aim #1 to evaluate anxiety (Generalized Anxiety Disorder 7-item scale [GAD-7]), depression (PHQ-9), functional status (Kansas City Cardiomyopathy Questionnaire short-form [KCCQ-12]), stress (Impact of Events Scale-Revised [IES-R]), and patient experience (Picker Patient). Patient-reported pain levels (BPI) and postdischarge opioid use and pain management practices (Postoperative Opioid and Pain Management Questionnaire [OPIOID]) were collected as part of specific aim #2.

Analytic Approach

Mean total GAD-7 and PHQ-9 scores at each of the 4 time-points (Table 1) will be compared between the 2 groups with two-tailed *t* tests, whereas categorical findings (eg, mild, moderate, or severe anxiety on the GAD-7 and minimal, mild, moderate, moderately severe, or severe depression on the PHQ-9) will be compared between groups using chi-square tests. In addition, repeated measures ANOVA (analysis of variance) tests will be performed for the GAD-7 and PHQ-9 across the 4 time-points to examine differences between groups while accounting for correlation over time within each patient. IES-R mean total scores will be compared between groups using a two-tailed *t* test, and the proportion of patients in each group meeting established cutoffs (≥24, ≥33, and ≥37) [64-66] will be compared with chi-square or Fisher exact tests, as appropriate. Chi-square tests will be used for the Picker Patient Experience Questionnaire to determine differences in mean proportions of *problems* reported out of the 15 items in the survey. The mean intrapatient difference between preoperative clinic and 30-day follow-up in functional status scores on the KCCQ-12 will be evaluated (≥5 point difference indicates a clinically important difference) and compared between study cohorts. Pain severity and pain interference scores will be determined (both out of 10) from the Brief Pain Inventory and generated for each patient. These 2 mean scores will be compared between groups using a two-tailed *t* test. Finally, pain score proportions on a 4-point scale (none, minimal, moderate, or severe) recorded through the 30-day postoperative questionnaire will be compared across groups using the chi-square test.

Table 1. Schedule of survey instrument administration. The survey administration schedule is indicated for both study cohorts (ie, all patients).

Preoperative clinic visit for History and Physical	Day of discharge	30-day postoperative clinic visit	90-day postoperative clinic visit or phone call
GAD-7[a]	GAD-7	GAD-7	GAD-7
PHQ-9[b]	PHQ-9	PHQ-9	PHQ-9
KCCQ-12[c]	BPI[d]	Picker Patient[e]	N/A[f]
N/A	N/A	IES-R[g]	N/A
N/A	N/A	OPIOID[h]	N/A
N/A	N/A	KCCQ-12	N/A

[a]GAD-7: Generalized Anxiety Disorder 7-item scale.

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

[c]KCCQ-12: Kansas City Cardiomyopathy Questionnaire 12-item short-form.

[d]BPI: Brief Pain Inventory.

[e]Picker Patient: Picker Patient Experience Questionnaire.

[f]N/A: not applicable.

[g]IES-R: Impact of Events Scale-Revised.

[h]OPIOID: Postoperative Opioid and Pain Management Questionnaire.

Aim 2: Measure Differences in Inpatient and Outpatient Opioid Use and Postsurgical Health Care Utilization

Inpatient postoperative opioid use will be recorded for 3 inpatient calendar days before discharge in oral morphine equivalents (OME) per day. Outpatient opioid use and pain scores will be assessed through an 11-item questionnaire administered at 1-month follow-up. Hospital length of stay, number of days in an extended care facility, emergency room, urgent care, unplanned doctor office visits, and readmission will be recorded in a composite endpoint defined as total days spent at home within the first 30 days after surgery. We hypothesize that patients who receive a comfort coach consume less opioids after surgery and demonstrate lower postsurgical health care utilization.

Outcomes Measures for Aim 2

Opioid Use

Opioid amounts will be converted to OME [67]. Inpatient opioid use will be obtained through electronic chart review for the 3 inpatient calendar days before discharge (intravenous and oral) and will be reported daily in OME. Outpatient opioid use will be collected using the 11-item questionnaire administered at the 30-day postoperative clinic appointment and will be reported as total OME consumed postdischarge. Additional data captured through chart reviews and clinic questionnaires include the type of opioid, the amount prescribed (OME), number of refills, outpatient storage location, and opioid education received regarding risks and proper opioid disposal.

Postsurgical Health Care Utilization

The primary endpoint of this trial is a composite outcome defined as the total number of days spent at home within the first 30 days after surgery. Each partial or full day spent in the hospital (during index or readmission hospitalization), at any extended care facility, emergency room, urgent care center, or doctor's office for an unplanned visit will be subtracted from 30 to generate the total number of full days spent at home. This number will reflect total health care utilization within the immediate postoperative period, with lower values indicating more utilization. The number of days in an extended care facility, outside hospital emergency room or urgent care visits, and readmissions are routinely discussed at the 30-day postoperative clinic appointment and will be captured through a combination of chart review by 2 study team members and conversations with patients. In addition, the number of telephone calls made by each patient or patient's family member to the University of Michigan hospital system regarding the clinical concerns of the patient within the first 30 postoperative days will be captured through chart review and independently verified by 2 study team members. If necessary, we will then use Michigan Value Collaborative data to quantify differences in health care utilization by comparing total and component 90-day episode payments among Medicare, Blue Cross Blue Shield of Michigan, and Medicaid beneficiaries, as our team has previously done in both coronary artery bypass (CABG) [31] and aortic valve replacement [30] studies in Michigan.

Analytic Approach

Mean inpatient opioid use, prescription size, postdischarge opioid use (in OME), and mean postsurgical health care utilization days will all be compared between groups using two-tailed *t* tests. Individual health care utilization outcomes will also be compared separately with two-tailed *t* tests for continuous data and chi-square tests for categorical data.

Aim 3: Qualitatively Evaluate the Effectiveness of the Comfort Coach Intervention

We will perform semistructured one-on-one interviews with 50 patients who had a comfort coach to understand (1) their experience with and perceived role of the intervention on their surgical experience and (2) the acceptability of the intervention. Insights from this thematic analysis will guide the identification and development of tools for broader implementation.

Semistructured Interviews

Interviews will be conducted by 2 study members (AB and MB) either in the FCVC cardiac surgery outpatient clinic area or over the telephone. Interviews will be audio recorded on an encrypted recorder, transcribed verbatim by an external HIPAA (Health Insurance Portability and Accountability Act)–approved professional transcriptionist, and redacted for all identifying information. Participants will be compensated with a gift card for their participation. After March 14, 2020, interviews were exclusively performed over the phone because of human subject research restrictions owing to the COVID-19 pandemic.

Analytic Approach

An initial interview guide will be developed and modified during the interview period through iterative steps. Data will be coded in MaxQDA20 (VERBI Software, 2019) qualitative analysis software. The team will meet to examine codes and identify emerging patterns and concepts that will be organized into themes. We will use the thematic analysis framework [68] to identify themes among patients who received a comfort coach and categorize these themes into 3 broad categories: (1) the role of the coach, (2) the impact of the coach, and (3) the acceptability of coaching. The data generated from these interviews will inform subsequent refining of our coaching intervention and development of tools for broader implementation of the intervention.

Power Analysis

Our primary endpoint is composite of health care utilization, defined as the total number of days spent at home within the first 30 days after surgery. Secondary endpoints include mean GAD-7 and PHQ-9, KCCQ-12, Picker Patient Experience Questionnaire, IES-R, and Brief Pain Inventory Scores and mean inpatient and outpatient opioid use.

We will compare mean days with a two-tailed *t* test and set the power of this study at 80% with alpha (Type I error) of .05 and the Cohen *d* effect size (defined as the difference in means divided by standard deviation) between medium (0.5) and large (0.8) [69,70], which yields a minimum sample size of 52 patients to detect a large effect size and 128 to detect a medium effect size [71]. Incorporating 20% missingness, a sample size of 154 patients will adequately detect a medium effect size. We next verified this statistically derived sample size with clinically relevant examples. Although most large series reporting opioid use report the median and interquartile range of OME [47,72], our sample size should be sufficient to satisfy the central limit theorem and use mean values. At our institution, the mean opioid use after sternotomy in 2017 was 200 OMEs. We estimated that to detect a 30% reduction in opioid use (mean 140 OMEs) with a standard deviation of 125 OME in the control and 100 OME in the intervention arms, a sample size of 114 would be required. For composite health care utilization, demonstrating a 3-day difference between the arms with a 6-day standard deviation would detect by a total sample size of 128 patients. With 154 patients, we should have adequate power to detect a difference in our primary outcomes for aims 1 and 2.

Results

Preliminary Data

An 11-patient feasibility study in aortic surgery patients (HUM00138828) was performed at the FCVC, 6 of whom were randomized to the control and 5 to the intervention arm. Extremely useful insight from this feasibility trial included feedback from intervention patients regarding the time-points at which their dedicated, trained comfort coach was most beneficial. This feedback was used to solidify the 6 touchpoints for our full clinical trial. In addition, an assumption about utilizing nonpharmacological interventions was that pain management and recovery after surgery were individualized processes. In contrast, we received feedback that family and relatives are intimately involved in patients' healing and emotional well-being. Furthermore, some patients indicated that their family members benefited from the comfort coach interventions, in some instances, even more than the patient. In addition, family interaction and socialization during the perioperative process were identified as important to pain management.

Executing the feasibility trial also provided direct insights for our study team. Using certified child life specialists in dual roles as full-time specialists at the children's hospital and on-call for the feasibility trial proved to be a barrier to effective intervention, primarily because of the distance between the hospitals creating time-related challenges for meeting each touchpoint. Accordingly, these experiences informed the development of the full clinical trial by highlighting the importance of hiring a full-time, dedicated comfort coach to enhance the number of touchpoints met and increase care continuity. Most importantly, this preliminary trial demonstrated that it would be feasible to perform the comfort coach study protocol at the University of Michigan.

After completing the feasibility study, the study team performed telephone interviews of study patients and former open-heart surgery patients through the FCVC's Patient Family Advisory Council to gain further insight into the patient experience and use this input to select the most appropriate survey instruments for the full clinical trial.

Full Clinical Trial

Our clinical trial is funded by Blue Cross Blue Shield of Michigan Foundation, and enrollment is currently ongoing. As of June 2020, 144 patients have been enrolled and randomized in the trial, and 50 semistructured qualitative interviews have been performed. Since March 14, 2020, all survey touchpoints and interviews have been conducted remotely via telephone, online, or mail because of human subject research restrictions implemented at the University of Michigan to limit exposure to patients and staff during the COVID-19 pandemic. Comfort coach touchpoints for patients in the intervention group have continued during their inpatient hospitalization, whereas 30-day follow-up visits with the comfort coach are now conducted remotely. We have completed our qualitative interview process and are currently evaluating our coded data, with plans to publish our qualitative findings by the end of 2020. We anticipate that enrollment, data collection, and analysis will be

completed by September 2020 and expect to submit our initial quantitative results for publication by the end of 2020.

Discussion

Significance and Impact

Aim 1: Assess the Effect of a Comfort Coach on Patient Experience

Nonpharmacological interventions administered by a comfort coach have the potential to decrease anxiety, self-reported pain, and stress while improving functional status and overall patient experience in the hospital for cardiac surgery patients, which would mirror findings in pediatric and nonsurgical adult populations [15,19]. These findings would have a significant impact on adult cardiac surgical care and establish a comfort coach role in a multidisciplinary perioperative care team. In addition, these findings justify the dissemination of these techniques and the role of the comfort coach in other types of surgery. Although cardiac surgery elicits significant preoperative anxiety and postoperative pain, other types of surgery such as oncologic, obstetrics, and orthopedic surgery are all associated with high amounts of anxiety, pain, and opioid use [9,40].

Aim 2: Measure Differences in Inpatient and Outpatient Opioid Use and Postsurgical Health Care Utilization

The role of surgery in the opioid epidemic has been well described [73] through widespread overprescribing [38,46], with the amount prescribed shown to be the most significant predictor of opioid consumption [47] and development of new persistent opioid use among previously opioid-naive surgical patients [74-81]. In cardiac surgery, persistent opioid use has been shown to confer higher rates of complications, length of stay, and health care costs [37]. Efforts have focused primarily on decreasing opioid prescription [72,82-85], whereas nonpharmacological interventions have not been well described in surgical patients. Comfort coaches may provide a nonpharmacological method for further decreasing opioid use, which would complement and enhance ongoing efforts to decrease prescribing. By addressing concurrent anxiety and decreasing perceived pain, nonpharmacological techniques may serve as valuable tools in addressing the opioid epidemic and improving surgical care.

The effect of the comfort coach's interventions on anxiety, pain, stress, and opioid use can also be measured through overall health care utilization. As patient anxiety and pain decrease while satisfaction and comfort increase, we expect them to be better equipped and more prepared to leave the hospital. In addition, whereas individual nonpharmacological techniques such as preoperative educational prompts [48,49], massage therapy [50], and music [34] have been tested within hospital settings, no trial has measured the effect of an individualized comfort coach utilizing individualized nonpharmacological techniques throughout the entire perioperative course, from preoperative clinic visit through 90-days of postoperative follow-up. An innovative aspect of this trial is sending different nonpharmacological tools home with patients based on their individualized preferences and continuing self-administered nonpharmacological techniques for 30 days postoperatively. We expect these sustained efforts to reflect decreased health care utilization through hospital length of stay, minimized or eliminated days spent in an extended care facility, prevented emergency room, urgent care, and unplanned doctor office visits, telephone calls, and readmissions, all of which may decrease health care costs.

Aim 3: Qualitatively Evaluate the Effectiveness of the Comfort Coach Intervention

We expect the comfort coach intervention to be extremely impactful. In contrast to testing 1 individual technique [50,86-88], the comfort coach intervention is a series of individualized nonpharmacological interventions administered by a trained coach incorporating patient preference and choice from a comfort menu. Qualitative analysis is essential to identify specific aspects of the comfort coach intervention, which were effective or ineffective, and answer *How?* and *Why?* to inform broader implementation. The findings from our qualitative study will prescribe how hospitals can expect to implement our findings efficiently. If the most impactful aspect of the intervention is the individual person, hospitals can focus on providing a companion for patients at critical moments in the perioperative process. If being coached were most impactful for patients, this would justify a certified comfort coach's role with training in administering these specific nonpharmacological techniques. If patients find specific techniques most effective, these can be packaged into a scalable paper or electronic tool, which can be broadly implemented for surgical patients. Insight into why different aspects of the intervention were effective will guide further implementation.

Economic Implications on the Cost of Health Care

Previous evaluations within pediatric [52,53] and adult nonsurgical populations [17,18] have established decreased health care utilization and, consequently, health care costs associated with nonpharmacological interventions. Much of the effect of coaching by certified child life specialists on reducing health care costs has been attributed to the reduced need for anesthesia in imaging procedures [52,53]. Furthermore, coaching interventions have been associated with decreased opioid use duration and length of hospital stay [15-18,51].

We anticipate that our coaching intervention may have more profound impact when evaluated within an adult inpatient surgical population. Relative to nonsurgical and many other types of surgical populations, our cardiac surgical population has greater anxiety, more pain and opioid use, and longer average lengths of stay. Even with our conservative effect sizes estimating a 10% reduction in the published mean episode payments for CABG and valve surgery [30,31], we anticipate savings within Michigan to be approximately US $54 to 80.4 million annually if our comfort coach intervention were disseminated across all 33 nonfederal cardiac surgical hospitals.

By decreasing health care utilization, the comfort coach intervention may have profound economic implications, particularly in decreasing the amount of time patients spend in the hospital. For payers, less health care utilization will decrease episode payments, which reach up to US $15 billion annually in the cardiac surgery population [29-32]. For hospitals,

decreasing individual patient health care utilization could mean an increase in new patient admissions and increased efficiency of patient throughput, which carries increased importance in the current era of value-based reimbursement.

Barriers to the Project

Healthy Volunteer and Placebo Effect

Whereas patients receiving the control treatment may report improvement because of the healthy volunteer effect [89], patients receiving intervention may report improvement in anxiety, pain, and satisfaction by virtue of the placebo effect of having a comfort coach. However, we feel that this *placebo effect* is a real effect that we hope to measure through this intervention. Our project's qualitative component aims to assess what works, what does not work, and even furthermore, how the intervention does or does not work. Accordingly, we feel the potential effect of having a designated coach to be an important measure.

Spillover Effects

Our trial may be susceptible to spillover effects, both internally in our intervention and from external forces such as competing institutional interventions. Specifically, opioid reduction efforts for specific general surgery procedures at our institution have demonstrated spillover effects into additional general surgery procedures, with corresponding reductions in opioid use found [83]. Similar efforts around perioperative education and opioid prescribing have taken place in cardiac surgery and may affect the opioid use secondary outcome if current prescribing and use are too low to observe significant changes. Internal spillover effects may also occur, such as nursing and other care team members observing comfort coach interventions and incorporating these nonpharmacological techniques into their usual care. We attempted to mitigate this effect by conducting in-service educational sessions with physicians, advanced practice team members, and nurses to make each stakeholder aware of the trial and the intervention being tested. In addition, if a trend of improvement in the control arm of this trial over time is observed, this difference over time will be treated as the effect size of spillover, and we will report it as such in the trial analysis.

Generalizability

If the intervention tested is beneficial, a generalizable implementation of trained comfort coaches for surgical patients may be questioned. To overcome this generalizability barrier, we will first consider our qualitative third aim to describe how these techniques were effective or ineffective. If specific techniques are effective, they can be translated into a scalable paper or electronic tool that can be broadly implemented. Second, the health care utilization is found to be lower among those who receive a comfort coach, we plan to financially quantify this difference with 90-day episode payments between arms and perform a cost-effectiveness analysis incorporating the cost of comfort coaching to demonstrate cost savings that can be used by other health systems to assess whether to implement these methods.

COVID-19 Effect

Approximately 20% of patients during the trial will have received inpatient care either during or after the peak of the COVID-19 pandemic. The usual amount of fear and anxiety elicited by cardiac surgery and the associated recovery period enhance patients' typical need for close physical, emotional, and psychological support from their loved ones. The hospital-wide policy prohibiting all visits during COVID-19 may cause an increase in the levels of fear and anxiety caused by surgery and recovery owing to enhanced feelings of isolation, separation, and possibly even abandonment—at such a crucial time of need—by the most important loved ones in their lives. These policy changes may enhance the impact of a comfort coach on the intervention arm, simply by adding more human contact through a caring and empathetic individual at these critical touchpoints of care, irrespective of the nonpharmacologic therapy the coach provided.

In contrast, the control patient group during the COVID-19 pandemic may be at a potential disadvantage compared with the control patient group before COVID-19 because the pre-COVID control group had the usual level of support from family, friends, and significant others. These 2 opposing effects, namely, a potential enhancement for the intervention group and additional tension and anxiety from isolation and separation among the control group, may have affected the study results. However, it is also possible that patients in the intervention group during COVID-19 remained anxious and fearful despite having a comfort coach because of separation from loved ones, fear of infection in the hospital, or other factors. Although we cannot mitigate the impact of COVID-19, we will perform a subset analysis of patients who received care during COVID-19 to evaluate for any significant differences in our data.

Conclusions

This clinical trial aims to evaluate the impact of a comfort coach administering nonpharmacological interventions on patient experience, opioid use, and health care utilization compared with usual care in adult cardiac surgery patients. Findings from this study may serve as the foundation for a subsequent multicenter trial, establishment of this role in the adult setting, and broader dissemination of these techniques to other types of surgery.

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Conflicts of Interest

DL served as consultant to AmSECT, and declares funding from NIH and AHRQ.

Multimedia Appendix 1
Supplemental material.
[DOCX File , 3621 KB - resprot_v10i2e21350_app1.docx]

Multimedia Appendix 2
Peer Review Comments and Author Responses.
[PDF File (Adobe PDF File), 770 KB - resprot_v10i2e21350_app2.pdf]

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Abbreviations

CABG: coronary artery bypass
FCVC: Frankel Cardiovascular Center
GAD-7: Generalized Anxiety Disorder 7-item scale
IES-R: Impact of Events Scale-Revised
KCCQ-12: Kansas City Cardiomyopathy Questionnaire short-form
OME: oral morphine equivalents
PHQ-9: Patient Health Questionnaire-9
TATUM: Treatment Assignment Tool-University of Michigan

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Protocol

An Asynchronous, Mobile Text-Based Platform (XatJove Anoia) for Providing Health Services to Teenagers: Protocol for a Quasiexperimental Study

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Abstract

Background: Due to the COVID-19 pandemic, it is more essential than ever to implement protective measures in primary care centers to ensure patients' safety. This protocol describes a quasiexperimental study on the use of a mobile chat platform as a clinical consultation tool for adolescents and primary health care physicians.

Objective: The purpose of the quasiexperimental study is to demonstrate that the use of mobile phones and messaging apps increases the number of health consultations. The study will be performed as part of the Health and School program in the Anoia region.

Methods: The quasiexperimental study will compare the number of face-to-face consultations to the number of consultations conducted on XatJove Anoia, as part of the Health in Schools program in the Anoia region. The study will involve the use of a new communication platform (ie, XatJove Anoia) for health care professionals and adolescents, and data on the number of face-to-face consultations will be collected as part of the same program in another region. Data will be collected from secondary schools during the academic year 2020-2021. Statistical analyses will be performed on the data that users will enter in the registration form. These data will be collected by means of a questionnaire, which will be submitted once the questionnaire is closed. The questionnaire will consist of multiple-choice questions, which will allow numerical values to be assigned to various responses in order to carry out statistical analyses.

Results: The study is projected to start at the beginning of November 2020 and finish in June 2021, which is when data analysis is expected to start.

Conclusions: The results of the quasiexperimental study may assist in the development and planning of school health programs.

Trial Registration: ClinicalTrials.gov NCT04562350; https://clinicaltrials.gov/ct2/show/NCT04562350.

International Registered Report Identifier (IRRID): PRR1-10.2196/25062

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KEYWORDS

mHealth; telehealth; teenager; health promotion and sexual health; health promotion; sexual health

Introduction

The World Health Organization defines "digital health" as the use of digital technologies for health purposes; digital health is a category that encompasses the increasing use of technologies for health services [1]. The internet has become an important tool for many people with health concerns, especially adolescents. Concerns regarding confidentiality, coupled with the stigma and shame associated with certain conditions, such as sexually transmitted infections and other health-related problems, make the internet an unsafe environment for adolescents who seek information.

Sex education is essential for the prevention of risky sexual behaviors, unwanted pregnancies, and the transmission of human immunodeficiency viruses and other sexually transmitted infections among adolescents. Young people receive sexual and reproductive health education from various sources, including formal education, school curricula, parents, fellow students, and media [2].

During the International Conference on Population and Development [2], several measures were established as a response to the need for providing relevant information that protects the sexual and reproductive lives of young people. Governments have been requested to provide sex education policies to promote the well-being of young people at a community level, especially in the school environment. Such policies will allow young people to make mature decisions regarding responsible sexual behavior much earlier than usual [3].

Finding information on health-related issues can be a major problem, as the underutilization of primary care services that provide information on certain topics and the untrustworthy nature of advice on the internet can subsequently lead to health-related complications that may require expensive and specialized medical interventions in the long term. These complications can ultimately lead to an increase in health care costs [4].

The Salut i Escola program (ie, the Health in Schools program) was launched by the Catalan Department of Health in the academic year 2004-2005. This program aims to improve the health of adolescents in Catalonia. The program involves health promotion, risk prevention, and early detection for problems related to mental health, emotional and sexual health, and drug, alcohol, and tobacco consumption. The program has been carried out in close collaboration with local schools and community health services.

This community-based outreach program requires intervention and cooperation from different professionals. One of the program's main lines of activity is the open consultation service, in which a health care professional visits schools to facilitate primary care accessibility among adolescents and guarantee privacy, confidentiality, and proximity.

Patients—particularly adolescent patients—are often reluctant to seek counselling and health treatment for embarrassing or stigmatized conditions, which can result in the underutilization of primary care health services. In addition, searching for medical information on the internet (eg, searching via Google) is increasingly common. Primary care health services, which are often made for young people, include consultations for sexual and reproductive health problems [5] and mental health disorders [6]. Finding information on health-related issues can lead to serious problems; the underutilization of primary care services that provide information on certain issues and the untrustworthy nature of advice on the internet can subsequently lead to health complications that may require expensive and specialized medical interventions in the long run, which may result in increased care costs [4].

To avoid health complications and increased care costs, a tool that adolescents have easy, constant, and effective access to is required. Digital health interventions have been shown to minimize hesitancy in seeking health advice for stigmatized and embarrassing problems. The digital health innovations proposed by the company Abi Global Health (AGH) could provide a possible solution [7]. AGH has developed an asynchronous, mobile text-based communication platform that connects users to health care professionals. These professionals provide users with appropriate guidance to help them make informed decisions about their health. AGH operates in more than 10 countries and has a network of more than 300 health professionals. This preexisting tool will form the basis of XatJove Anoia (ie, YouthChat Anoia), which is a platform that attempts to provide resources for mobile communication and message exchanges between adolescents and primary care professionals. A quasiexperimental study on XatJove Anoia will take place in Anoia, which is a country in Central Catalonia.

According to a pilot study, cystitis and contraceptive problems are among the top 10 reasons why patients have used a web-based tool to conduct a consultation [8]. Although these conditions can be embarrassing and difficult to talk about, it is important that they are dealt with by health care professionals. If ignored, these conditions can lead to serious, unwanted, and costly complications (eg, a failure to use contraception can lead to unwanted pregnancies and sexually transmitted diseases) [9,10]. The fact that users have routinely reported these problems by means of digital health interventions, such as e-consulta (ie, an asynchronous teleconsulting service for primary care professionals and health service users that is connected to primary care electronic medical records), is a positive sign with regard to the greater use of health services for sensitive and serious conditions. As an anonymous digital health intervention,

XatJove has the potential to address the inefficient costs resulting from the underutilization of health services for embarrassing and stigmatized disorders.

Due to the current climate of the health crisis caused by the COVID-19 pandemic [11] and the need to reduce the risk of infection, it makes more sense than ever to avoid face-to-face consultations with nursing staff in schools and primary care center visits by young people. It should be noted that this does not mean that there will be a reduction in the number of consultations for health-related issues and the number of school programs. On the contrary, the health crisis is expected to generate an increase in the need for emotional support for young people, and such support requires tools that allow for the quick use of technology (ie, technology that adolescents and primary care center professionals are familiar with and use regularly).

The main objective of this protocol is to describe a quasiexperimental study that shows that the use of mobile phones and messaging apps leads to an increase in the number of health consultations for adolescents aged between 12 and 16 years, as part of the Health and School program in the Anoia region. The study also seeks to evaluate the degree of satisfaction among XatJove users via an electronic survey.

Our main hypothesis is that the use of XatJove will improve the early detection of health problems, the accessibility of reliable information for young people, and communication among nursing professionals in primary care centers, in terms of issues related to drugs, diet, emotional health, and sexuality. We also believe that XatJove can help with the detection of child abuse cases.

Methods

Study Design

A quasiexperimental study that compares the total number of face-to-face consultations and XatJove consultations will be conducted as part of the Health and School program in the Anoia region (ie, the intervention group) during the 2020-2021 academic year. Data on the number of face-to-face consultations will be collected from the same program in the Osona region (ie, the control group). Problems that affect adolescents and relate to mental health, emotional and sexual health, drug use, alcohol, and tobacco will be recorded. The study population will include adolescents aged between 12 and 16 years who attend secondary schools in the Anoia region. We will use a pragmatic sample of 100 XatJove consultations. The total number of visits (ie, face-to-face visits and XatJove visits) that relate to the Health and School program in the Anoia region during the 2020-2021 academic year will be recorded.

The following variables will be recorded: (1) universal variables, including gender and age; (2) dependent variables, including the total number of visits (ie, face-to-face visits and XatJove visits) that relate to the Health and School program; and (3) independent variables, including the topic of consultations (ie, consultations for sexual health, alcohol, drugs, eating disorders, bullying, domestic abuse, mental health, COVID-19, and other topics).

To learn more about the usefulness of XatJove, students will be asked to participate in a follow-up study that involves a focus group.

Data Collection and Sources of Information

Data regarding the total number of visits will be obtained from the Primary Care Services Information Technologies System (ie, Sistemes d'Informació dels Serveis d'Atenció Primària in Catalan), which belongs to the Catalan Institute of Health in Barcelona, Spain.

The asynchronous, mobile text-based communication platform that is made available by AGH makes it possible to collect information on cases that involve a written query. User data will be obtained from the platform's database, and users will remain anonymous. The information collected will include age, gender, the date and time of the query, and the answer to the query. In addition, all the professionals involved in the study will sign a document, in which they will agree to respect data confidentiality.

After a response from a health care professional is received, users will be able to respond to a questionnaire, in which they can evaluate the quality of the service and their level of satisfaction (Multimedia Appendix 1). The data in this questionnaire will be collected and processed by AGH.

Statistical Analysis

Spreadsheets will be used to record the means and medians of various data. Statistical analyses will be performed on the data that users will enter in the registration form and the data collected from the questionnaire. The questionnaire will be sent to participants after their consultation concludes. The questionnaire consists of multiple-choice questions, which makes it possible to assign a numerical value to various responses. These values will be used in the corresponding statistical analyses.

Limitations of the Study

It is possible that an insufficient number of users will rate the service and respond to the questionnaire. If this happens, the deadline for collecting data will be extended.

Although it will be possible to send questions via XatJove 24 hours per day, answers will only be sent during specific time slots (ie, from 8 AM to 8 PM, including weekends). This may limit the accessibility of the service. However, any inquiries made outside of this time slot will be answered by medical professionals at the start of their next working day.

Since XatJove is an anonymized service, it will not be possible to verify whether users meet the inclusion criteria. Nevertheless, the service will only be offered to students who attend secondary schools in Anoia.

Ethical Considerations

The Institut Universitari d'Investigació en Atenció Primària Jordi Gol independent ethics committee in Barcelona, Spain approved the trial study protocol (code 20/137-P). Written informed consent will be requested from all patients who participate in the study. The study was registered on the

ClinicalTrial.gov registry (NCT04562350) on September 24, 2020.

Availability of Data and Materials

All principal investigators of the study will have access to the complete dataset. The datasets generated and analyzed during the study will be made available by the corresponding author. The results generated during the study will be published in peer-reviewed journals and presented at national/international congresses.

The study has been designed in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines. The registration of the study on ClinicalTrials.gov is expected to facilitate transparency and reporting.

Results

The study is projected to start at the beginning of November 2020 and finish in June 2021, which is when data analysis is expected to start.

Discussion

This aim of the pilot quasiexperimental study is to investigate the use of a mobile phone health chat service for adolescents from secondary schools in Anoia and nursing professionals from primary care centers in the same region.

The various studies that we previously participated in have shown that the use of a web-based communication tool for patients and professionals reduces the number of face-to-face visits [12,13], which is a very positive aspect with regard to the COVID-19 pandemic. Furthermore, the results of the study and the long-term and short-term impacts of XatJove will be used to revise the Health and School program, which is offered by the Department of Health. In other words, XatJove is a tool that will serve in the review of existing protocols. Web-based visits and consultations are gaining in popularity in the new health care environment that has resulted from the COVID-19 pandemic.

Web-based consultations can help with avoiding self-diagnoses, as it is common for people to search for information on the internet, which is not always a reliable source. Current evidence points to the importance of innovating and improving the treatment processes offered by health and school programs. One of our study's strengths is that the results will be obtained from usual clinical practices, without having to implement any considerable organizational or structural changes.

Acknowledgments

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Authors' Contributions

All authors contributed to the design and content of the study protocol. GSV, JVA, and VV, are responsible for the coordination of the study. More specifically, JVA, GSV, FS-R, GT, VV, and AE are responsible for designing the study, and GSV, JVA, VGF, KE, FS-R, and NC are responsible for writing the initial manuscript draft. GSV, JVA, VV, NC, KE, VGF, NC, AE, IS, and GT are responsible for data collection, fieldwork, and fundraising. VV, AE, and GT have epidemiological and statistical expertise. All authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire for evaluating the quality of the service.
[DOCX File , 13 KB - resprot_v10i2e25062_app1.docx]

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Abbreviations

AGH: Abi Global Health
CONSORT: Consolidated Standards of Reporting Trials

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Protocol

Leadership in Digital Health Services: Protocol for a Concept Analysis

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Abstract

Background: Due to the rapid digitalization of health care, leadership is becoming more complex. Leadership in digital health services is a term that has been used in the literature with various meanings. Conceptualization of leadership in digital health services is needed to deliver higher quality digital health services, update existing leadership practices, and advance research.

Objective: The aim of this study is to outline a concept analysis that aims to clarify and define the concept of leadership in digital health services.

Methods: The concept analysis will be performed using the Walker and Avant model, which involves eight steps: concept selection, determination of aims, identification of uses, determination of defining attributes, construction of a model case, construction of additional cases, identification of antecedents and consequences, and definition of empirical referents. A scoping literature search will be performed following the search protocol for scoping reviews by the Joanna Briggs Institute to identify all relevant literature on leadership in digital health services. Searches will be conducted in 6 scientific databases (CINAHL, MEDLINE, Scopus, ProQuest, Web of Science, and the Finnish database Medic), and unpublished studies and gray literature will be searched using Google Scholar, EBSCO Open Dissertations, and MedNar.

Results: An initial limited search of MEDLINE was undertaken on October 19, 2020, resulting in 883 records. The results of the concept analysis will be submitted for publication by July 2021.

Conclusions: A robust conceptualization of leadership in digital health services is needed to support research, leadership, and education. The concept analysis model of Walker and Avant will be used to meet this need. As leadership in digital health services appears to be an interprofessional and intersectoral collaboration, defining this concept may also facilitate collaboration between professionals and sectors. The concept analysis to be conducted will also expand our understanding of leadership in digital health services.

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KEYWORDS

health care; leadership; health services; concept analysis; telehealth

Introduction

Background

Several health care programs and reforms introduced in recent years have highlighted the importance of digitalization and health information technology for solving problems in modern health care [1,2]. This importance has been increased further by the COVID-19 pandemic [3]. Health care digitalization, also referred to as *digital transformation*, means that health services and systems are undergoing a transition whereby increasing numbers of these services and systems are becoming digitalized [4]. Although there is a rapidly growing body of research on health care digitalization [5], the viewpoint of health care leadership in digital health services has been de-emphasized [6-9]. Health care leaders have traditionally been responsible for clinical health services and their management [10]; however, now they are also responsible for developing and managing health care organizations' health information technologies (HITs) [11-13]. Nurse leaders seem to be particularly active in planning the implementation of digital health services and bear the chief responsibility for its use [14]. This may be because nurses are often more involved in the early-stage implementation of digital transformation projects, whereas physicians join during later phases [15]. It has, therefore, been suggested that more research should focus on how to develop continuously evolving health care leadership that is well placed to cope with changes such as the current rapid digital transformation [16].

However, the literature provides little clarity as to what leadership in digital health services means or entails [17,18]. Researchers have used terms such as e-leadership [6,8] and virtual leadership [19] in reference to nurse leaders; however, their definitions are inconsistent. For example, e-leadership has several different definitions; among other things, it has been understood as a process of social influence that takes place in the context of an organization where work is supported by information and communication technology (ICT) [20]. In contrast, virtual leadership has been defined as leading remotely working teams [21]. In addition to these terms, expressions such as *physician leadership in eHealth* have been used [6]. The existence of several inconsistently defined concepts and meanings relating to leadership in digital health services makes it difficult to hold dialogs about the phenomenon. A recent scoping review by Strudwick et al [22] concluded that it is essential to understand the informatics competencies of nurse leaders because nurse leaders play key roles in all issues relating to technology in health services.

What Is Known About Leadership in Digital Health Services?

Conceptualization of leadership and leadership-related issues is quite common in health care research. Previous concept analyses relating to health care leadership have focused on transformational leadership [24], staff nurse clinical leadership [25], nurse manager engagement [26], and nurse manager succession planning [27], among other things. As there has been limited research on leadership in digital health services [17,18], conceptualizing leadership in digital health services could provide important guidance for service development and future research. In this concept analysis, health care leadership will be considered to encompass both leading people and managing systems and structures [28]. The theory of transformational leadership, according to which leaders see change as an opportunity, has occasionally been linked to health care digitalization [17,29]. However, health care digitalization also seems to involve elements of management because implementing HITs requires decision making on various issues, including financial issues [30]. Health care organizations are among the most complex in society [31], and the increasing number of HITs makes them even more complex and challenging to manage for health care leaders [32-34].

Previous studies have mainly examined leadership in digital health services from the viewpoint of HIT implementation and adoption [7,13]. A recent scoping review by Laukka et al [13] found that roles adopted by health care leaders during HIT implementation include supporters, change managers, advocates, project managers, decision makers, facilitators, and champions. Another review by Ingebrigtsen et al [7] identified 7 leadership behaviors associated with successful outcomes in HIT adoption: communicating clearly about visions and goals, providing support, establishing a governance structure, establishing training, identifying and appointing champions, addressing work process change, and following up. These reviews synthesized leadership roles and behaviors important in HIT implementation and adoption. However, making the most of HIT also requires proper health care leadership in other processes [35]. For health care leaders, managing technology is also about the 3 *Ps*: people, processes, and (computer) programs [35]. The information age paradigm is transforming health care delivery and, in the process, may also shift leaders' perspectives and shape their leadership responses [17].

Several studies have aimed to define the concept of e-leadership [36,37]; however, the definition has not been made in the context of health care, which is unique compared with other fields of businesses. According to Avolio and Kahai [36], "e-leadership takes place in a context where work is mediated by information technology." Health care has lagged behind other areas of business in terms of the use of ICT [33,38,39], and efforts to implement HIT fail relatively frequently in health care settings [33,40]. This may be partly because of poor leadership in health care organizations [41,42].

To conclude, conceptualization of leadership in digital health services is needed to better understand how leadership can support health care digitalization and improve the likelihood of successful HIT implementation. For example, the integration of HIT is necessary for nurse leaders to lead effectively in the future [8]. Advancing digitalization and HIT implementation will enable the delivery of higher quality digital health services while also supporting health care professionals' work related to HIT. In addition, a robust conceptualization will facilitate further research in this area and help reshape leadership models to establish digitalization as a core part of health care leaders' core competency, thereby contributing to the provision of adequate education. Keijser et al [6] noted the importance of researching health care leadership in the context of digital health care and highlighted the importance of research in educating leaders.

Objectives

Precise conceptualization of leadership in digital health services is needed to support health care leaders working on digitalization on the frontline and at middle and senior management levels, to help create better digital health services, to facilitate continuously evolving leadership, and to advance research. To this end, the concept of leadership in digital health services was analyzed using the concept analysis model of Walker and Avant [23]. The use of a protocol based on this model was expected to increase the quality of the final concept analysis.

Methods

This Study

Aim

The protocol outlines a concept analysis procedure designed to clarify and define the concept of leadership in digital health services.

Design

The concept analysis model of Walker and Avant [23], which has become one of the most influential concept analysis models in health care [43], will be used. The strength of the model by Walker and Avant [23] is that it provides a structural guideline. Walker and Avant [23] define concept analysis as the process of defining a concept carefully by understanding and examining its basic elements and underlying attributes. The 8 steps of their concept analysis procedure are described in the following sections.

Step 1: Selecting a Concept

The concept analysis process starts with the selection of a concept to be analyzed [23]—in this case, leadership in digital health services. Analysis of this concept is needed to establish an up-to-date definition and framework of leadership for the era of health care digitalization.

Step 2: Defining the Aim of the Analysis

The next step is to define the aims or purpose of the study [23]. Our specific aims in this study are to clarify the concept of leadership in digital health services and develop a theoretical definition of leadership in digital health services. Conceptualization of the construct of leadership in the context of digital health services is needed to better understand the phenomenon of health care digitalization, to guide future research, and to construct a modern leadership framework for health services.

Step 3: Identifying All Uses of the Concept

The third step involves first identifying all previous uses of the concept when collecting material for analysis [23]. In this study, diverse sources will be used to identify different definitions of leadership in digital health services. These sources will then be subjected to critical analysis to identify different definitions, descriptions, and applications of leadership in digital health services. The reported ways of using and describing leadership in digital health services will finally be recorded for future reference.

Step 4: Determining the Defining Attributes of the Concept

After identifying the different uses of the concept under investigation, the uses will be read through to find the characteristics that appear repeatedly to define the key attributes of the studied concept (in this case, leadership in digital health services). This process will generate *a cluster of attributes that are frequently associated with the concept* [23].

Step 5: Constructing a Model Case

This step involves developing one or more model cases to represent a real-life example of *the use of concept that includes all the critical attributes of the concept* [23]. This will be done using data extracted during the earlier phases.

Step 6: Constructing Additional Cases

After identifying at least one model case, additional cases relating to the concept under investigation will be identified. This is necessary because it will not be possible to complete the concept analysis if there are overlaps between the identified attributes or contradictions between the defining attributes and the model case [23]. The purpose of this step is to determine which characteristics or attributes best fit with the concept under study and to identify the attributes that define the concept [43]. The additional cases should include examples that are (1) related, (2) borderline, (3) contrary, (4) invented, and (5) illegitimate [23]. Related cases closely resemble the model case but can be seen to lack at least some of the defining attributes when examined closely. Borderline cases display some of the defining attributes but lack several others. These 2 cases help to clarify the concept and to show what it is not. A contrary case is one that is clearly not an instance of the concept, whereas an invented case is used to illustrate the essential features of a concept. Finally, an illegitimate case illustrates improper use of the concept [43].

Step 7: Identifying Antecedents and Consequences of the Concept

Antecedents and consequences will be identified in the penultimate step. Walker and Avant [23] defined antecedents and consequences, respectively, as events or incidents that occur before or as a result of the *occurrence of the concept.*

Step 8: Defining Empirical Referents

The final step of the concept analysis will be to integrate the critical attributes with real-world empirical referents. According to Walker and Avant [23], empirical referents are measurable ways to demonstrate the occurrence of the concept.

Scoping Review

To identify all relevant literature on leadership in digital health services, a literature review will be conducted in accordance with the search protocol for scoping reviews by the Joanna Briggs Institute (JBI) [44]. Scoping reviews are useful for mapping the key concepts of a research topic and clarifying its working definitions and/or conceptual boundaries [45]. The search strategy used in a scoping review should be as comprehensive as possible [44]. This requirement aligns well with the principles of concept analysis, which call for the use

of diverse sources to obtain varied definitions of the concept under investigation [43]. Unlike in a systematic review, quality assessment is not a necessary part of the scoping review process [44], and it is also not relevant in concept analysis [46,47]. Quality assessment is not needed in concept analysis because the data to be extracted relate to the definitions and attributes of leadership in digital health services, not the results of the study [46,47]. Therefore, all published uses of the concept under investigation are relevant, irrespective of the quality of the research in which they are used.

Eligibility Criteria

The Population, Concept, and Context (PCC) framework will be applied when defining eligibility criteria for the scoping review [44]. Initial inclusion and exclusion criteria relating to the PCC of studies considered for inclusion in the scoping review are presented in Textbox 1.

Textbox 1. Eligibility criteria based on the Population, Concept, and Context framework for publications included in the scoping review.

Inclusion criteria

- Population: Studies on health care leaders regardless of their management position or health care field
- Concept: Health care or service leadership
- Context: Digital health services

Exclusion criteria

- Population: Studies on leaders working solely with information technology management
- Concept: Not related to health care or service leadership
- Context: Health services with no digitalization of any kind

Both peer-reviewed publications and papers from gray literature will be included in the review. The studied population will consist of health care leaders or managers regardless of their management position and health care field. Leaders working solely with information technology management will be excluded because they are not responsible for clinical health services and management. Publications eligible for inclusion in the review will be those that somehow define or clarify the concept of leadership in the context of digital health services.

Search Strategy

A 3-step search strategy [44] will be used to retrieve both published and unpublished studies. An initial limited search of MEDLINE was undertaken on October 19, 2020, as part of this study protocol, resulting in 883 papers (Table 1). Relevant papers were identified by analyzing their titles, abstracts, and index terms. MEDLINE was used in this preliminary search because its large database includes several papers relating to health care leadership; as such, the search was expected to provide a rough estimate of the number and availability of relevant papers. An information specialist was consulted when developing the initial search strategy and will be consulted about other search strategies as well. During the main concept analysis study, a search strategy using all the relevant identified keywords and index terms will be used for each information source to be searched. The reference lists of all included studies will also be screened to identify additional relevant studies.

The databases to be searched will include CINAHL, MEDLINE, Scopus, ProQuest, Web of Science, and the national Finnish database Medic. These databases collectively provide a comprehensive coverage of publications relating to health care leadership and digital health services. Searches for unpublished studies and gray literature will be conducted using Google Scholar, EBSCO Open Dissertations, and MedNar. Gray literature types eligible for inclusion will include editorials, opinion papers, and dissertations. Papers published in English, Finnish, and Swedish will be considered for inclusion. Only papers published between 2010 and the present (2020) will be considered for inclusion because the rapid digitalization of health services over the past decade [48] makes older studies less relevant to the current situation. Keywords to be used will be related to eHealth, information technology, digitalization, health care, health services, and leadership. Keywords will be truncated, where appropriate. In addition, index terms or headings such as Medical Subject Headings will be used in MEDLINE and CINAHL.

Table 1. Search strategy applied in MEDLINE using Medical Subject Headings terms and search terms with abstract, title, and keyword limitations. The search was undertaken on October 19, 2020.

Searches	Results, n
exp Telemedicine/	30,325
exp Leadership/	41,537
exp Telemedicine/ and exp Leadership/	85
(eHealth or e-health).tw[a]	4649
exp Telemedicine/ or (eHealth or e-health).tw[a]	33,067
(information technology or digital*).tw[a]	150,808
(health* or medic* or nursing*).tw[a]	4,352,122
(information technology or digital*).tw[a] and (health* or medic* or nursing*).tw[a]	36,072
exp Telemedicine/ or (eHealth or e-health).tw[a] or (information technology“ or digital*).tw[a] and (health* or medic* or nursing*).tw[a]	66,516
“leader*”.tw[a]	76,359
exp Leadership/ or “leader*”.tw[a]	97,028
Telemedicine/ or (eHealth or e-health).tw[a] or (information technology or digital*).tw[a] and (health* or medic* or nursing*).tw[a] and exp Leadership/ or “leader*”.tw[a]	1217
limit Telemedicine/ or (eHealth or e-health).tw[a] or (information technology or digital*).tw[a] and (health* or medic* or nursing*).tw[a] and exp Leadership/ or “leader*”.tw[a] to y=“2010-Current”	883

[a]Text word terms are searched from the titles, abstracts, and keywords.

Study Selection

All citations identified by implementing the search strategy described earlier will be collated and uploaded into the Covidence systematic review systematic software package (v2422), which will also be used to remove duplicates. Titles and abstracts will then be screened by two team members independently using the inclusion or exclusion criteria. For papers without abstracts, the full text will be retrieved. After title and abstract screening, the potentially relevant studies will be retrieved in full. Two independent team members will assess these studies in detail and evaluate their suitability based on the inclusion criteria. Reasons for exclusion will be reported for studies that do not satisfy the inclusion criteria. Any disagreements at any stage of the study selection process will be resolved by discussion or by asking the opinion of a third team member. The results of the search will be reported in the final study and will be presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [49]. All search methods, strategies, and sources will be described or named in the final report and will be replicable.

Data Extraction and Synthesis

The extracted data will include definitions of leadership in digital health services; its key domains; the setting and population of the study described in the paper; and data needed for the 8-step concept analysis, such as attributes, antecedents, and consequences [23]. Two researchers will participate in data extraction.

Ethical Considerations

As concept analyses use only secondary publicly available data from primary research studies and gray literature, no research ethics approval will be needed.

Validity and Rigor

Several activities will be performed to enhance the study’s validity and rigor, including the following:

1. Method: The scoping review, which will identify all relevant literature on leadership in digital health services, will be conducted following the JBI guidelines [44].
2. Search: An information specialist with expertise in health sciences and management research will be consulted when developing the search strategy to increase credibility. In addition, several databases and gray literature sources will be included to ensure the richness of the data.
3. Screening, data extraction, and synthesis: Each of the previously mentioned phases will be conducted independently by 2 team members. Having 2 independent team members to select papers, extract data, and conduct synthesis will enhance reliability.
4. All members of the research team will repeatedly evaluate the manuscript during meetings that will be held as the process progresses.

Results

The search for the relevant studies was performed on November 31, 2020, resulting in 2861 studies after duplicates were removed. The screening of the studies will be completed by the end of January 2021. We expect to begin other phases of concept

analysis in February 2021. The concept analysis is anticipated to be ready for submission by July 2021.

Discussion

Principal Findings

In recent years, leadership in digital health services has been scrutinized in relation to issues including HIT adoption and implementation [7,13,50], informatics competence [51,52], and virtual teams [6,21]. Previous studies suggest that there is no consistent treatment of different elements of digitalization (eg, implementation, informatics competence) within leadership in health services and that current approaches to leadership in digital health services are therefore fragmentary and incomplete.

The literature indicates that all health care leaders, regardless of their management position, are involved in health care digitalization [9,13-15] and that nurse leaders play a particularly important role in the early use of HIT [15]. The roles of frontline nurse or physician leaders seem to be essential in supporting health care professionals in the use of HIT [13]. Nurses and physician leaders working in middle management also play an important role in implementing HIT [14], and senior nurses and physician managers seem to be responsible for making decisions about obtaining new HIT [30,53]. Collaborations between nurse leaders and chief information officers have also been scrutinized [50,54]. Overall, leadership in digital health services seems to require interprofessional and intersectoral collaboration involving working together with other health care leaders, chief information managers, health care professionals, research and educational centers, and HIT vendors [14,50,54,55].

Glaser [56] suggested that HIT implementation failures are often because of the *actions and inactions of senior leadership*. This may be because health care leaders might have insufficient informatics skills. For example, according to Sharpp et al [57], some nurse leaders are inexperienced users of ICT. Several studies have proposed that health care leaders have not received enough, or any, education on informatics [13,29,58]. HIT, thus, seems to be a *black box* for some health care leaders, and this issue should be examined more thoroughly [30].

Limitations

The preliminary search of MEDLINE conducted while developing this study protocol retrieved many potentially relevant papers. Therefore, the search strategy (especially for the largest databases) will involve only title and abstract searches to ensure that the review balances feasibility with comprehensiveness. Limiting the searches to titles and abstracts may cause some relevant studies to be excluded from the concept analysis. However, title limitation appears to be quite common in reviews focusing on health care digitalization [13,59]. The concept analysis model by Walker and Avant [23] provides the analyst 8 steps to guide their analysis. However, despite these 8 steps, the more detailed analysis has been left to the analyst to figure out individually [43].

Conclusions

There is a clear need to conceptualize leadership in digital health services because leadership in health services seems to be incoherent, providing no consistent perspective on the phenomenon. In addition, this study shows that the concept analysis model of Walker and Avant [23] is suitable for conceptualizing leadership in digital health services. Such a concept analysis could be beneficial in several ways. First, it could help guide research on and modelling of leadership within health care studies. Second, providing a clear definition of leadership in digital health services could guide health care leaders and managers in their work, facilitate interprofessional and multisectoral collaboration, and advance clinical practice, especially in relation to digitalization. Third, conceptualization could be used to guide the training of health care leaders to help them better meet current and future challenges relating to health care digitalization.

Our evaluation of the need to conceptualize leadership in digital health services made it clear that in addition to providing a basis for further research, defining and clarifying the concept of leadership in digital health services could facilitate the development of higher quality digital health services by actualizing the roles and responsibilities of leaders in digitalized health care. A clear definition may also help educational and health care organizations to provide better education and training for health care leaders in ICT, which would, in turn, support the digitalization of health care.

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Conflicts of Interest

None declared.

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Abbreviations

HIT: health information technology
ICT: information and communication technology
JBI: Joanna Briggs Institute
PCC: Population, Concept, and Context

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Protocol

Using Flow Disruptions to Examine System Safety in Robotic-Assisted Surgery: Protocol for a Stepped Wedge Crossover Design

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Abstract

Background: The integration of high technology into health care systems is intended to provide new treatment options and improve the quality, safety, and efficiency of care. Robotic-assisted surgery is an example of high technology integration in health care, which has become ubiquitous in many surgical disciplines.

Objective: This study aims to understand and measure current robotic-assisted surgery processes in a systematic, quantitative, and replicable manner to identify latent systemic threats and opportunities for improvement based on our observations and to implement and evaluate interventions. This 5-year study will follow a human factors engineering approach to improve the safety and efficiency of robotic-assisted surgery across 4 US hospitals.

Methods: The study uses a stepped wedge crossover design with 3 interventions, introduced in different sequences at each of the hospitals over four 8-month phases. Robotic-assisted surgery procedures will be observed in the following specialties: urogynecology, gynecology, urology, bariatrics, general, and colorectal. We will use the data collected from observations, surveys, and interviews to inform interventions focused on teamwork, task design, and workplace design. We intend to evaluate attitudes toward each intervention, safety culture, subjective workload for each case, effectiveness of each intervention (including through direct observation of a sample of surgeries in each observational phase), operating room duration, length of stay, and patient safety incident reports. Analytic methods will include statistical data analysis, point process analysis, and thematic content analysis.

Results: The study was funded in September 2018 and approved by the institutional review board of each institution in May and June of 2019 (CSMC and MDRH: Pro00056245; VCMC: STUDY 270; MUSC: Pro00088741). After refining the 3 interventions in phase 1, data collection for phase 2 (baseline data) began in November 2019 and was scheduled to continue through June 2020. However, data collection was suspended in March 2020 due to the COVID-19 pandemic. We collected a total of 65 observations across the 4 sites before the pandemic. Data collection for phase 2 was resumed in October 2020 at 2 of the 4 sites.

Conclusions: This will be the largest direct observational study of surgery ever conducted with data collected on 680 robotic surgery procedures at 4 different institutions. The proposed interventions will be evaluated using individual-level (workload and attitude), process-level (perioperative duration and flow disruption), and organizational-level (safety culture and complications)

measures. An implementation science framework is also used to investigate the causes of success or failure of each intervention at each site and understand the potential spread of the interventions.

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KEYWORDS

robotic surgical procedures; patient safety; ergonomics; crossover design

Introduction

Background

The integration of technology into health care systems is intended to provide new treatment options and improve the quality, safety, and efficiency of care. Robotic-assisted surgery (RAS) is an example of high technology integration in health care, which has become ubiquitous in many surgical disciplines. RAS cases have tripled over the past decade [1] largely replacing both open and traditional laparoscopic surgeries for many common procedures [2]. Similar to many other types of technology in health care, RAS has changed tasks and workflow [3,4], demanding additional skills or training and introducing new complexities ranging from skill building and learning curves to workspace and organizational issues associated with operating room (OR) layout. Although RAS is associated with less postoperative pain [5], blood loss [6], and conversion to open surgery [5], safety incidents in RAS may be higher than in traditional laparoscopy [7], which has led to concerns about the speed of adoption and implementation [8]. Similar to other advanced technologies, the spread of RAS has preceded these system-level considerations, which are difficult to predict, so risks may not be immediately apparent and often go unaddressed [9-12].

RAS implementation focuses on establishing the technical skills of the surgeon operating via the robotic console [13]. However, the physical separation of the surgeon from the OR team also introduces additional communication challenges [14,15], which can lead to errors [16] and even patient harm [17,18]. RAS has particularly acute effects on equipment congestion, the movement paths of staff, and the safe positioning of data and power cables necessary for function [19]. The learning curve required to counter this multitude of systems integration challenges may continue in RAS well beyond those required in open surgery cases [2,19] and account for a steady increase in the experience recommended to achieve competency [7]. Thus, increasing task demands, combined with unique teamwork and communication challenges and existing workspace issues, may predispose to safety incidents in RAS. However, organizations are left to identify and resolve these risks without formal guidance and, in many cases, without available expertise to create formal solutions [7,20]. Human factors engineering techniques, which have been applied across many different industries to improve safety and performance [21], can be used to identify and alleviate risks in RAS. Using ethnographic approaches and systems analysis tools, human factors engineering seeks to enhance clinical performance through an understanding of the effects of teamwork, tasks, equipment, workspace, culture, and organization on human behavior and abilities.

As models of surgical processes have improved, it has become possible to reliably observe the disruptive effects of systems issues on intraoperative performance and their downstream effects on mortality and morbidity. For nearly 2 decades, direct observation of surgical work has been used to understand potential hazards in the surgical process [22,23]. Direct observation remains the best way to record variations in a process, the impact of system design on individual patterns of work, and the wider systems effects of implementing surgical technology. Unlike laboratory or simulated settings, direct observation allows us to distinguish between *work as done* (ie, what really happens) and *work as imagined* (ie, what should happen, what we think happens, or what we are told happens), illuminating the reality of how work is accomplished outside of an idealized expected or desired occurrence of events. In this paper, we discuss the design of a methodological framework and study execution applied to improve the processes of care in RAS.

Study Objectives

This 5-year study will take a human factors engineering approach to improve the safety and efficiency of RAS across 4 US hospitals. The primary objective of this study is to generate a set of integrated, evidence-based tools for improving the safety and efficiency of robotic surgery by (1) improving teamwork and communication skills, (2) improving and standardizing technical tasks such as instrument changes and robotic docking, and (3) improving the working environment. The secondary objectives are to (1) understand the effects of organizational and work context on the spread of good practice in high-technology surgery and (2) generate a computational model of the mechanisms by which small, seemingly innocuous events escalate to create serious surgical complications. This will fundamentally improve our understanding of how innovative surgical technologies can be safely deployed and integrated within clinical work systems.

Methods

Study Design

This 6-phase study includes the observation and analysis of RAS cases sampled across 4 hospitals. The study will use a pseudostepped wedge crossover design with 3 individual interventions—teamwork training (TT), task design (TD), and workspace design (WD), introduced in different sequences at each of the 4 hospital sites over 4 phases (phases 3-6) of 8 months each. We elaborate on the proposed interventions below.

TT Interventions

TT interventions will be built based on teamwork training and nontechnical skills frameworks and will support the skills needed for teams to address RAS-specific communication challenges. The TT approach will consist of a TeamSTEPPS [24,25] driven training package (4- to 6-hour meeting for surgeons and anesthesiologists via small group teaching and successive 1-hour meetings for OR staff) complemented by on the spot coaching by human factors experts to offer reminders and encouragement.

TD Interventions

TD interventions will focus on specifying, ordering, and allocating tasks to specific roles to improve efficiency, visibility, and reliability [26]. A previously performed failure modes and effects analysis [27,28] will be used to prioritize tasks for redesign. The Systems Engineering Initiative for Patient Safety model [21] will be used to determine a human-centered systems model of each task, and task analysis will be used to define roles, sequences, and allocation. Finally, we will practice and refine these redesigns using in situ simulation trials.

WD Interventions

WD involves proposing and implementing new OR layout configurations to improve the use of space in RAS. OR layouts will be configured to ensure (1) the surgeon can see the patient and the team from the console, (2) the team can see the surgeon, (3) staff can move freely in the room, (4) robot docking can occur from multiple angles, (5) minimize cable tensions and trip hazards, and (6) optimization of OR equipment preparation and instrument storage. Key movement-oriented tasks will be used to plot ideal movement paths on existing room layouts, and new layouts will be proposed and tested to reduce unnecessary movement and disruption.

Stacking Interventions

Given the close interactions between technology, tasks, teamwork, and process [29-32], we hypothesize that multiple interventions will function synergistically. Teamwork benefits from visual cues, sightlines, and face-to-face communication [33,34]; TD benefits from improved teamwork to allow better coordination of complex, interdependent tasks [29,31,35]; and better efficacy of teamwork-related checklists [16], improved equipment storage, and visibility through better WD allows for improved task performance [30,36,37]. Thus, this study is designed to specifically test each of these interactions.

This design allows for sufficient implementation and sampling of the interventions, introduces individual components of an overall improvement strategy, and evaluates how each change contributes to a larger *whole* (Table 1).

Table 1. Study design.

Project phase	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6	Analysis
Months	1-12	13-20	21-28	29-36	37-44	45-52	53-60
Medical University of South Carolina	Intervention refinement	Baseline	TT[a]	TT+TD[b]	TT+TD+WD[c]	TT+TD+WD[d]	Analysis
Cedars-Sinai Medical Center	Intervention refinement	Baseline	TD	TD+WD	WD+TD[d]	TD+WD+TT	Analysis
Marina del Rey Hospital	Intervention refinement	Baseline	WD	WD[d]	WD+TT	WD+TT+TD	Analysis
Ventura County Medical Center	Intervention refinement	Baseline	Baseline[d]	Baseline	TT+TD+WD	TT+TD+WD	Analysis

[a]TT: teamwork training.

[b]TD: task design.

[c]WD: workspace design.

[d]Control phases.

Power Analysis

Using multiple regression with 10 predictor variables (4 sites, 5 data collection phases, and 3 interventions and 1 baseline period) and assuming a normal distribution, 40 observations per site per time per intervention will provide at least 80% power to find a statistically significant effect of the intervention on surgery duration. Achieving this level of statistical power remains possible with 23 observations per phase per site, making our planned sample of 40 robust, should data collection be more challenging than anticipated.

Study Setting

The study will be conducted at 4 hospitals in the United States, which include 2 tertiary centers with very different geography and demographics, a public *safety net* hospital, and a small private community hospital. The Medical University of South Carolina (MUSC) is an 864-bed level 1 trauma academic medical center in the southeastern United States. MUSC uses a Si da Vinci robot for general surgery procedures and Xi (X generation) for urology and gynecology procedures. Cedars-Sinai Medical Center (CSMC) is a large nonprofit tertiary care center with 958 beds and a level 1 trauma center designation in the western United States. CSMC currently has 7 da Vinci robots: 5 dual Xi consoles and 2 Xi single consoles. Marina del Rey Hospital (MDRH) is a 145-bed community hospital, acquired by the Cedars-Sinai Health System in 2018. The hospital has a small yet active robotic surgical program dating back to 2012. There is one Si robot that is used daily (up to 10 cases weekly). Ventura County Medical Center (VCMC)

is a designated level 2 trauma center *safety net* hospital in the western United States and acquired its first da Vinci robot (Xi) in 2017, which is actively being used in general surgery, urology, and gynecology.

At MUSC, CSMC, and MDRH, we will sample from the following RAS procedures: urogynecology (sacrocolpopexy with and without hysterectomy), gynecology (hysterectomy for benign and malignant conditions), general and colorectal surgery (colon resection, abdominal wall hernia repair, hiatal hernia repair), bariatric (sleeve gastrectomy), and urology (simple and radical prostatectomy and nephrectomy). These cases are performed with enough volume to facilitate comparison through statistical analysis. At VCMC, an opportunity sampling approach, in which we collect any RAS procedure available, will be used because of the low RAS case volume.

Measures

Measures will be evaluated across 3 dimensions of RAS—individual (clinicians), process (RAS case), and system (hospital) levels—and will be collected using hospital databases, observation, surveys, and interviews (Table 2).

Table 2. Measures and administration.

Method and measures/and variables	Phases	Administration	Dimension
Extraction from hospital database			
Covariates including perioperative duration, blood loss, conversion to open returns to the OR[a]	Intervention+baseline	Data collected for all patients in each intervention phase via hospital databases (n=680)	System
Direct observation			
Patient details (age, BMI, ASA[b])	Intervention+baseline	Collected during direct observation in the OR (or retrospectively collected from patient's health record)	System
Flow disruptions	Intervention+baseline	Direct observation of number, type, and rate per observation (n~27,200)	Process
Surgical phase duration	Intervention+baseline	Collected during direct observation in the OR	Process
Oxford NOTECHS 2	Intervention+baseline	Direct observation for each phase of surgery for surgeon, OR staff, and anesthesia subteams	Process
Intervention adherence metric	Intervention	Direct observation once during each surgical observation (for intervention phases (3-6); n=520)	Process
Surveys			
SURG-TLX	Intervention+baseline	Completed once per observed surgery by surgeon, anesthesiologist, circulating nurse, and scrub tech (n~2270)	Individual
Safety attitudes questionnaire	Intervention+baseline	Administered on web via REDCap[c] once per phase for all RAS[d] practitioners (n~425)	System
Concurrent acceptability	Intervention	Administration on web via REDCap [38] twice per intervention phase (phases 3-6) for all RAS staff and clinicians (n~950)	Individual
Interviews			
Intervention implementation facilitators and barriers	Intervention	Observations and in-person interviews conducted with a diverse sample of OR staff following the implementation of all interventions (n=8-10 individuals per site)	System

[a]OR: operating room.

[b]ASA: American Society of Anesthesiologists.

[c]REDcap: Research Electronic Data Capture.

[d]RAS: robotic-assisted surgery.

Covariates

Contextual covariates of known influence include patient details (age, sex, BMI, American Society of Anesthesiologists [ASA] Physical Status classification), surgery details (procedure description, procedure category, date, robot model (S, Si, Xi), hospital, OR number, approximate room size), and personnel details (number of surgical trainees, OR staff trainees [circulating nurses and surgical technicians], and anesthesia trainees). These covariates will be collected during the observations and/or retrospectively from the patient's electronic health record. We will also record operative and in-room time, intraoperative complications, blood loss, conversion to open surgery (which requires undocking the robot and making an abdominal incision), and returns to the OR via hospital electronic records for each intervention period.

Flow Disruptions

Deviations from the natural progression of a task (ie, flow disruptions [FDs]) [39] were collected throughout all phases of each operation. Data collection includes a brief description of the event observed, time of occurrence, major category, and severity. FDs will be assigned a category and severity score during observation. With respect to classification, each FD will be assigned one of 8 possible categories: communication, coordination, equipment, training, external factors, environment, patient factors, and surgical task considerations (Table 3) based on an adapted taxonomy developed by Catchpole et al [40]. Minor categories may be developed for a more granular analysis of the data following data collection. FDs will also be assigned a severity score, ranging from 0 to 2: (0: potential disruption to the process, 1: disruption to the process, and 2: increased patient safety risk).

Table 3. Flow disruption taxonomy.

Category	Description	Examples
Communication	Any miscommunication that impacts surgery progress	Repeat information, misunderstanding, irrelevant conversation
Coordination	Any lapse in teamwork to prepare for or conduct surgery that affects surgery flow	Equipment adjustment or reposition, personnel rotation, personnel unavailable, lack of knowledge
Equipment	Any equipment issue that affects surgery progress	Robot inoperative, equipment or /instrument inoperative, suture issues, insufflation problems
Environment	Any room conditions that impact surgery progress	Outlet positioning, untangling wires and tubing, architectural design, lighting, noise
External factors	Any interruption that is not relevant to the current case	External personnel, hospital-wide alarm, personal electronic devices
Patient factors	Any patient characteristic that impedes efficient surgery	Unexpected patient reaction, patient allergy, individual differences
Surgical task considerations	Any surgeon pauses to determine the next surgical step	Surgeon decision-making, instrument changes
Training	Any instruction given to surgical team members related to the case	OR[a] staff training, anatomy discussion, robot technical instruction

[a]OR: operating room.

Surgical Phase Duration

Each RAS procedure will be evaluated throughout 5 distinct surgical phases: (1) wheels in until incision, (2) incision to the surgeon on console (including the docking process), (3) surgeon on console to surgeon off console, (4) surgeon off console to patient closure, and (5) patient closure to wheels out. The duration of each phase will be recorded by the observers during data collection.

Oxford NOTECHS 2

The Oxford NOTECHS 2 [41] rating system will be used to evaluate the nontechnical skills of the OR team. The scale includes 4 dimensions—leadership and management, teamwork and cooperation, problem-solving and decision-making, and situation awareness—rated on an 8-point scale. Observers will record NOTECHS ratings for each team member during the case.

Intervention Adherence Metric

The extent to which interventions are fully used following implementation will be assessed using the intervention adherence metric [42-44], a metric developed based on the developed interventions. It will consist of a series of observational scores (Likert and check boxes) that will be deployed during each surgical observation to evaluate the use of interventions, based on observable components of each intervention. This will be deployed uniformly at baseline and all intervention phases, allowing us to understand the use of intervention during each operation.

SURG-TLX

Subjective workload ratings will be obtained using the SURG-TLX (Task Load Index) [42]. This visual-analog workload measure asks each surgical team member to select a score from 1 to 20 on 6 parameters: mental demands, physical demands, temporal demands, task complexity, situational stress, and distractions, which are then aggregated and rescaled to generate a workload score between 0 and 100.

Safety Attitudes Questionnaire

Safety culture will be assessed using the Safety Attitudes Questionnaire (SAQ) [45], which has been extensively used for nearly 2 decades. The teamwork subscale has been sensitive to teamwork interventions [46], whereas the perceptions of management subscale has identified barriers to such interventions [43]. This will be administered via REDCap (Research Electronic Data Capture, a web-based Health Insurance Portability and Accountability Act–compliant survey platform) [38] in the last 2 weeks of each data collection phase to all staff involved in robotic surgery during that trial period. Subanalysis via surgical specialty and specific operations performed will allow us to track subtle changes over time.

Concurrent Acceptability

To gauge team members' responses to the interventions, we will administer the concurrent acceptability [44] measure (7 items, 5-point Likert scale) to all involved staff after the first month and at the end of the last month of each intervention phase (estimate 30-50 staff per site per phase). The measure is based on the Theoretical Framework of Acceptability model (version 2), which reflects the extent to which people deliver or receive a health systems intervention consider it to be appropriate based on anticipated or experiential cognitive and emotional responses to the intervention.

Study Procedures

Observer Training

Ensuring observers are effectively trained to perceive FDs and collect data on teamwork above the *noise* of otherwise normal system function is a critical requirement for this study [23]. During the prebaseline phase, observers will receive extensive training that includes initial classroom instruction (human factors and FD classification frameworks) and practice and familiarization (eg, identification of OR team members and the components of the operating room environment) in the OR with 2 human factors researchers with extensive experience with direct observation and FD measurement in surgery. Observers will be trained to understand the basic steps for each surgery type and are familiarized with the surgical subspecialties and components of the surgical robot. Trainees will also be provided with relevant reading material on FDs, NOTECHs, and RAS and given an example of a completed data collection tool.

Familiarization observations will take place across 3 stages: (1) orientation to the OR, (2) practice observations, and (3) simultaneous observation of interrater reliability (Table 4). Weekly meetings, including the observers and principal investigators, will be initiated to combat drift and allow observers to review their observations with the team.

Table 4. Observation protocol.

Observation stage	Number of observations	Description
Orientation	1	• Trainee and trainer observe one full RAS[a] procedure together. This serves to orient the trainee to the OR[b] • Trainer demonstrates the following behaviors: • Checking in with the charge nurse before entering OR • Checking in with circulating nurse on entry to OR • Where to stand in the OR and what to avoid • Discuss different personnel and steps of the procedure • Trainer engages in postobservation discussion • Discussion of individuals in the room • Answers any questions the observer had
Practice	3	• Trainee and trainer observe 3 full RAS procedures together, each using the data collection tool but without discussing their observations with one another • Debrief after surgery • Trainer to read off their observations and times at which they observed FDs[c]. Concurrently, trainee checks observations they caught and discussion of those that they did not
Interrater reliability	5	• Trainee and trainer observe 5 observations for interrater reliability • If IRR[d] (kappa>0.7) observers were considered trained and they could observe independently

[a]RAS: robotic-assisted surgery.

[b]OR: operating room.

[c]FD: flow disruption.

[d]IRR: interrater reliability.

In-Services

Before conducting observations, 15-minute in-services will be conducted with the staff on each unit at each study site to explain the research, introduce them to the research team, and allow them to ask questions and express their concerns. In-services will be led by a human factors expert and surgeon team member(s). Furthermore, an information sheet will be provided to staff to educate them about the purpose of the study and

provide contact information for members of the study team whether they have any questions.

Data Collection

Observations

A total of 4 trained human factors researchers will observe 680 RAS cases over the course of the study period. For MUSC, CSMC, and MDRH, observers will capture 40 cases during each of the 5 data collection phases (phases 2-6, each 8 months in duration). For VCMC, 40 cases will be captured in each of 2 phases: baseline (which spans across phases 2-4) and intervention (phases 5 and 6; Table 5).

Observers will collect FDs, NOTECH ratings, and all relevant case-related covariates, including patient details (age, sex, BMI, ASA classification), surgery details (procedure description, date, hospital, OR number, room size), personnel details (number of surgical trainees by type, OR staff trainees, and anesthesia trainees by type), and robot details (S, Si, or Xi model). During the intervention phases, the intervention adherence metric will also be collected during each surgical observation to evaluate the use of interventions.

Field notes will also be collected monthly by the observers at each of the 4 sites. Field notes generally consist of 2 parts: descriptive and reflective information. Descriptive information attempts to accurately document factual data (eg, date and time) and the settings, actions, behaviors, and conversations observed. Reflective information documents your thoughts, ideas, questions, and concerns as you are conducting the observation. These notes will provide additional context for the implementation of the intervention using the Consolidated Framework for Implementation Research (CFIR) [47].

Data will be collected in the OR using Microsoft Surface Pro 6 tablets. Urban Armor Gear Hand Strap & Shoulder Strap Military Drop Tested Cases are also used to provide ergonomic support and handling of tablets for observers standing or seated on stools for long period. XCOREsion 15-45 by J-Go Tech Microsoft Surface Portable Chargers were given to each observer to provide external battery life when collecting data over 2 or more consecutive cases with no opportunity to charge their tablets between cases.

Table 5. Data collection schedule.

Project phase	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6	Total
Medical University of South Carolina	40 (5 per month)	40 (5 per month)	40 (5 per month)	40 (5 per month)	40 (5 per month)	200
Cedars-Sinai Medical Center	40 (5 per month)	40 (5 per month)	40 (5 per month)	40 (5 per month)	40 (5 per month)	200
Marina del Rey Hospital	40 (5 per month)	40 (5 per month)	40 (5 per month)	40 (5 per month)	40 (5 per month)	200
Ventura County Medical Center	13 (1-2 per month)	14 (1-2 per month)	13 (1-2 per month)	20 (2-3 per month)	20 (2-3 per month)	80
Total	133	134	133	140	140	680

Surveys

The SURG-TLX will be collected in person during direct observation and will be administered on a Microsoft Excel form located on the observer's Microsoft Surface Pro tablets. The SAQ and concurrent acceptability will each be collected via a REDCap survey emailed to surgeons and OR staff.

Postimplementation Evaluation

We will evaluate interventions as multiple case studies using in-depth interviews and observations to gain an understanding of how these process changes are adapted in each setting and what facilitates success and barriers to these changes. A diverse sample of OR managers, nurses, surgeons, assistants, and technical support personnel (n=8-10 individuals per site) will be interviewed using semistructured interview guides to elicit narratives of individual experiences surrounding RAS implementation, teamwork, surgical safety, and facilitators and /barriers to successful RAS workflow. Interviews will be guided by the CFIR [47] to examine how the interventions were implemented in each setting, considering intervention characteristics, inner and outer context, and characteristics of individuals and process involved. Our qualitative analysis will examine convergence and divergence of narratives and will present those in a case study approach. An Olympus voice recorder will be used, and audio files will be professionally transcribed. Interview transcripts and field notes will be uploaded to NVivo (QSR International, Victoria, Australia), a qualitative and mixed methods analysis software, for the analysis.

Data Analysis

Statistical Analysis

We will use multivariable regression models to explore the relationship between the covariates (ie, site, specialty, BMI, and teamwork) and process measures (ie, FDs and durations), examining how these relationships are modified by interventions. The following are the specific questions we seek to answer: (1) What interventions are used (intervention adherence metric)? (2) Did OR staff like the interventions (concurrent acceptability)? (3) Did the interventions change attitudes (SAQ)? (4) Did the interventions change individual workload (TLX) and/or improve teamwork (NOTECHS)? (5) Did the interventions result in a better process (FD)? and (6)

Did the interventions reduce surgical durations and/or blood loss and/or OR returns? Statistical analysis will be conducted using the R programming language (R CORE TEAM, version 3.5.2) and assessed at the significance level of α .05.

Point Process Analysis

Direct observation of surgical processes may be useful in modeling adverse event causation by looking at the concatenation of smaller, seemingly innocuous errors to larger, more clinically serious situations [48-50]. The primary purpose of the proposed analyses is to develop a quantitative framework that allows for the evaluation of the *snowball* hypothesis. The rationale behind this hypothesis is that accidents and injuries arise from the sequence of multiple, frequently occurring individual errors. Adverse outcomes can be seen both as the *unlucky* coincidence of multiple randomly occurring errors and/or as a causative *chain of events* where one error leads to the next, creating an error *cascade* (or *snowball*). A range of exploratory Markov chain, Poisson process, and changepoint modeling techniques will be applied with the R programming language to analyze data across more than 1000 procedures and identify error causation mechanisms as random coincidences or as a deterministic error *cascade*. This mode of analysis aims to be a profound advance, not solely in understanding and addressing surgical complications and adverse events but in the entire way in which accidents are viewed.

Intervention Analysis

An inductive and deductive thematic content analysis approach will be used to analyze the qualitative data [51]. In total, 2 research team members will individually code all interviews and field notes, first in a deductive pass, using a codebook to tag segments of text specific to the CFIR constructs and systems model concepts. Next, an inductive pass through the data will identify new concepts to develop themes that have not been previously identified. Codes will identify causes, explanations, relationships, patterns, and themes related to the implementation of new RAS workflows. After iterative analyses, the 2 coders will immerse and crystallize [52] the final set of themes, confirm these findings with the research team, and develop a case study of comprehensive user experiences that promote successful implementation of RAS.

Results

Funding and Ethics

The study was funded in September 2018 and approved by the institutional review board of each institution in May and June of 2019 (CSMC and MDRH: Pro00056245; VCMC: STUDY 270; MUSC: Pro00088741).

Data Collection

After refining the 3 interventions in phase 1, data collection for phase 2 (baseline data) began in November 2019 and was scheduled to continue through June 2020. However, data collection was suspended in March 2020 due to the COVID-19 pandemic. We collected a total of 65 observations across the 4 sites before the pandemic. Data collection for phase 2 was resumed in October 2020 at 2 of our 4 sites.

Discussion

Overview

The overall goal of our research involves conducting multiple system-level interventions in RAS to validate a methodological approach to understanding and addressing latent systemic threats from new surgical technologies and measure both the effects of improvements that result as well as the utility of the interventions. Multiple interventions will be developed, tested, and planned to substantially expand our understanding of surgical safety in high-technology health care settings. This project will be the most comprehensive study to apply a human factors framework to study safety and efficiency, as it relates to technology integration in surgery. Although focused on RAS, the proposed observational, implementation, and evaluative methods of this study can be successfully applied to other health care settings integrating advanced technological systems. The study aims to address challenges and concerns using a mixed methods approach, including interviews, observations, work systems approaches, longitudinal ethnographic sampling techniques, and statistical modeling. This design is intended to capture the etiology of failure modes resulting from the mismatch between technology and existing culture. The combination of approaches will allow us to address how small, otherwise innocuous incidents can snowball into accidents and injuries in health care settings [48,49,53,54]. We also apply an implementation science framework to understand barriers to implementation, particularly of distal influences [55] or where staff may not always be supportive [7]. Understanding how and why observed effects differ among settings will allow for improved spread and sustainability. Implementing and sustaining improvements requires an ongoing involvement of stakeholders across organizational levels and boundaries [56].

Our sample includes a high volume of RAS cases performed using the da Vinci robot and conveniently sampled; this will limit the range of surgical procedures observed and will likely result in an unbalanced sample across the 4 sites. Scheduling is complex, and case cancelations and delays are an inherent deficiency in collecting observational data. The presence of the observer impacts the nature of data collected, whether as a result of implicit bias or obstructed views, and will thus affect how the data are analyzed. Although the methods described earlier are imperfect, future research teams may explore better ways to conduct these types of studies, such as through the use of video monitoring and other innovative approaches.

Limitations

Although direct observation provides a unique opportunity to gain a true understanding of the current state of the system [16], there are challenges in conducting observational research in health care settings. These challenges include the time and effort required to train observers and organize observations [17], the costs of employing researchers to conduct observations, and the potential for the Hawthorne effect [18]. In addition, good interrater reliability among observers needs to be established and maintained throughout the course of the study, and observers need to be supported, as they may view traumatic events and feel unwelcomed in the OR [23]. Previous research has used

video capture and remote video monitoring to identify teamwork, communication, and other challenges in the OR and RAS [57]. However, these methods introduce logistic and ethical challenges, including institutional review board concerns related to the identifiability of participants and data capture of adverse events. Poor fidelity and recording quality, limited viewing angles, and obstructions may also limit the usefulness of the recorded data. Moreover, the use of video recording still requires that observers conduct several videos to record observations, possibly extending the time required and expenses associated with data collection. Video capture and observations together, as was used by Randell et al [57], may represent the most comprehensive approach.

Conclusions

This project will demonstrate the value of understanding technologies *in the wild*; the nature of partnerships between human factors experts, clinicians, administrators, and OR staff; the integration and understanding of surgical technologies; and the implications for future technological development and clinical practice. Ultimately, this study will fundamentally improve our understanding of how innovative surgical technologies can be safely deployed and integrated into complex clinical work systems. We welcome the development of similar methodologies for the evaluation and integration of various kinds of technology in health care.

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Authors' Contributions

TC, LN, AA, JA, and KC conceptualized and designed the study and interventions. SS, DS, and JA facilitated OR access and data collection. MA, JG, KC, FK, and EC collected data under the supervision of TC, KC, and AA. MA, TC, and KC wrote the first draft, and the manuscript was edited by KC, LN, JA, DS, and SS. All remaining authors reviewed, provided feedback, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ASA: American Society of Anesthesiologists
CFIR: Consolidated Framework for Implementation Research
CSMC: Cedars-Sinai Medical Center
FD: flow disruptions
MDRH: Marina del Rey Hospital
MUSC: Medical University of South Carolina
OR: operating room
RAS: robotic-assisted surgery
SAQ: Safety Attitudes Questionnaire
TD: task design
TLX: Task Load Index
TT: teamwork training
VCMC: Ventura County Medical Center
WD: workspace design

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Protocol

App-Based Salt Reduction Intervention in School Children and Their Families (AppSalt) in China: Protocol for a Mixed Methods Process Evaluation

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Abstract

Background: The app-based salt reduction intervention program in school children and their families (AppSalt) is a multicomponent mobile health (mHealth) intervention program, which involves multiple stakeholders, including students, parents, teachers, school heads, and local health and education authorities. The complexity of the AppSalt program highlights the need for process evaluation to investigate how the implementation will be achieved at different sites.

Objective: This paper presents a process evaluation protocol of the AppSalt program, which aims to monitor the implementation of the program, explain its causal mechanisms, and provide evidence for scaling up the program nationwide.

Methods: A mixed methods approach will be used to collect data relating to five process evaluation dimensions: fidelity, dose delivered, dose received, reach, and context. Quantitative data, including app use logs, activity logs, and routine monitoring data, will be collected alongside the intervention process to evaluate the quantity and quality of intervention activities. The quantitative data will be summarized as medians, means, and proportions as appropriate. Qualitative data will be collected through semistructured interviews of purposely selected intervention participants and key stakeholders from local health and education authorities. The thematic analysis technique will be used for analyzing the qualitative data with the support of NVivo 12. The qualitative data will be triangulated with the quantitative data during the interpretation phase to explain the 5 process evaluation dimensions.

Results: The intervention activities of the AppSalt program were initiated at 27 primary schools in three cities since October 2018. We have completed the 1-year intervention of this program. The quantitative data for this study, including app use log, activity logs, and the routine monitoring data, were collected and organized during the intervention process. After completing the intervention, we conducted semistructured interviews with 32 students, 32 parents, 9 teachers, 9 school heads, and 8 stakeholders from local health and education departments. Data analysis is currently underway.

Conclusions: Using mHealth technology for salt reduction among primary school students is an innovation in China. The findings of this study will help researchers understand the implementation of the AppSalt program and similar mHealth interventions in real-world settings. Furthermore, this process evaluation will be informative for other researchers and policy makers interested in replicating the AppSalt program and designing their salt reduction intervention.

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KEYWORDS

mobile health; mobile phone; process evaluation; salt reduction; health education

Introduction

Background

Dietary salt intake is a major risk factor for high blood pressure and cardiovascular diseases [1,2]. In 2017, 3 million deaths worldwide were attributable to excess salt intake [3]. Salt reduction is one of the *best-buys* recommended by the World Health Organization for the prevention and control of noncommunicable diseases (NCDs) [4]. Many countries have implemented their national strategies to reduce population salt intake through comprehensive strategies, including consumer education to raise awareness, food industry engagement to reformulate products, and front of package labeling to inform consumers' choices [5]. Among these widely used strategies, reformulation is the most effective salt reduction strategy in high-income countries, where the majority of dietary salt intake comes in processed food [6]. For example, the United Kingdom, as the pioneer for salt reduction, achieved a 15% reduction in population salt intake between 2003 and 2011 by the gradual reformulation of prepackaged foods [7].

China is faced with a severe threat from NCDs, where more than 80% of the total disease burden is due to NCDs [8]. Salt intake in China is among the highest in the world [9]. The average salt intake of Chinese adults is about double the recommended maximum limits [9,10]. A study showed that approximately 80% of salt consumed in China is added by house cooks in daily cooking [11]. This dietary pattern makes it challenging to reduce salt intake because of the difficulties in changing individuals' diet behaviors. To improve public awareness of high salt intake and its impacts, the Chinese government has initiated several national programs, such as the National Healthy Lifestyle Campaign [12]. However, an international study suggests that only 1.3% of the surveyed Chinese participants reported a reduced salt diet, which is much lower than that in Japan, the United States, and the United Kingdom [13]. Evidence indicates that sustained efforts are needed to effectively raise public awareness of salt and nudge behavior change in their daily lives.

People's eating patterns and preferences are established early in life [14]. Hence, childhood is essential for building healthy dietary lifestyles to prevent related diseases, including cultivating low-salt diet habits. A salt reduction program in primary schools, named School-EduSalt, was conducted to investigate the potential benefits of salt reduction intervention among school children [15]. This one-term health education program on salt reduction among students achieved remarkable intervention outcomes and resulted in a 25% decrease in salt intake among adult family members [15]. This study shows that health education at schools can benefit not only school children but also their family members. This School-EduSalt program developed an intervention approach for salt reduction in the Chinese context with low cost [16]. However, the generalizability of this intervention model is limited because of its high requirements for health education teachers and the extra workload to schools.

With the development of modern technology during the past decades, mobile phones and apps have become a popular platform for lifestyle interventions. A review shows that eHealth technologies have been widely used in school settings to deal with multiple risk factors among students [17]. A systematic review of mobile health (mHealth) interventions for salt reduction identified more than 10 relevant intervention programs, which used short messaging services or other mHealth technologies to deliver salt reduction information to people [18].

Recent national data indicate that approximately 904 million Chinese have access to the internet [19]. This widespread access provides an opportunity for spreading health information via apps or other web-based tools. As yet, there has not been a salt reduction education program targeting primary school students using smartphone apps. We decided to take advantage of modern technologies to translate the successful experience of the School-EduSalt program and develop a more sustainable salt reduction program for broader scale-up in the future. Therefore, the AppSalt program was invented.

AppSalt Program

The AppSalt program is an mHealth intervention program built upon the experience of the School-EduSalt program. In this program, a smartphone app named *AppSalt* will be designed to provide a platform for delivering standardized health education courses to grade 3 students (aged 8-9 years) and their parents. In addition to the app, we will also design and implement some offline activities. In total, there will be 5 intervention components in this program, aiming to mobilize children's influence on family members to reduce the whole family's salt intake. The intervention design is based on the health belief model [20] and the socioecological model [21]. The details of the 5 intervention strategies of the AppSalt program are described below:

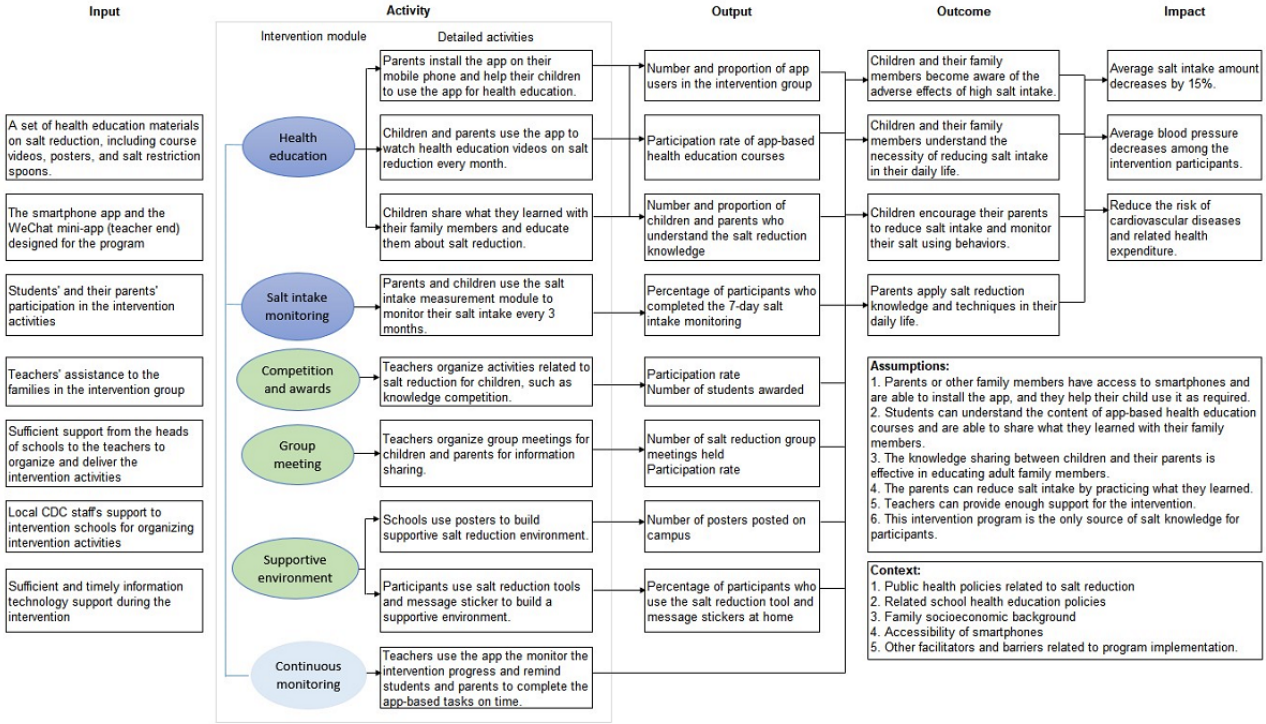
- App-based health education on salt reduction: Health education courses on salt reduction will be delivered once every month through the app installed on a family member's smartphone. Each lesson consisted of a 10-min video and a quiz to re-enforce important messages. Most of these lessons will have a practical session to help participants put what they have learned into practice. Health education lessons will cover essential knowledge and techniques for salt reduction, including the adverse effects of high salt intake, recommended salt intake amount, low-sodium salt, and skills in reducing salt used in cooking. The students and their family members can decide when and where to learn the lesson at their convenience. Parents will need to take the lessons with their children; students will be encouraged to share what they learned with their family members, especially the person responsible for home cooking. Through knowledge sharing between children and

adults, the program aims to educate the whole family on salt reduction.

- Salt intake monitoring: The salt measurement module in the app can help participants monitor their salt intake and major salt contributors in their diet. This measurement consists of a 7-day food diary for the family, which requires the users to fill out on a daily basis and record the condiments used in home cooking, type and weight of processed food consumed at home, and frequency of eating out during the 7 days. After completing this 7-day diary, the app will calculate the average salt consumption using an embedded algorithm, which was proven to be highly consistent with salt intake measured by 24-hour urine collection in a previous validation study [22]. In addition, the app will automatically generate a salt reduction action plan for each family member according to their salt intake level and major sources of salt intake. In the action plan, we will suggest the participants try to reduce half of their salt intake. In addition, some practical skills for reducing salt intake will also be included in the action plan. The participants will be required to use the salt measurement module to monitor their progress in salt reduction every 3 months during the intervention period. Regular monitoring will inform the participants of their salt intake level and the gap between their current salt intake and the recommended amount.
- Competitions and awards: The AppSalt project team will design several school-based competitions and awards to motivate parents and children to engage in the app-based modules and enable interpersonal communication between students during their participation in these competitions. At each school, 4 competitions will be organized by the schoolteachers, including 1 art competition, 2 knowledge competitions, and 1 writing competition. After each competition, the top 30 students at each study site will be awarded certificates and prizes. The competitions will be organized once every 2 or 3 months.
- Parent meetings: Each intervention school will need to organize 3 to 4 parent meetings to encourage peer communication among the parents and to collect their feedback on the program. The parent meetings will be arranged at the beginning and end of each term. Each group meeting will have a specific topic related to recent courses or activities.
- Supportive environment: Posters will be provided to the schools to help create a supportive environment for salt reduction on campus. The themes of these posters will correspond to the topics of the health education videos delivered through the app. In addition, some practical tools for reducing salt intake will be provided to families in the intervention group, including salt-restriction spoons, salt containers, and reminding message stickers.

The logic model of the AppSalt program is shown in Figure 1, which outlines the inputs, intervention activities, intended outputs and outcomes, and long-term impacts. The central program office will manage the app and the web-based intervention activities in this program. The teachers in the intervention schools will deliver the offline intervention activities following the program office's instructions. The teachers will be trained to keep activity logs of the offline intervention activities, which will be used as a data source for this process evaluation. We will develop a WeChat mini app (teacher end) for teachers to send messages to the families, check families' progress, and ensure that all families complete the tasks in time.

Figure 1. Logic model of the AppSalt program. CDC: Center for Disease Control and Prevention.



Effectiveness Evaluation

To test the effectiveness and cost-effectiveness of the AppSalt program, we will design a cluster randomized controlled trial and recruit 54 primary schools from 3 cities to participate in the trial. Half of the schools will be randomized to the intervention group and participate in the AppSalt intervention activities for 1 year. The other half will be the control group and continue with their usual health education curriculum. The primary outcome of the trial will be evaluated by the difference between the intervention and control groups in the change of salt intake measured by 24-hour urinary sodium from baseline to the end of the trial. The published protocol provides more details on the effectiveness evaluation of the AppSalt program [23]. This trial was registered at Chinese Clinical Trial Registry (ChiCTR1800017553).

Process Evaluation and Objectives

The AppSalt program is the first multicomponent mHealth intervention program for salt reduction conducted at Chinese primary schools. The smartphone app used in this program will be an innovative tool for health education in the primary school context. Its acceptability and sustainability remain a question. In addition, multiple stakeholders will be involved in this program, including students, parents, teachers, school heads, and government officials. Their perceptions and experiences are valuable for refining the intervention design for future scale-up.

This process evaluation is designed to analyze the implementation of an mHealth tool in a real-world setting. Evaluating the implementation process will help researchers better understand contextual factors affecting the implementation, the feasibility of mHealth tools in real settings, and key stakeholders' opinions on scaling up such a program in the future. Furthermore, this process evaluation will be helpful for other researchers and policy makers to replicate the AppSalt program and design their salt reduction program. The specific objectives of the AppSalt process evaluation are as follows:

- To evaluate the implementation of the AppSalt program in real-world settings, including fidelity, reach, dose delivered, and dose received
- To understand the underlying intervention mechanism of AppSalt program
- To identify the facilitators and barriers of implementing this program
- To collect stakeholders' opinions and suggestions for scaling up the program.

Methods

Study Design

This process evaluation is informed by the theoretical framework proposed by Linnan and Steckler [24] and the UK Medical Research Council process evaluation guidance for complex interventions [25]. The fidelity of the implementation, intervention dose delivered and received, reach of the intervention strategies, and the contextual factors influencing the intervention will be evaluated. The definition of each evaluation component and data sources are listed in Table 1.

This process evaluation will be embedded in the full cluster randomized controlled trial of the AppSalt program. A mixed methods approach will be used to collect the process evaluation data of the AppSalt program throughout the intervention process. The major data sources and time of data collection are provided in Table 2.

Table 1. Process evaluation components and data collection methods.

Evaluation components	Definition	Data collection methods
Fidelity	To what extent is the intervention implemented as planned and carried out according to the principles of the intervention. Are there any adaptations made during the program?	App log and routine monitoring data
Dose delivered	Of the intended intervention strategies, how many were delivered and in what quantity?	App log, routine monitoring data, and interviews with teachers
Dose received	How satisfied are the teachers, children, and adults with the intervention? What is the extent to which children and adults engaged with and are receptive to the intervention?	Interviews with selected students, parents, and teachers
Reach	Of the intended participants, what percentage is reached by each strategy?	App log, routine monitoring data, and interviews with participants
Context	What are the barriers and facilitators to implementing each intervention strategy?	Interviews with local education and health authorities

Table 2. Time and methods of collecting process evaluation data.

Type of data	Time of collection
Quantitative data	
App use logs	Automatically generated during the intervention process when the users log in to the app and use it for app-based intervention activities
Offline activity logs	Collected by the teachers when holding offline activities, including competitions and group meetings, during the intervention process
Routine monitoring data	Collected by a program coordinator every 2 weeks during the intervention process
Qualitative data	
Semistructured interviews with selected participants and key stakeholders	Within 1 month after completing the intervention

Data Collection

Quantitative Data Collection

The app use logs, offline activity logs, and routinely collected monitoring data will be the major quantitative data sources for process evaluation. The app use log will be automatically generated when the student or parent log in the app and use it for app-based intervention activities, including the time spent watching health education videos, marks gained from the quizzes, and frequency of 7-day salt intake monitoring. The app use log will be exported through the managing website by an authorized administrator after completing the 1-year intervention. The offline activity logs will be uploaded by teachers using the management tool (teacher end). We can extract detailed information about offline activities from these activity logs, including date, topics, and number of participants. Routine monitoring data will be collected every 2 weeks by a program coordinator during the intervention to evaluate the implementation of web-based courses and offline activities. If any problems identified were from the routine monitoring data, these problems will be provided to local collaborators for optimizing the intervention process. We will also monitor the dropout during the intervention and collect the reasons for dropping out.

Qualitative Data Collection

Qualitative data will be collected through semistructured interviews with participants and key informants to obtain more in-depth knowledge of their experience and feedback on the intervention [26]. Only the intervention group in the AppSalt program will be interviewed because of time and personnel constraints. In total, we plan to interview 27 students, 27 adult family members, 9 teachers, 9 school heads, and 9 representatives from local health and education authorities. The sample size of interviewees is based on similar process evaluation research [27,28] and might be increased if information saturation could not be reached.

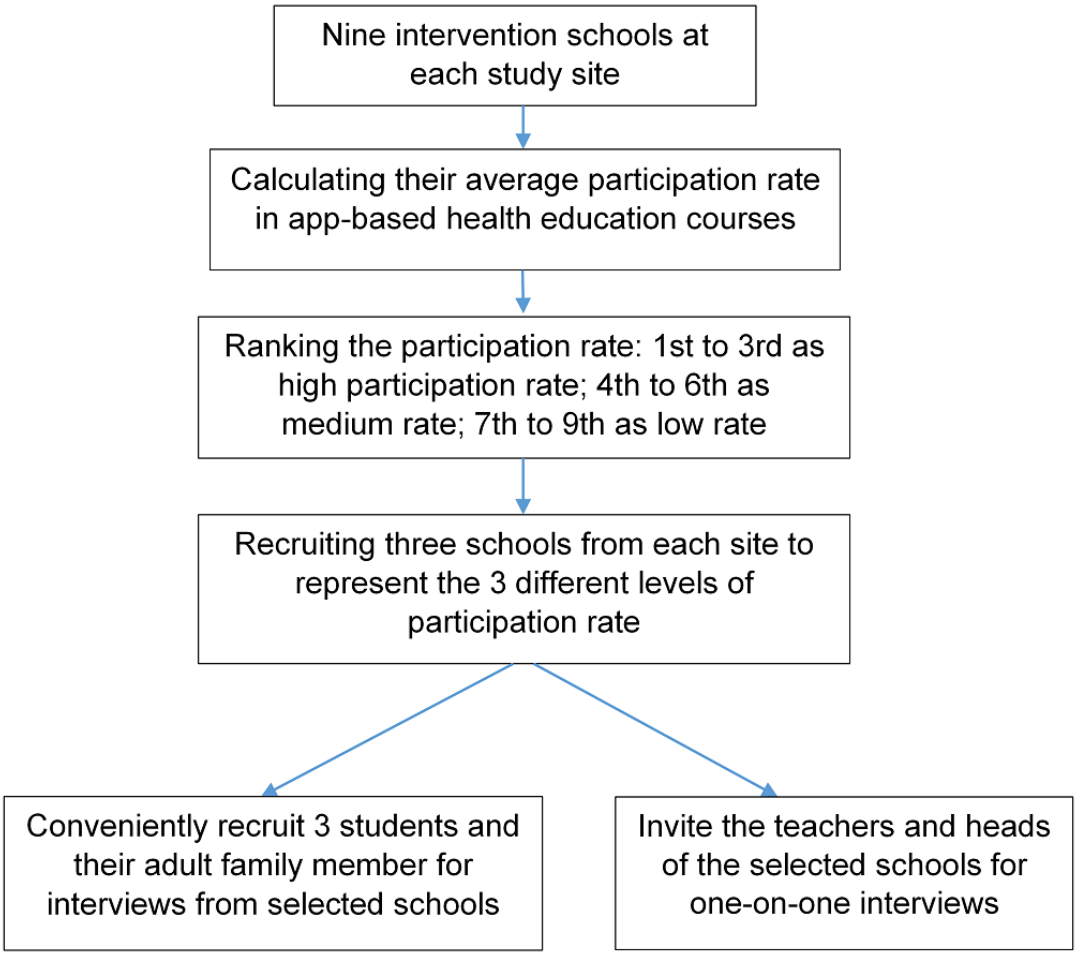
The maximum variation sampling method will be used for selecting intervention participants for interviews [29]. The process of choosing interviewees is shown in Figure 2.

A total of 3 intervention schools will be purposively selected from each site to represent different levels of implementation performance. The primary indicator of implementation performance will be the average participation rate of web-based health education courses, calculated from the app use log. Intervention participants, including students and their family members, will be conveniently recruited from the purposively selected intervention schools. The family member should be the person who installs the app on his or her smartphone. In addition, the teachers and school heads at each selected school will also be invited to participate in an individual interview.

For key stakeholders, we will interview local health and education authorities who are responsible for designing the primary school health education curriculum. The interviewees from these government departments will be nominated and invited by our local program partners. They will be interviewed for potential pathways of promoting salt reduction courses at primary schools for future scale-up. The interview guides are provided in Multimedia Appendix 1.

The interviews will be performed by trained interviewers who are experienced researchers from the George Institute and are not involved in the implementation of the AppSalt program. Key topics of the semistructured interviews will include the experience of intervention participation, difficulties encountered during their participation, suggestions for improvements, and transferability to other settings. All interviews will be audio recorded and transcribed verbatim for analysis. The transcripts will be checked for accuracy against the audio files, and corrections will be made as appropriate.

Figure 2. Process of selecting interviewees from intervention schools.



Data Analysis

Quantitative Data Analysis

The participation rate of app-based health education courses and offline activities will be the key variable to represent participants' adherence to the intervention program. The participation rate will be compared across sites. Descriptive statistics (comparisons of means, medians, or percentage as appropriate) will allow the research team to assess intervention delivery and provide information about the differential implementation rates of the 5 intervention components of the AppSalt program.

Qualitative Data Analysis

Qualitative data analysis will be performed in NVivo12 (QSR) using thematic analysis and following the step-by-step guide to increase its trustworthiness [30,31]. Initially, 2 researchers will individually code the first 10% (9/90) of the transcripts to familiarize themselves with the data and formulate their individual preliminary coding scheme, which should be generated deductively based on the process evaluation framework used to guide this study design [24]. The 2 coders will then discuss their coding schemes to reach a consensus before coding the remaining transcripts. The coding scheme will be discussed and refined iteratively during the coding process. After completing the initial coding of all transcripts, the researchers will search for themes from the patterns of codes. The themes will be generated using a deductive approach following the process evaluation components.

Data Triangulation

The qualitative data will be triangulated with the quantitative data during the interpretation phase to explain the 5 process evaluation dimensions. The preliminary plan for data triangulation is provided in Table 3. The quantitative data will evaluate how the implementation of the AppSalt program is achieved in different settings. The qualitative data will provide complementary information to the 5 evaluation components, which will allow researchers to investigate the in-depth reasons behind the varied implementation performance [32].

Table 3. Preliminary plan of quantitative and qualitative data triangulation.

Evaluation components	Quantitative indicators	Qualitative indicators
Fidelity	Frequency of intervention activities delivered and adaptation of intervention strategies in the process	Perceived level of implementation of key stakeholders, difficulties encountered in the implementation process, and parents' and teachers' feedback on the adaptations
Dose delivered	Number of app-based sessions, activities, and group meetings and intervention tools delivered to the families	Teachers' experience and perception of the program and the difficulty of delivering the activities encountered by teachers and school heads
Dose received	Participation rate of intervention activities, length of viewing health education courses, and salt reduction knowledge received	Participants' experience of the program, including satisfaction and perception of the program, and the most effective intervention module in participants' opinions
Reach	Proportion of eligible students who participated in each intervention strategy, number of dropout, and retention rate	Reasons for participation and reasons for dropping out
Context	N/A[a]	Related contextual factors affecting the implementation of the program, including barriers and facilitators identified by multiple stakeholders

[a]N/A: not applicable.

Results

This study was approved by the Peking University Institutional Review Board (No. IRB00001052-19096) and the Queen Mary Ethics of Research Committee (QMERC2020/22). The AppSalt program has completed its 1-year intervention in 27 selected schools at the end of 2019. The collection of quantitative process data was conducted alongside the intervention. Preliminary analysis of monitoring data was performed during the intervention to optimize the implementation process. Semistructured interviews of participants and key informants were conducted from October 2019 to December 2019. We interviewed 32 parents, 32 students, 9 teachers, 9 school heads, and 8 representatives from the local health and education authority. The audio recordings have been transcribed. Data analysis is currently underway. The results are expected to be published in 2021.

Discussion

Process evaluation is becoming more recognized for its importance in evaluating program implementation and collecting evidence for better research translation [33,34]. This paper presents a mixed methods process evaluation protocol for the AppSalt program, an app-based program among primary school students and their families to translate the previous research evidence of the School-EduSalt program [15].

Salt reduction is challenging in China because of Chinese dietary habits, where the primary source of salt intake is home cooking [35]. The AppSalt program is designed to explore practical and sustainable intervention models for Chinese settings using modern technologies. This program is a complex salt reduction intervention program consisting of 5 intervention modules, which is innovative in its use of mHealth tools for salt reduction in school children and their families. In addition, the AppSalt program will be implemented at 3 study sites of different socioeconomic status. It would be unrealistic to expect perfect delivery of this complex intervention program across different contexts [36]. This process evaluation will help us investigate how this program will be delivered in different contexts and what level of implementation can be achieved by each intervention strategy using a mixed methods approach. The quantitative process data will be readily collected with the electronic intervention management system's assistance during the intervention, which could well represent the real implementation situation [37]. For qualitative data, multiple stakeholders will be interviewed to provide in-depth feedback regarding implementing such a program in the real world [38]. These findings will help researchers refine the intervention design to a replicable model for scaling up.

Nevertheless, we acknowledge the limitations of this study because of some compromises made for time and resource constraints. First, only the intervention group in the AppSalt program will be interviewed. Therefore, potential contamination of the control group and other confounding factors during the intervention process might be neglected. Second, representatives from local health and education authorities will be invited for the interviews by our local research collaborators. This recruitment process might cause some recruitment bias. Third, the interviews will be performed after completing the 1-year intervention, which might cause some recall bias. To minimize potential recall bias, we will conduct all interviews within 1 month after the intervention.

Despite these limitations, this process evaluation of the AppSalt program can help researchers better understand the implementation of the AppSalt program in real-world settings and identify the barriers and facilitators of its implementation. This process evaluation will also make the causal mechanism of the AppSalt program explicit and will provide some experience of a lifestyle intervention for salt reduction in China and other countries.

Acknowledgments

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Authors' Contributions

FH, PZ, YL, and RL designed the AppSalt trial with a process evaluation in mind. YS and RL designed this process evaluation protocol with substantial support from the program management team, especially YL and PZ. YS drafted the first version of this manuscript. All coauthors contributed to the review and approved the final manuscript.

Conflicts of Interest

FH is a member of the Consensus Action on Salt and Health (CASH) group, a nonprofit charitable organization, and its international branch World Action on Salt and Health (WASH) and does not receive any financial support from CASH or WASH. GM is the Chairman of Blood Pressure UK (BPUK), Chairman of CASH, and Chairman of WASH and does not receive any financial support from any of these organizations. BPUK, CASH, and WASH are nonprofit charitable organizations. All other authors have no conflicts interest to declare.

Multimedia Appendix 1
Interview guides.
[DOCX File , 34 KB - resprot_v10i2e19430_app1.docx]

Multimedia Appendix 2
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1174 KB - resprot_v10i2e19430_app2.pdf]

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Abbreviations

BPUK: Blood Pressure UK
CASH: Consensus Action on Salt and Health
mHealth: mobile health
NCD: noncommunicable disease
NIHR: National Institute of Health Research
WASH: World Action on Salt and Health

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Protocol

Tablet-Based Apps for Phonics and Phonological Awareness: Protocol for Evidence-Based Appraisal of Content, Quality, and Usability

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Abstract

Background: The use of mobile apps to manage and promote health is becoming increasingly popular. Mobile apps are gaining popularity particularly in educational and interventional settings owing to their perceived advantages including support for and engagement of individuals with reading difficulties. In the context of COVID-19, the need for technology-based tools has increased. For practitioners and educators who wish to use apps in their practice or recommend apps to individuals with reading difficulties, it is challenging to identify high-quality apps in app stores.

Objective: This protocol describes a systematic search, selection, and appraisal process for tablet apps targeting phonics knowledge and phonological awareness skills. This protocol aimed to (1) provide a systematic method for identifying tablet apps targeting phonics knowledge and phonological awareness skills in the Google Play Store and Apple's App Store and (2) describe an evidence-based approach for quality appraisal of these apps by using structured tools.

Methods: This protocol describes an evidence-based method guided by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework to systematically search, select, and appraise apps targeting phonics knowledge and phonological awareness skills, present in Google Play and the App Store. We intend to perform a systematic and comprehensive search and a 2-step process for screening: (1) broad screening (app titles) and (2) narrow screening (marketing descriptions). Quality appraisal of the included apps will involve two structured appraisal tools: (1) the Mobile Application Rating Scale and (2) the Appraising Apps for Reading Checklist.

Results: This method will help determine the number of apps targeting phonics knowledge and phonological awareness, present on the Android and iOS platforms. The content, quality, and usability of these apps will be determined using structured appraisal tools. We have planned to conduct searches on Google Play and the App Store in January-March 2021; broad and focused screening, from April 2021; and data extraction and quality appraisal in October 2021.

Conclusions: This protocol provides a basis for locating and evaluating apps targeting phonics knowledge and phonological awareness skills. This protocol will support practitioners, educators, and families to make informed decisions when purchasing apps for instructional use.

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KEYWORDS

app; appraisal; characteristics; COVID-19; health management; mHealth; mobile apps; phonics; phonological awareness; quality; reading; usability

Introduction

Mobile Health

Mobile health (mHealth) apps are transforming health service delivery worldwide [1]. mHealth is defined as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices" [1]. More than 5.2 billion individuals worldwide own a mobile device, representing approximately 67% of the world's population [2]. The use of mobile apps to manage and promote health is becoming increasingly popular [3]. Apple recorded 45,478 health care apps in the App Store during early 2020 [4] and a total of 204 billion app downloads in 2019, which equates to US $120 billion on app-related spending [5].

In particular, educational apps have become popular [6]. Considering the enforced remote learning periods during COVID-19, the need for technology-based educational tools has increased. Educational apps are being integrated into the classroom, in speech pathology, and in educational intervention settings owing to their perceived advantages for engaged and interactive learning [7], despite limited information supporting their use [6]. The production and public use of educational apps has overtaken the research that is needed to inform their use, with hundreds of new apps being released on the app stores every day.

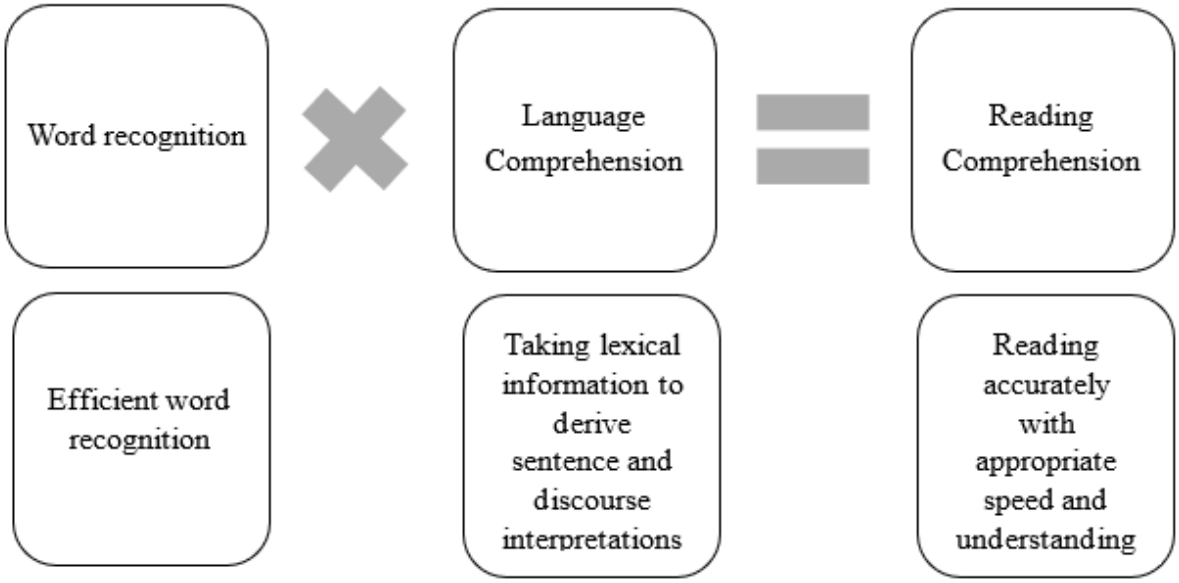
Worldwide, up to 40% of all children experience reading difficulties [8] potentially associated with limited early language and literacy experiences, home background [9], long absences from school [10], low socioeconomic status [11], and ineffective instruction at school [12,13]. Some children with reading difficulties have dyslexia, a specific learning disorder with impairment in word decoding, due to congenital and neurobiological differences [14]. Reading difficulties do not resolve spontaneously [15]; therefore, these individuals require timely, intensive, and explicit evidence-based interventions [11,16]. Emerging evidence suggests that mobile apps can be affordable, accessible, engaging, and effective learning tools for this population.

A systematic review by Griffith et al [17] included 11 studies evaluating outcomes related to letter knowledge, phonological awareness, letter writing, and vocabulary upon using commercially available mobile apps. Of these, 6 studies reported favorable outcomes in the app intervention group, in comparison with a control group (eg, usual classroom instruction, paper-based tasks, or the use of an app for an unrelated goal). Furthermore, Carson [18] investigated the efficacy of mobile apps for literacy among 4-year-old children with developmental language disorder and low emergent literacy skills. This between-groups pretest/posttest study revealed significant improvements in phoneme blending and segmentation and letter-sound knowledge among experimental children receiving instruction with Reading Doctor apps in comparison with control children receiving usual teacher-led emergent literacy instruction [18]. These findings have led to cautious optimism and suggest that mobile apps have the potential to improve student literacy outcomes. However, in the absence of evidence-based recommendations, it is challenging to identify high-quality mobile apps in the app stores. An initial search using terms related to two foundational literacy skills ("phonics" and "phonological awareness") yielded approximately 2933 apps in the App Store and 4128 apps in the Google Play Store. For consumers accessing the app stores, the challenge is not only navigating through the magnitude of available apps but also being able to determine their quality, appropriateness of their content, underlying therapeutic principles, and key features of high-quality apps [17].

The Simple View of Reading

The theoretical framework in this study is the empirically valid Simple View of Reading proposed by Gough and Tunmer [19-21] (Figure 1), which claims that reading comprehension is the product of two equally important components: decoding and linguistic comprehension [22]. Both components weigh equally to achieve reading comprehension [22,23].

Figure 1. The Simple View of Reading.



The focus of this study is on the decoding component of the Simple View of Reading [19], which is defined as the ability to accurately segment and blend the elements within a word to enable an individual to read it. This involves 3 main skills: (1) phonics knowledge, (2) phonemic awareness skills, and (3) word-specific knowledge [24]. Phonics deals with written or printed language [24] and is defined as the ability to decode words, using knowledge of the relationships between letters (graphemes) and sounds (phonemes) [25]. Explicit teaching of systematic synthetic phonics usually occurs separately from text reading by teaching children how to build up words from graphemes. A carefully planned sequence of a small group of graphemes is taught at a time, and then blending is introduced after learning a few phoneme-grapheme correspondences [25]. Phonemic awareness skills are related to sounds in spoken language (unlike phonics, which deals with written language) [24]. Phonemic awareness skills are an essential subset of skills necessary for reading proficiency, falling under the umbrella term "phonological awareness," which refers to "the ability to recognize and manipulate the sound properties of spoken words, such as syllables, initial sounds, rhyming parts, and phonemes" [24]. Word-specific knowledge refers to the knowledge of specific words, based on past experience [24]. This study is focused on the content, quality, and usability of apps targeting phonics knowledge and phonological awareness skills.

Study Objectives

We provide a protocol for a systematic search, selection, and appraisal of apps targeting phonics knowledge and phonological awareness skills. This protocol addresses the following questions:

1. What tablet-based apps are currently available on the Android and iOS platforms to address phonics knowledge and phonological awareness skills?
2. What are the characteristics and features of tablet-based apps for phonics knowledge and phonological awareness skills?
3. How do the characteristics and features of tablet-based apps for phonics knowledge and phonological awareness skills compare to evidence-based principles of instruction according to the Appraising Apps for Reading Checklist (AARC)?
4. How do apps for phonics and phonological awareness rate on the Mobile Application Rating Scale (MARS) indicators of engagement, functionality, aesthetics, information quality, subjective quality, and perceived impact?

Methods

Study Design

Using our previously described method [26], replicated by Vaezipour et al [27], the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework will be used to systematically search and select apps for quality appraisal. PRISMA is an evidence-based framework for reporting systematic reviews and meta-analyses; however, it has previously been adapted and successfully applied to review mobile health apps [27-29].

Sources, Search Terms, and Search Strategy

Both Google Play and the App Store will be searched. These app stores have been chosen because they represent the two largest app stores, containing approximately 2.56 million and 1.85 million apps, respectively, in January-March 2020 [30]. Both app stores are linked to the most widely used operating platforms in the mobile market: Android (Google Play) and iOS (the App Store). These operating platforms accounted for approximately 99% of the global mobile market share in 2019 [31].

Google Play and the App Store will be searched using a selection of predefined search terms. These terms will be entered into the search fields of these 2 app stores, using a Samsung Galaxy Tab A (Google Play) and a 7th generation Apple iPad (the App Store). These terms (Textbox 1) have been defined in consultation with experts in the literacy domain and with consultants at Google and Apple. Preliminary searches on the app stores also contributed to these search terms, including key words obtained from potentially relevant app titles and marketing descriptions. Search results will be filtered by device to only return those items available on a tablet. The search terms include relevant synonyms and layperson terms to account for the wide variety of users accessing the app stores.

Textbox 1. Search terms.

Phonics search terms

- Phonics
- Letters
- Letter sounds
- Alphabet
- Graphemes
- Phonemes
- Vowels
- Consonants
- Initial code
- Phonograms
- Word build
- Reading
- Spelling
- Digraphs

Phonological awareness search terms

- Phonological awareness
- Phonemic awareness
- Phoneme awareness
- Rhyme
- Syllables
- Segmenting sounds
- Blending sounds
- Sounding out words

Eligibility Criteria and App Selection

The selection process aims to identify apps that can be used by individuals with reading difficulties (including children), families, educators, and interventionists to develop phonics knowledge and phonological awareness skills. For this study, the definitions previously provided for the terms “phonics” and “phonological awareness” will be used to guide decisions on app selection in addition to the following inclusion criteria: the app must run on Android or iOS, be available on a tablet, be developed for speakers of English only, be suitable for individuals of all groups (ie, no age restriction), be interactive (ie, it must not involve passive listening or watching of content), and have a word-level focus. The rationale for only including apps with a word-level focus is that explicit teaching of systematic synthetic phonics usually occurs separately from text reading by initially teaching students how to build up words from graphemes. The exclusion criteria are as follows: decodable book apps, apps for nursery rhymes, apps that teach foreign languages, apps providing only assessments, apps targeting only letter names (ie, no corresponding sounds, such as the alphabet song), sight word apps, and apps targeting only letter formation (ie, handwriting).

Our justification for focusing on only tablet-based apps is that tablet sales have exceeded those of computers worldwide owing to their increasing popularity, and students are commonly using tablets in the classroom [32]. In contrast, the use of mobile phones is not permitted in the classroom in numerous educational institutions in Australia, and an Australian policy for all government schools stipulates that mobile phones must be switched off and stored securely during the school day [33].

A review of mobile apps for childhood speech sound disorders reported that apps may be more compatible with tablets than with phones, and that few differences appear to exist between tablet and phone versions of apps, other than their layout, owing to a smaller screen size in phones [29]. These factors informed our decision to only search, select, and appraise tablet-based apps.

A 3-step process will be used to screen the apps: (1) collation of the apps for inclusion in the review, (2) broad screening, and (3) narrow screening.

Collation of Titles Generated by the Search

A research assistant will enter the defined search terms individually into the search field of Google Play and the App Store. Results will be filtered by tablet only. Each search term will be completed in its entirety in one sitting because app listings in the app stores constantly change depending on their relevance, popularity, and the release of new apps. A screenshot of all titles and icons of all sourced apps will be copied into a Microsoft Word document on the basis of the search term from which they were sourced. Titles will then be manually transferred to a Microsoft Excel spreadsheet on the basis of the app store in which they were located. This process is necessary as the app stores prevent copying of app data (including marketing descriptions) from their app stores. Icons will be available for reference in the Word document during screening, in case of ambiguous app titles. Duplicate app titles from different search terms from the same app store will be removed; for example, if the search terms “phonics” and “letter sounds” both yield the same app in the App Store, then one app title will be removed. When a set of app titles appears in addition to the bundle option, the bundle option will be highlighted but not be considered a separate, unique title. Non-English app titles will be removed prior to broad screening.

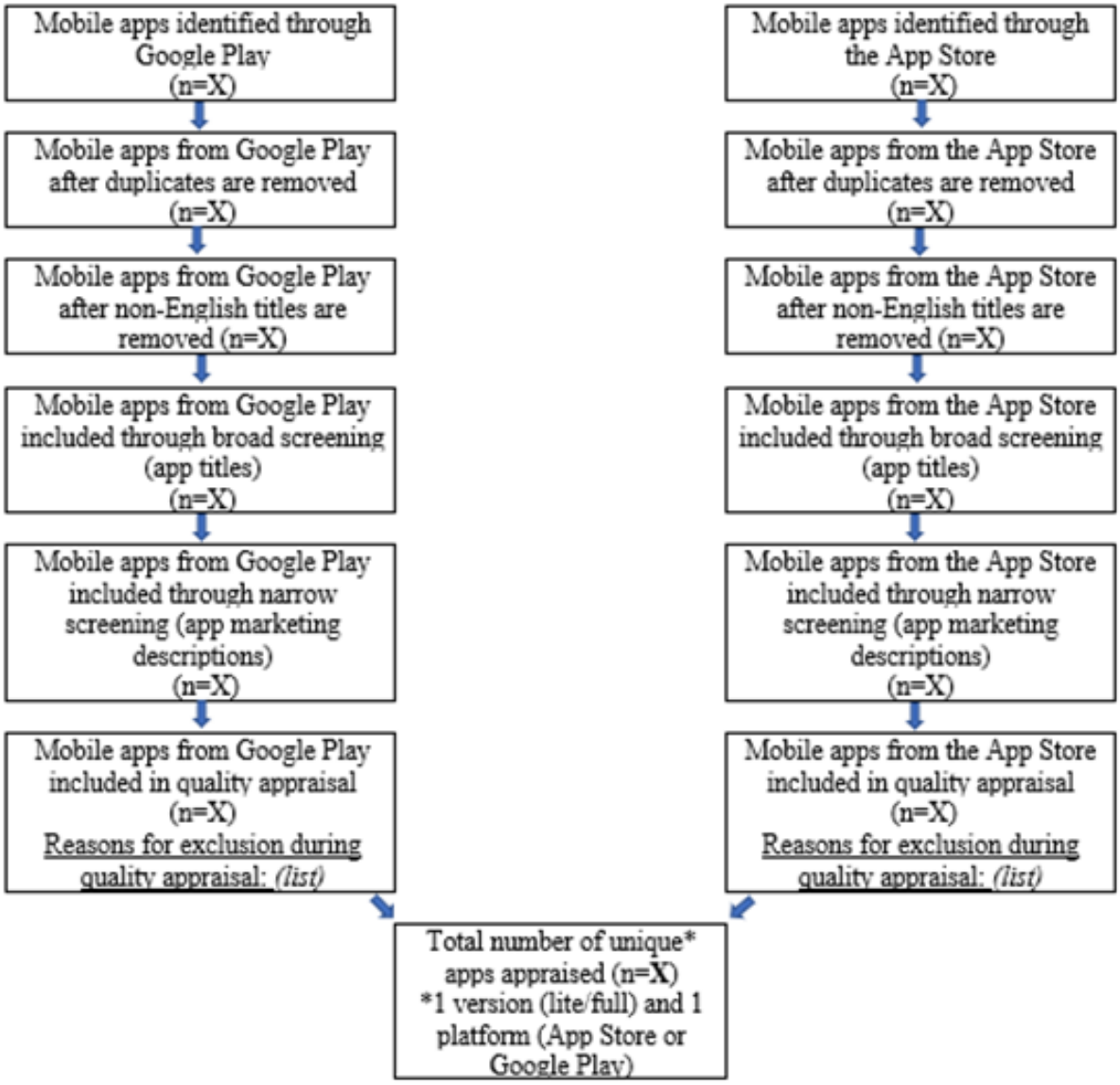
Broad Screening

Titles will be manually screened using Microsoft Excel. Two speech-language pathologists with expertise in the literacy domain will serve as reviewers during broad screening and will manually screen all titles independently and discuss the included apps for subsequent screening. Disagreements between reviewers will be resolved through discussion until consensus is achieved. If consensus cannot be achieved, a third reviewer (a speech-language pathologist with expertise in the literacy domain) will be invited to review the apps in question. A majority rule will determine the inclusion of those apps.

Narrow Screening

Narrow screening will involve the screening of marketing descriptions of apps included during broad screening. Marketing descriptions will be extracted from the app stores by a research assistant and entered into the same Microsoft Excel spreadsheet used in broad screening, alongside the app titles and icons. The reviewers involved in broad screening will independently review the marketing descriptions of the included apps. They will select apps on the basis of the previously described eligibility criteria and discuss those to be included in narrow screening. Similar to broad screening, reviewer disagreements will be resolved through discussion or in consultation with a third reviewer, and a majority rule will determine the inclusion of those apps. Apps finally included after narrow screening will be downloaded for quality appraisal. Figure 2 illustrates the proposed search and selection process.

Figure 2. Search and selection process.



Data Extraction

For complete assessment, apps included after narrow screening will be downloaded on two devices: a 7th generation Apple iPad (10.2 inch, Wi-Fi, 128 GB) and a Samsung Galaxy Tab A (10.1 inch, Wi-Fi, 128 GB). Both tablets will operate on the most recent software version. When individual apps from one developer are available as a bundle, the bundle will be downloaded for cost efficiency. The following app classification data will be extracted from the marketing description and the app store by the first author and entered into a Microsoft Excel spreadsheet: app name and version, search terms used to identify the app, time of the latest update, app update frequency (average), number of updates, ratings for current versions, developers, number of ratings for current versions, cost (basic/upgrade), platform, bundle option, and marketing descriptions. A second reviewer will confirm the accuracy of the data extracted from 20% of the apps.

Data Analysis

The quality of the included apps will be rated by the same reviewers involved in the screening process. Both reviewers will have clinical experience in the literacy domain and familiarity with mobile apps. Each reviewer will test the included apps for 20 minutes per app and rate each app using two structured appraisal tools: the MARS and the AARC. The MARS is a reliable tool for evaluating the quality of mobile health apps. It was developed by an expert multidisciplinary team from the Institute of Health and Biomedical Innovation, Queensland University of Technology [34]. It consists of 4 objective quality subscales using a 5-point Likert scale (engagement, functionality, aesthetics, and information quality). In addition, there are 4 questions related to subjective quality and 6 scales related to the perceived impact of the app on the user's knowledge, intentions to change, and likelihood of actual change on the target health behavior [34].

A review of mobile apps for childhood speech sound disorders [29] reported that a key limitation of the MARS is its evaluation

of an app's potential for behavioral change; that is, how the use of the app is likely to increase or decrease the target health behavior. Based on the 4 objective indicators, an app may achieve a high total MARS score but have limited potential for behavioral change, since the subjective scales and perceived impact ratings are not included in the calculation of the total MARS score [29]. This review identified a need to evaluate various constructs related to the target health behavior objectively and comprehensively. In this study, this would involve evaluating the likelihood that use of the app would improve phonics knowledge and phonological awareness skills in accordance with the predetermined criteria. Other than tools that broadly evaluate the potential of mobile health apps to promote behavioral changes (eg, the App Behavior Change Scale [35]), there are no known or validated tools for specifically evaluating apps for phonics and phonological awareness. As this study aims to recommend apps supporting the development of phonics knowledge and phonological awareness skills, comprehensive appraisal of the content, quality, and usability of these apps is required. This appraisal should consider how the characteristics and features of these apps compare to evidence-based principles of literacy instruction and their potential to facilitate changes in phonics knowledge or phonological awareness skills.

Subsequently, the AARC—a custom-designed 19-item checklist—was developed specifically for this study. The AARC has been designed for educators and practitioners to support decision-making for the selection of apps for use in professional practice and to support the provision of evidence-based recommendations to end-users of apps intended for phonics and phonological awareness. Of the 19 AARC items, a maximum of 15 checklist items contributes to an app's final AARC score. These 15 items are scored as 2 (yes), 1 (mostly), 0 (no), and not applicable (item excluded from the final score calculation). Based on this scoring system, the maximum total possible score is 30 (all 15 items have been rated at 2 ["yes" to all items] for an app). The AARC developers recommend interpreting the final AARC score as a percentage (ie, total points/maximum points × 100) across a continuum; that is, a high percentage would indicate a high-quality app. Furthermore, individual ratings across the AARC items can be interpreted qualitatively. For example, an app might achieve maximum scores of 2 across all 15 items except for items 4 ("Does the app allow the user to change the accent?") and 16 ("Is the feedback or cueing therapeutically beneficial?"), for which it achieves a score of 0. In this example, the rater might consider how important it is for these features to be present in the app when the individual they are working with shares the accent of the voice present in the app and when the interventionist provides live feedback while using the app.

The AARC identifies the target of the app (ie, phonics, phonological awareness, or both) and how the skills are addressed in relation to the scope, sequence, complexity, structure, appropriateness of stimuli, delivery of instruction, practice opportunities, and feedback. The AARC also evaluates the linguistic and phonological accuracy of the app, the interactive features of the app, the potential for independent use of the app, and the likeliness of the app to improve phonics knowledge and phonological awareness skills on the basis of the rater's subjective evaluation. This checklist was developed in consultation with academics with expertise in education (literacy), speech pathology, and mHealth.

The AARC has been piloted independently on 4 apps by two speech-language pathologists with clinical expertise in the literacy domain and mobile apps for literacy. The same overall score was obtained by both speech-language pathologists for 3 of the 4 apps. An analysis of individual AARC items revealed differences between the speech-language pathologists' ratings. Interrater reliability was calculated on the basis of 15 items rated across 4 apps (60 items in total) for which both speech-language pathologists agreed on a rating for 54 items; therefore, the interrater reliability was 90%. The AARC is provided in Multimedia Appendix 1.

In addition to the qualitative ratings, data analysis will also include the evaluation of the total number of apps returned for each search term, the percentage of relevant apps from the yield of each search term (to guide consumers search for apps by knowing which search terms yield the most relevant results), and the correlation between consumer app ratings and ratings assigned by the speech-language pathologists involved in quality appraisal of the included apps.

Results

Google Play and the App Store are intended to be searched in January-March 2021. Broad and narrow screening is expected to commence in April 2021. Data extraction and quality appraisal of the selected apps is expected to commence in October 2021.

Discussion

Principal Findings

This protocol will help identify apps that support the development of two core skills required for decoding: phonics knowledge and phonological awareness skills. Decoding is a key component of the Simple View of Reading (Figure 1) [19]—an empirically valid theoretical model of reading [20,21]. A fundamental task for beginning readers is understanding how printed language maps to their existing spoken language [23]. Automation of the process of decoding facilitates the most efficient route to reading comprehension by allowing children to focus their emerging cognitive resources to extract meaning from text [24]. These rationales support our decision to focus this study on apps for decoding, specifically those targeting phonics knowledge and phonological awareness skills.

It is difficult for consumers to identify mobile apps targeting phonics knowledge and phonological awareness skills, since >7000 apps are available on Google Play and the App Store. This protocol presents and justifies methods to systematically search, select, and appraise apps designed to target phonics knowledge and phonological awareness skills. This method includes a critical evaluation of included apps by speech-language pathologists, using structured appraisal tools. The outcomes of this method will help practitioners, families, and educators make informed decisions when selecting and

recommending apps for phonics and phonological awareness. Furthermore, the outcomes of this method may support the future design and development of apps for phonics and phonological awareness by considering the characteristics and features of high-quality apps presented in this study, in collaboration with key stakeholders such as app developers, educational practitioners, literacy interventionists, and app end-users.

Limitations

This study has some limitations of note. While the search aims to be comprehensive, the authors can only report on apps available at the time of searching and acknowledge the potential for new apps relevant to the study to be released after the search is completed. The study will only report on apps in English, thus limiting the application of this method for non-English apps. Two appraisal tools will be used to evaluate the apps: the MARS [34] and the AARC. While the AARC reportedly has good interrater reliability (90%) based on a pilot of 4 apps, it has not been evaluated extensively; therefore, the psychometric properties of validity and reliability are not available and warrant further assessment in future studies. In this study, the AARC is being used to complement the MARS by providing further information on app content and how this compares to evidence-based principles of literacy instruction, as well as the apps' potential to bring about changes in phonics knowledge or phonological awareness skills. Another limitation of the AARC is the absence of an established quality threshold; however, considering the intended users of the AARC, app quality is expected to be determined from the total AARC score as a percentage across a continuum and by analyzing individual AARC items. Future studies on the AARC are required to establish quality descriptors based on the total AARC score. Finally, the apps will be evaluated by two speech-language pathologists rather than end-users of these apps; however, as professionals who work in the literacy domain and provide app recommendations, the outcomes may support end-user uptake of high-quality apps to support the intervention and instruction provided by educational practitioners and interventionists.

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Authors' Contributions

All authors contributed equally to the conceptualization and design of the protocol. LF wrote the protocol with contributions and feedback from all coauthors. LF and TS designed the protocol in consultation with all coauthors. All authors reviewed and approved the final protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The Appraising Apps for Reading Checklist.
[DOCX File , 34 KB - resprot_v10i2e23921_app1.docx]

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Abbreviations

AARC: Appraising Apps for Reading Checklist
MARS: Mobile Application Rating Scale
mHealth: mobile health
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Design of a Game-Based Training Environment to Enhance Health Care Professionals' E–Mental Health Skills: Protocol for a User Requirements Analysis

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Abstract

Background: E–mental health (EMH) offers various possibilities for mental health care delivery, with many studies demonstrating its clinical efficacy. However, the uptake of EMH technologies by mental health care professionals remains to be low. One of the reasons for this is the lack of knowledge and skills in using these technologies. Skill enhancement by means of serious gaming has been shown to be effective in other areas but has not yet been applied to the development of EMH skills of mental health care professionals.

Objective: The aim of this paper is to describe a study protocol for the user requirements analysis for the design of a game-based training environment for mental health care professionals to enhance their skills in EMH.

Methods: The user requirements are formulated using three complementary outputs: personas (lively descriptions of potential users), scenarios (situations that require EMH skills), and prerequisites (required technical and organizational conditions). We collected the data using a questionnaire, co-design sessions, and interviews. The questionnaire was used to determine mental health care professionals' characteristics, attitudes, and skill levels regarding EMH and was distributed among mental health care professionals in the Netherlands. This led to a number of recognizable subuser groups as the basis for personas. Co-design sessions with mental health care professionals resulted in further specification of the personas and an identification of different user scenarios for the game-based training environment. Interviews with mental health care professionals helped to determine the preferences of mental health care professionals regarding training in EMH and the technical and organizational conditions required for the prospective game-based training environment to be used in practice. This combination of requirement elicitation methods allows for a good representation of the target population in terms of both a broad view of user needs (through the large N questionnaire) and an in-depth understanding of specific design requirements (through interviews and co-design).

Results: The questionnaire was filled by 432 respondents; three co-design sessions with mental health care professionals and 17 interviews were conducted. The data have been analyzed, and a full paper on the results is expected to be submitted in the first half of 2021.

Conclusions: To develop an environment that can effectively support professionals' EMH skill development, it is important to offer training possibilities that address the specific needs of mental health care professionals. The approach described in this protocol incorporates elements that enable the design of a playful training environment that is user driven and flexible and considers the technical and organizational prerequisites that influence its implementation in practice. It describes a protocol that is replicable and provides a methodology for user requirements analyses in other projects and health care areas.

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KEYWORDS

mental health; skill development; eHealth; games; user-centered design

Introduction

Background

Technology can offer significant benefits to mental health care delivery. This includes lowering the threshold to seek help, the possibility of more time- and place-independent health care delivery, and the enhancement of patients' autonomy [1-3]. Despite the proven efficacy of technology in mental health care [2,3], the uptake of technology among mental health care professionals has remained slow [4-6]. The threshold may even be higher in mental health care than in other health care areas where technology is introduced [7]. This may be because of the focus on the interpersonal relationship between a client and a therapist, where the need to create rapport is high but the perceived possibility to establish this using eHealth remains low [8]. This creates the need to take action to address the causes of these barriers and give room to the potential benefits of technological innovations in mental health care and in other health care areas. Scientific research on the factors that influence the uptake of eHealth reveals that this is dependent on factors such as the characteristics of technological innovation, the internal and external context of the organization, the characteristics of the health care professionals, and the way the implementation process is managed [9]. This also applies to the use of eHealth tools in mental health care, hereafter referred to as e–mental health (EMH) [4,10,11]. One of the most important factors hampering the adoption of EMH by mental health care professionals concerns the lack of knowledge and skills of mental health care professionals in effectively finding and using web-based technologies [8,12-14]. The skills that enhance the ability of health care professionals to effectively use EMH tools include, besides having general digital skills, the use of different communication approaches (eg, compensating for the lack of nonverbal cues and contextual information), choosing the appropriate digital communication channels in each situation, handling boundaries in web-based contact, and knowledge about up-to-date technological possibilities [13,15,16]. In other words, to increase the adoption of EMH, mental health care professionals need to find opportunities to enhance these different skills. To achieve a sense of self-efficacy among mental health care professionals to use EMH, a potential strategy is to offer mental health care professionals training possibilities based on the concept of serious gaming [17].

Serious Games for Skill Enhancement

Games are usually seen as a leisure activity in which the main aim is to entertain the user. Serious games are (digital) games that are applied for purposes other than entertainment [17-20]. There is usually an educational purpose that is offered in a playful and engaging way [17,19]. Serious games are increasingly used for training in several areas, for example, in aviation, in the military, and in various health care disciplines [20]. The effectiveness of using serious gaming elements in training has been demonstrated in a number of studies [17,21]. One of the most important advantages of using serious gaming elements is that it offers the possibility to learn by gaining new hands-on experiences, instead of merely reading or hearing about it [21,22]. In addition, adding serious gaming elements to regular training methods offers a unique combination of simultaneously educating and engaging users [23]. Furthermore, serious games have multiple learning outcomes (eg, cognitive skills, motor skills, affective learning outcomes, and communicative learning outcomes) that cannot always be gained through more traditional learning methods [24]. Several studies have shown that serious gaming is an effective method for training health care professionals [17]. Examples are simulations to practice surgery, games to practice diagnostic reasoning, and quizzes to practice knowledge about pathology. Wang et al [17] conducted a review that showed that overall serious gaming as a training or learning tool is growing in different health care areas and that most studies included in the review report about this as an effective way for skill development. The characteristics of serious gaming (ie, an engaging form of education, enabling hands-on experiences, engaging, and serving multiple learning outcomes) and the proven effectiveness for training health care professionals are strong arguments to believe that providing serious game–based training to mental health care professionals can be an effective way to enhance their skills in using EMH. In addition, serious games offer a safe and social environment to develop skills in multiple situations and for multiple purposes that could otherwise be difficult, expensive, or unethical to experiment with in a real therapeutic setting [25,26]. Such training possibilities have not been designed yet specifically for mental health care professionals.

The Identification of the User Requirements

To address such a design challenge, the first step is to identify the user requirements that such an environment should meet. By addressing these needs, professionals are more likely to engage in and benefit from the game-based training possibilities that are offered [27]. Having a clear picture of user needs regarding the innovation or, in other words, answers to the questions "For whom are we developing this product?" and "Why would someone want to use this specific tool?" is essential for users to eventually adopt an innovation [27]. On the basis of the assumption that real-life situations should be at the forefront of the design process, the interaction between users and designers within this process is crucial to make decisions about the design. Therefore, end users should be actively involved from the beginning [28-32]. Before a first prototype can be designed, it is important to determine the core functionality of the innovation and how it can become a meaningful solution by establishing the perspective of the target user group [33-35].

Objective

This study protocol describes research to define the user requirements for a serious game–based training environment for mental health care professionals to train their EMH skills. The user requirements analysis resulted in three complementary outputs: personas (lively descriptions of potential users or user groups), scenarios (a detailed description of situations that require EMH skills), and prerequisites (the required technical and organizational conditions). This protocol describes the methods used to deliver these 3 outputs and can be used for similar projects in (mental) health care by providing a detailed description of the procedures in a user requirements analysis.

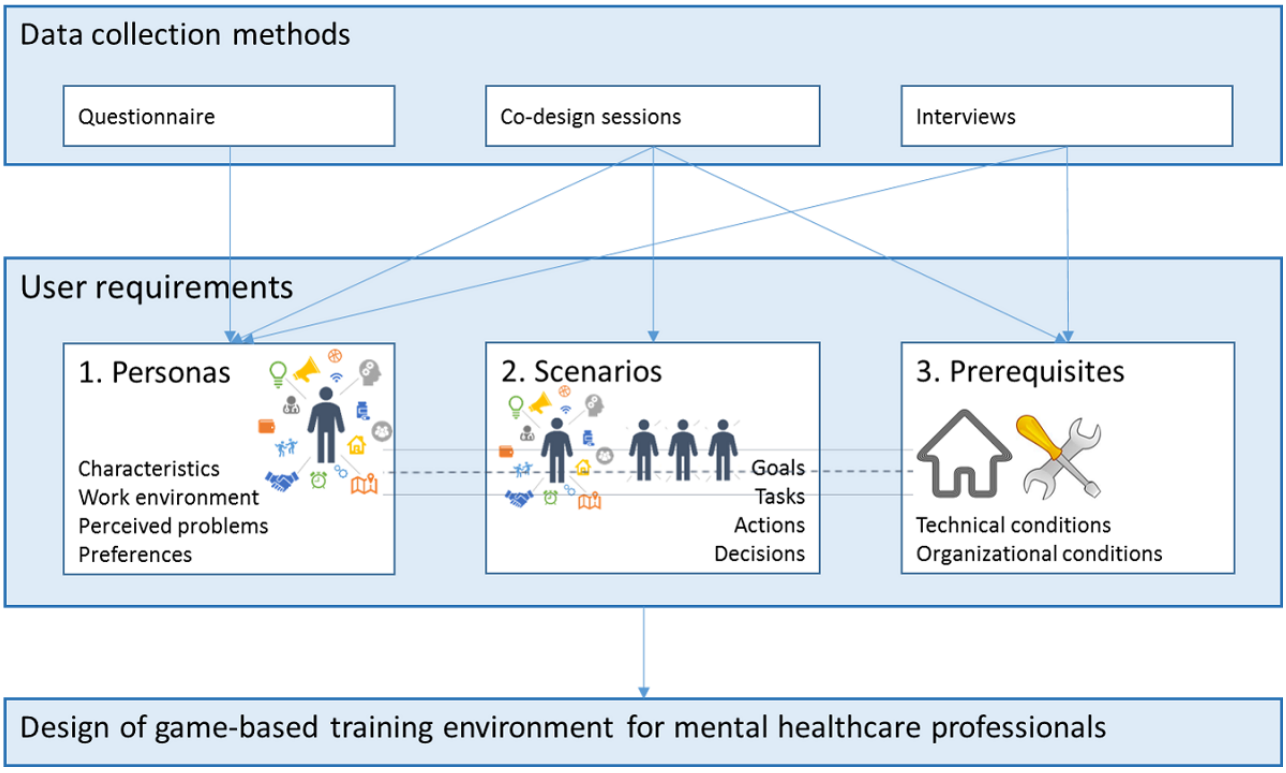
Methods

Study Design

Multiple Methods

This study entails an explorative research design using quantitative and qualitative methods: a questionnaire, co-design sessions, and interviews. The multiple methods approach adopted here incorporates the use of two or more different methods in one study. Unlike a mixed methods design, it does not depend on the integration of data gathered from the different methods, rather provides space to a variety of methodological combinations [36-39]. In this study, a multiple methods design is a more suitable approach as the different methods address different questions, and it would therefore be difficult to truly integrate the data. First, a questionnaire was used to explore the relevant characteristics, work contexts, and practices of mental health care professionals. This includes their attitude and acceptance regarding EMH and respondents' experienced skill levels to use EMH in their clinical practice. The data provided insights into a wide variety of different and sometimes conflicting user needs. Following this, we grouped user needs to identify a number of different user types within the end user group (mental health care professionals). This provides information about possible differences in user needs regarding a game-based training environment. In addition, mental health care professionals participated in a co-design session to gain a more detailed understanding of the work context of mental health care professionals and the general needs and preferences they have in relation to a game-based training environment. Parallel to this, mental health care professionals were interviewed about specific individual needs regarding a game-based training environment. Subsequently, 2 more co-design sessions were held to develop specific user scenarios for a game-based training environment. This multiple methods approach generates a more in-depth and specific understanding of the requirements, because the data collection identifies different types of end users, with different needs, skill levels, and preferences regarding a game-based training environment (Figure 1).

Figure 1. Study design: multi output approach.



Quantitative and Qualitative Data Collection Methods

The use of both quantitative and qualitative methods for identifying user requirements is grounded in the literature about the development of personas within the context of interaction design [40,41]. In his seminal book *The Inmates Are Running the Asylum*, Alan Cooper [42] introduced the use of personas as a practical design tool. While the Cooper method was originally more qualitative in nature, Pruitt and Grudin [43] used a mix of quantitative and qualitative data to identify and describe user needs. In a later stage, Cooper also added quantitative research to the development of personas [41].

Conducting quantitative research can be seen as an efficient way to assemble as much reliable data as possible [43]. However, in general, there also appear to be many difficulties in the interpretation of this quantitative data for the purpose of distinguishing user groups and truly understanding user needs [42,43]. Therefore, in this study, we combined quantitative and qualitative methods that led to results that are (1) highly representative because of the large and varied number of respondents that can be reached (questionnaire), (2) in depth and specific about the different types of users and their needs in a game-based training environment (interviews), (3) an integration of different user perspectives into a common understanding of the design requirements (co-design session), (4) useful for a number of different scenarios that promote the game-based training environment to fit in the clinical practice of mental health care professionals (co-design sessions), and (5) useful for a specification of the technical and organizational prerequisites that need to be met to foster a successful implementation of the envisioned environment (interviews).

The multiple methods design generates a specification of the requirements in terms of personas, scenarios, and technological and organizational prerequisites (Figure 1), which are commonly used aspects within user requirements specifications [43-47]. In this study, these aspects are used as complementary outputs.

Outputs: Personas, Scenarios, and Prerequisites

By developing *personas*, designers try to understand the different types of users and what drives them, in order to truly empathize with them and connect to their needs in the design process [46-48]. Personas are lively and concrete descriptions of potential end users, made by adding attributes to a number of identified subgroups within the potential user group of a product [43,48,49]. In these personas, users' characteristics and possible goals and needs regarding the achievement of these goals are described and the way in which these differ between the subgroups [43,47-51]. In this study, personas are described by (1) the characteristics of the professionals (age, gender, work experience, and educational level); (2) their work context and practices, including the type of patients they see, the type of interactions these professionals have with their patients, and the situations that they come across that could be supported by using EMH; (3) the perceived potential value and actual adoption of different EMH applications for therapeutic interactions with their patients (attitude) in relation to their current skills regarding the use of these different tools; and (4) their preferences, that is, their ideas about how to acquire these skills and increase their use of EMH. By creating *scenarios*, designers are able to create story lines, related to the personas, for the content development of a game-based training environment [52,53]. These scenarios incorporate details about different situations in which mental health care professionals potentially use EMH. Such scenarios can also be seen as the situation a persona *walks through* [50]. This entails a description of several scenarios that specify the expected benefits of a variety of EMH tools (goals), a step-by-step description of the process (tasks), the execution of these steps (actions), and the decisions mental health care professionals make in these situations. Each scenario ends with a conceptual idea of how a solution can be designed within the game-based training environment that addresses that specific situation. Furthermore, the data collection generated knowledge about the issues that need consideration when transferring from design to implementation in terms of the *technical and organizational prerequisites* that influence users' (mental health care professionals) intention to actually make use of a game-based training environment. This offers a more holistic perspective on the process by not only focusing on the end user but by also considering what is needed from other stakeholders, such as managers and Information and Communication Technology departments [44,45]. This delivered a set of prerequisites related to the design, content, and facilitation by the organization, which are required to launch the game-based training environment.

Recruitment

To ensure a good representation of the target user group for each data collection method, professionals from various disciplines that are involved in the direct care delivery process within mental health care were included in the research. The structure of mental health care professions that was officially acknowledged by the Dutch Health Care Authority was used to determine these disciplines, leading to the following clusters of professionals: medical professionals, psychotherapists, psychologists, nursing professionals, social workers, expressive therapists, and paramedical professionals in mental health care. Professionals working in mental health care that are not directly involved in client care (eg, technical support, finance employees, housekeeping) are not likely to use EMH and are therefore not included in this study. The research population that was approached represents the primary users of EMH and therefore the users of the anticipated training environment. This enhances the accessibility of the intended training environment for professionals from multiple disciplines within mental health care with a variety of skill levels and subsequent training needs. In the following sections, the recruitment strategy for each data collection method is specified.

Questionnaire

Respondents for the questionnaire were recruited directly at 5 large mental health care organizations in the Netherlands. Furthermore, respondents were recruited through web-based communication platforms of professional associations from different disciplines in mental health care specified earlier. Owing to the explorative nature of this questionnaire, we were not able to execute a statistical power analysis to define a sample size aim. According to Daniel [54], the sample size determination largely depends on the research design. For exploratory research focusing on a single topic and being performed at a national level, which is the case for our questionnaire, a general rule of thumb is that one should have at least 400 respondents [54]. The sample size in our study of 432 respondents complies with the recommendation by Daniel [54]. The responses were collected over a period of 3 weeks for each participating organization. Respondents initially received a message to complete the questionnaire in 2 weeks. After 2 weeks, a reminder was sent to the potential respondents of the 5 participating mental health care organizations, which allowed for 1 week additional response time. The introduction of the questionnaire informed respondents about the purpose of the

research project and the protection of their personal data and provided an informed consent button.

Co-Design Sessions

To contribute to the description of users and ideas about a game-based training environment from multiple viewpoints, a co-design session was organized involving 9 participants, including mental health care professionals, EMH supporting staff, designers, and researchers. In recruiting participants for this first co-design session, maximum variation purposive sampling was applied using *profession* to maximize the variation. This led to the inclusion of mental health care professionals from a broad range of mental health care disciplines in the sample (eg, psychologists, psychiatrists, nurses, etc) with various levels of adoption of EMH [8] and subsequently a variety of needs regarding knowledge and skill enhancement. Around 6 to 10 participants are considered optimal for a focus group with maximum variation; however, it depends on the context [55]. Although we intend to develop a training environment that is usable for different disciplines in mental health care, we included 9 participants for maximum variation. The participants were recruited at GGzE, a mental health care provider in the southern part of the Netherlands. GGzE is also a partner in this project and a committed stakeholder in the co-design process. The participants were invited by email and were informed about the purpose of the study. When participants agreed to participate, they received more specific information and informed consent forms that they needed to sign when they decided to join. For the 2 co-design sessions that were aimed at developing scenarios for our game-based training environment, we used an expert purposive sampling method in which the same participants took part in each of the sessions to build on the ideas that were expressed earlier. The experts represented the users of the game-based training environment (n=3), game developers (n=3), innovation experts (n=2), and researchers (n=2).

Interviews

The interviewees were also selected using a maximum variation purposive sampling strategy and were also recruited at GGzE. We aimed to recruit between 15 and 20 interviewees to guarantee maximum variation in profession and level of adoption of EMH. The interviewees were approached through email. Upon written confirmation of their intended participation, an interview was scheduled. The interview started with a short explanation of the purpose and procedure of the interview and the interviewees were asked if they agreed to the recording of the interview. Upon confirmation, the interviewees were asked to fill in an informed consent form. After 17 interviews, we found that no new data were collected and that data saturation was reached.

Data Collection Procedures

Questionnaire

To determine mental health care professionals' characteristics, attitude, use, and skill levels on different EMH tools, a questionnaire was developed that uses the current state of the art in EMH and relevant literature on EMH adoption, literacy, and skills [8,12-14]. The questionnaire (Multimedia Appendix 1) started with a general introduction and informed consent. Subsequently, a definition of EMH was given that underlies the different questions that followed. The respondents were then asked to answer 7 questions regarding their adoption of EMH, the type of clients they see, the type of treatments they provide, and the extent to which they think EMH is beneficial to these types of clients and treatments (Multimedia Appendix 1, questions 1-7). These questions were followed by 3 questions where the respondents were asked to self-assess their skills regarding EMH on a scale from 1 to 5 (Multimedia Appendix 1, questions 8-10). General skill levels and specific levels for different types of skills (eg, digital skills, communication skills, etc) were measured. Then the respondents were asked to score 29 statements (Multimedia Appendix 1, question 11) regarding their attitude, beliefs, and perceptions on EMH on a Likert scale from 1 to 5. Finally, 8 general background questions were posed (Multimedia Appendix 1, questions 12-19) with the purpose of gathering descriptive information about the population's characteristics and their work environments (eg, age, gender, work experience, type of organization, profession).

Co-Design Sessions

In the first co-design session (March 2018), the aim was to generate a common understanding about mental health care professionals' work context and detailed descriptions of the client trajectories that they encounter. Furthermore, the possibilities of applying EMH in this context and their need for knowledge and skill enhancement regarding EMH were identified and discussed. Participants were asked to jointly reflect on these insights and translate this in to ideas for a game-based training environment. This co-design session took 3 hours and demanded no preparation time for the participants. During the session, cards were used to reflect different possible treatment situations, to support participants in *drawing* a client journey. Following this, scoring cards were used on which participants could indicate in which situations EMH tools could be valuable. Finally, the participants were asked to use drawing and crafting materials to visualize their ideal game-based training environment. The 2 co-design sessions that were aimed at developing scenarios (December 2019) took place after analyzing the data from the questionnaire, interviews, and the first co-design session, which means that information about the potential users of the game-based training environment, or the *persona*, was available. In the 2 co-design sessions aimed at scenario development, further elaboration took place regarding story lines that could serve as a basis in a skill-developing game. The session was led by a facilitator, and participants were asked to brainstorm in small groups about different story lines in which a mental health care professional treats a fictional client. Afterward, the different results of the 3 groups were discussed and used by the design team to create 2 story lines. These 2 story lines were refined in a second co-design session in which mental health care practitioners were asked to reflect in detail on the stories that were drawn by the designers.

Interviews

The interviews consisted of 2 parts. The first part of the interview was used to gather in-depth information about the specific needs and preferences of mental health care

professionals regarding skill enhancement in EMH. This in-depth information was added to the questionnaire data by making more elaborate descriptions of the user groups resulting in personas. These detailed descriptions of the users of the envisioned game-based training environments enable designers to make choices that strongly align with the needs of mental health care professionals. The second part was aimed at identifying the technical and organizational prerequisites to use this environment. The interviews were semistructured to allow for exploring different views on what is needed to develop and implement the envisioned training environment. The topic list was based on the literature on technology acceptance [56] and game-based learning [57,58]. The first questions covered the respondents' general view on EMH, their current use of EMH, and their experienced skill levels. Subsequently, items were discussed regarding their learning goals on using EMH and how they would perceive a game-based training environment as a tool to enhance their EMH skills. Finally, questions were asked about technical and organizational requirements that should be met to successfully implement such an environment. The topic list was reviewed by another researcher and slightly adapted. After 2 interviews, minor changes were made to the topic list based on the perceived interview flow. The interviews were conducted between May and November 2018.

Data Analysis

Questionnaire

On the basis of the data gathered through the questionnaire, the users could be clustered into a number of subgroups based on shared characteristics that were found in the data. From the literature, we know that there are differences in the perceived drivers and barriers to using innovations [8]. It is therefore important to capture these differences and to understand the important variations that may influence the choices made in developing a game-based training environment. This identifies different possible user groups that may lead to a variance in the solutions offered to serve the target population. Clustering the data is a mode of variance testing that enables us to capture these differences. Clustering can be performed based on a key differentiator that is determined a priori [48-50] or the clusters can flow from the data without appointing specific variables that should determine the clusters [59] or a combination of both in multiple iterations [49,60]. In this study, we used a combination of both approaches in a 2-step analysis: (1) by performing a statistical cluster analysis [61] to identify the number of subgroups in the data set and (2) by performing an analysis using descriptive statistics (eg, frequencies and crosstabs) to identify the detailed characteristics of these user groups and determine whether changes should be made in the initial clustering. In this second iteration, the levels of adoption of EMH [8] were used as a key differentiator to assess the subgroups. Data on the perceived value of EMH and the assessment of different EMH tools, the skill levels, and the type of skills that professionals feel they need to acquire were attributed to the different subgroups. The results of both clustering methods were synthesized, after which the prefinal subgroups were determined based on the variance within the data. Qualitative data forthcoming from the co-design sessions and interviews led to the final clustering solution.

Co-Design Sessions

The co-design sessions were recorded using a video camera, microphone, and live note-taking. The recordings and observations were organized and analyzed using thematic coding [62]. Thematic coding is used to cluster qualitative data according to predefined, often theoretically driven, themes by organizing and analyzing the data [62]. It is a useful method to gather information on experiences, viewpoints, attitudes, and social phenomena [62]. In this study, themes were determined based on the purpose of the analysis. For the first co-design session, the purpose was to gather more in-depth information about mental health care professionals' context and their ideas and perspectives on a game-based training environment for EMH. This resulted in the following main themes: client journey, valued EMH tools, self-assessed skills, perceived learning needs, and game requirements. The second and third co-design sessions were aimed at developing scenarios that led to an approach in which the themes were derived from the elements that constitute a scenario or story line. These elements are the main goal or purpose of a game-based training environment, the tasks and actions that are important for mental health care professionals in their health care delivery, and the situations in which a decision may take place on whether to use EMH. The main themes for each type of co-design session were broken down into a number of elements that contributed to the relevant knowledge (subthemes). The data of the co-design sessions were coded according to these subthemes. Next, based on all different codes, the initial themes were reassessed and combined until all data were accurately attributed to the different themes. The data of the first co-design session were combined with the data of the questionnaire and were processed into the initial user requirements document. This was done by a junior researcher and checked by a senior researcher. The results of the second and third co-design sessions were used to further specify specific game requirements and to decide on the type of solution and content. This part of the data analysis was performed in cooperation between developers and researchers.

Interviews

The interviews were recorded (only with explicit permission from the respondent) and were transcribed verbatim. The transcripts were then coded using a thematic coding method and appropriate software for qualitative data analysis [62]. This is in congruence with the overall hybrid research design and with the analysis method that was applied for the co-design sessions. The analysis complemented the needs and requirements analysis by finding users' perspectives regarding a game-based training environment. Established theory [57,58] was used to define the scope and themes, and at the same time, full space was given to the participants to add to this theoretical knowledge from a more practice-based viewpoint. Thematic coding consisted of a first round of open coding in which the main themes were derived from the data using an open coding approach. These main themes were technical requirements, social requirements, personal factors, managerial requirements, and game requirements. Following the first round, a second coding round was used to find subthemes within the main themes. Examples of subthemes are *perceived ease of use* (technical requirements) and *affinity with computers* (personal

factors). The analysis in different coding rounds was conducted by a junior researcher, after which the codes were checked by a senior researcher.

Outputs

The data analysis resulted in 3 outputs: personas, scenarios, and prerequisites. These were used to describe the user requirements of the game-based training environment in the design documents. Personas were developed based on data from all 3 sources, scenarios were developed based on co-design sessions, and the prerequisites were based on data from the interviews.

Results

The research protocol was approved by the Ethical Review Board of Tilburg University in April 2018. At the time of writing this paper, the questionnaire was distributed, 432 people had responded, and the results were available for the design process. A co-design session was conducted to define specific contextual information (n=9) and 2 co-design sessions (n=10) were held to develop the scenarios. The interviews (n=17) were conducted, and the data were analyzed. We aim to report these findings elaborately in a scientific paper describing the results of the user requirements analysis in 2021. The unpublished results are currently used to inform the design process of a game-based training environment.

Discussion

Main Discussion of the Protocol

Digital tools are currently underused in mental health care. This is because, in part, of a lack of knowledge, skills, and sense of self-efficacy of mental health care professionals when engaging with a wide variety of available EMH tools. To address this challenge, we are in the process of developing a game-based training environment that offers safe and engaging ways to explore digital tools and become more proficient at their use.

This protocol describes the research and design methods and processes aimed at developing the requirements for such a game-based training environment. This study protocol contributes to an understanding of how user requirements analysis for a game-based training environment in mental health care can be carried out using synthesized expertise from social sciences, clinical practice, and design sciences. To establish this study protocol, researchers from these different disciplines are needed to closely interact to create common ground about the purpose and approach of the project. Knowledge about design thinking [27-29] yields valuable insight into design processes and how to perform research in support of such design processes (eg, a user requirements analysis). The perspectives of social sciences and clinical practice are combined to generate insight into human attitudes and behaviors when confronted with the introduction of technology in mental health care. This resulted in an approach that combines these perspectives to identify user requirements.

While a user requirements analysis in itself is more common in design research, in this protocol, it describes how to approach such an analysis in a health care area where such approaches are rather novel. This has led to a more specific approach that also reflects on the elaborate interactions between researchers in different areas. Although this protocol describes a user requirements analysis for mental health care, it may also be very useful in other projects in mental health care and in health care areas where similar research and design questions may be at hand.

This protocol is particularly valuable because of its holistic approach, in which complementary outputs are proposed. In this multioutput approach, the development of personas and scenarios play an important role in describing users' needs. More traditional ways of describing user needs are often too generic to fit a variety of potential users of a product [40]. Personas and scenarios allow for differentiation in describing the user group, where distinctive characteristics and situations are used to determine the specific requirements in the design of a product [52,53]. By complementing the personas and scenarios with the technical and organizational preconditions (prerequisites), a more holistic approach is provided to start the design process [45]. The benefits of such a multioutput approach have been discussed in several research papers [43-47]. For example, it is pointed out that personas and scenarios can serve as an interface between the design model and the user model, providing the design team information about users' goals, skills, and needs and the specific context (ie, treatment situations and organizational context) they are operating in [43-47].

Furthermore, this line of thinking can support multidisciplinary teams in understanding user needs early on in the design process [28,29,31]. Another benefit is the articulation of the *why* of a product in an environment where design thinking is not commonly applied [46]. Owing to the multidisciplinary nature of the research project, we hope that our effort to describe the research approach will contribute to the credibility and reproducibility of this kind of research approach, particularly in health care settings [63-65]. With this protocol, we also aim to contribute to the production transparency and analytic transparency in qualitative research, particularly in design research. To this end, we have transparently reported the aim, methods, and procedures that are used, thereby improving the possibility for the research community to scrutinize the research [63-65] and adopt relevant methods and procedures within their own qualitative research setting. Besides the research community, this particular research project itself benefits from this protocol, as it has added to the common understanding of the purpose of the project and to a shared research approach.

Conclusions

The envisioned game-based training environment offers an approach that is simultaneously safe, challenging, and engaging. It particularly aims to enhance a number of relevant 21st-century skills that mental health care professionals increasingly need, in addition to their clinical skill set: media and technology literacy, web-based communication skills, flexibility, collaboration, and technology self-efficacy. To develop an environment that can lead to a significant improvement in professionals' EMH skills, it is important to (1) address real-world issues that mental health care professionals experience and (2) offer training possibilities that address their

specific (individual) needs. The approach described in this protocol incorporates elements that enable the design of a product that satisfies these needs. It is user driven and flexible; at the same time, it considers contextual factors that influence its implementation in practice.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire (Dutch).
[DOCX File , 59 KB - resprot_v10i2e18815_app1.docx]

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Abbreviations

EMH: e–mental health

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Protocol

Perspectives Toward Seeking Treatment Among Patients With Psoriasis: Protocol for a Twitter Content Analysis

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Abstract

Background: Psoriasis is an autoimmune disease estimated to affect more than 6 million adults in the United States. It poses a significant public health problem and contributes to rising health care costs, affecting people's quality of life and ability to work. Previous research showed that nontreatment and undertreatment of patients with psoriasis remain a significant problem. Perspectives of patients toward seeking psoriasis treatment are understudied. Social media offers a new data source of user-generated content. Researchers suggested that the social network Twitter may serve as a rich avenue for exploring how patients communicate about their health issues.

Objective: The objective of this study is to conduct a content analysis of Twitter posts (in English) published by users in the United States between February 1, 2016, and October 31, 2018, to examine perspectives that potentially influence the treatment decision among patients with psoriasis.

Methods: User-generated Twitter posts that include keywords related to psoriasis will be analyzed using text classifiers to identify themes related to the research questions. We will use Symplur Signals, a health care social media analytics platform, to access the Twitter data. We will use descriptive statistics to analyze the data and identify the most prevalent topics in the Twitter content among people with psoriasis.

Results: This study is supported by the National Center for Advancing Translational Science through a Clinical and Translational Science Award award. Study approval was obtained from the institutional review board at the University of Southern California. Data extraction and cleaning are complete. For the time period from February 1, 2016, to October 31, 2018, we obtained 95,040 Twitter posts containing terms related to "psoriasis" from users in the United States published in English. After removing duplicates, retweets, and non-English tweets, we found that 75.51% (52,301/69,264) of the psoriasis-related posts were sent by commercial or bot-like accounts, while 16,963 posts were noncommercial and will be included in the analysis to assess the patient perspective. Analysis was completed in Summer 2020.

Conclusions: This protocol paper provides a detailed description of a social media research project including the process of data extraction, cleaning, and analysis. It is our goal to contribute to the development of more transparent social media research efforts. Our findings will shed light on whether Twitter provides a promising data source for garnering patient perspective data about psoriasis treatment decisions. The data will also help to determine whether Twitter might serve as a potential outreach platform for raising awareness of psoriasis and treatment options among patients and implementing related health interventions.

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KEYWORDS

infodemiology; infoveillance; internet; surveillance; patient opinion; psoriasis, treatment; Twitter; social media; social network

Introduction

Background and Rationale

Psoriasis is an autoimmune disease that causes patches of thick red skin and silvery scales and affects more than 6 million adults in the United States [1,2]. The condition can impact the quality of life and psychological and social functioning [3] and poses a significant public health problem [2,4,5]. A total direct cost of $649.6 million for approximately 1.4 million individuals with clinically significant psoriasis was reported [6], affecting employment and individuals' ability to work [7]. The condition occurs mostly in adults, men and women alike (ages 18 years and older) but can also affect children and is most common in people aged 50 to 69 years [4].

Previous research showed that nontreatment and undertreatment of patients with psoriasis remain a significant problem in the United States [2,8,9]. Despite several treatment options, 9% to 30% of patients with severe and nearly 50% of patients with mild psoriasis symptoms do not receive treatment, and patients report widespread treatment dissatisfaction [10]. More specifically, up to 30% of patients with severe and nearly 50% of patients with mild psoriasis symptoms do not receive treatment [8]. Known barriers to seeking treatment include a limited understanding of the disease, insurance coverage and out-of-pocket costs, and safety profile concerns [11]. However, perspectives among psoriasis patients toward seeking treatment are understudied. For example, a PubMed search including the terms "psoriasis," "patients," and "seeking treatment" results in 4 reports, of which only one identifies treatment-seeking motivations of psoriasis patients [12]. In this study, we define perspective as any expression of thought, viewpoint, or attitude toward health issues and concerns. Efforts that improve the understanding of patients' perspectives could inform and enhance advocacy and education to ensure that effective treatments are accessible to these patients.

Social Media and Health Research

Social media includes widely accessible web-based and mobile technologies that allow users to participate in social networking and view, create, and share information online [13]. These communication tools provide a unique source for data mining of health conditions and concerns, serving as a massive focus group of sorts [14-16]; 72% of American adults use at least one social media platform [17].

The emergence of social media has created new sources of analyzable data [11] and led to new research fields (ie, infodemiology and infoveillance) [16,18]. The data social media users generate through their online activities are referred to as their digital footprint [19] or social mediome [20]. Recently, the US Food and Drug Administration (FDA) encouraged the use of unstructured patient-generated health data (PGHD) from different sources including social media to generate insight into patient-experienced outcomes in the real world [21-23]. On Twitter, for example, health surveillance researchers have used these data to gain insight into public perspectives on a variety of diseases and health topics such as influenza, autism, schizophrenia, smoking, HIV/AIDS, and sun-related issues and skin cancer [24-30]. In some cases, social media user data demonstrated a correlation between the disease prevalence and frequency with which Twitter users discussed a disease [31]. The use of PGHD from social media offers a new opportunity to learn about patients' disease experience and networks that are not otherwise easily captured through traditional surveys or administrative data [32].

The Social Network Twitter

Nearly 22% of US adults use the social network Twitter including Hispanics (25%), Blacks (24%), and Whites (21%); more than 40% use the platform daily [17]. Twitter users can post short messages (tweets) of up to 280 characters and search for any public message and further engage with these tweets (ie, they can like, reply, and retweet [share] them). Twitter is a primarily public social network; by default, basic Twitter account information such as the profile name, description, and location are public unless a user decides to opt out and make an account private. Due to the more public nature of Twitter, previous research suggested that Twitter provides a "rich and promising avenue for exploring how patients conceptualize and communicate about their specific health issues" [33]. The increasing use of Twitter among members of disease communities is further evidenced by the abundance of disease and health topic hashtags used in the messages [34-36]. A hashtag is a word or phrase preceded by a hash or pound sign (#) and used to identify messages on a specific topic (eg, #psoriasis, #skinchat, #PsoriaticArthritis). These hashtags are used by Twitter users to assign their message to a topic and join ongoing conversations. Users can click on a hashtag and view all of the messages that include the same hashtag and, hence, discuss the same topic. This allows users to form online communities and share their health concerns, disease experience, and questions with like-minded users [37]. However, there is little information about the use of social media among psoriasis patients.

Previous Work

Few studies have examined social media content about psoriasis. Three studies of YouTube videos showed that misinformation is prevalent on social media and patients are exposed to a wide variety of information, with most of the content being of low quality [38-40]. Another study of dermatology-related content including psoriasis on the photo-sharing social network Instagram demonstrated that information by private offices, cosmetic products, and some patient advocacy groups dominates the user experience, while the use of a large number of hashtags related to dermatological conditions suggests that people use Instagram to post personal experiences with skin conditions [41]. While preparations for this study were underway, Menzies et al [42] published their Twitter analysis of attitudes toward psoriasis treatment among Twitter users. However, there were a few issues with their methodology that weakened their findings

[43]. One of the major issues pertained to the fact that the authors did not account for commercial and bot-like content within their dataset. Bots (robots) are purely automated accounts or human-assisted automated accounts (cyborgs) [44-48]. Identifying commercial and bot-like content, which is abundant on social media [44], is critical to discern patients' perspectives. Furthermore, the authors did not discuss whether and how they controlled for bias introduced by Twitter posts from commercial groups and bots in their analysis. As part of the preparations and data collection for our study, we found that 75.51% (52,301/69,264) of psoriasis tweets in English sent between February 2016 and October 2018 by users in the United States were commercial or bot-like in nature. To our knowledge, there are no additional studies that have used Twitter to gain a more profound understanding of patients' attitudes toward seeking psoriasis treatment.

Study Objective and Research Questions

The objective of this study is to conduct a content analysis of Twitter posts (in English) published by users in the United States between February 1, 2016, to October 31, 2018, to examine perspectives that potentially influence the treatment decision among patients with psoriasis. We intend to answer the following research questions:

1. What perspectives toward seeking treatment are being expressed by psoriasis patients on Twitter?
2. What are the demographics (ie, gender, race/ethnicity) of these psoriasis patients on Twitter?
3. What is the volume of unique Twitter users who talk about this topic?
4. What are the predominant themes in the conversations among psoriasis patients?
5. For commercial and bot-like tweets, what types of treatments are being promoted?

This protocol paper provides a detailed description of a social media research project including the process of data extraction, cleaning, and analysis. It is our goal to contribute to the development of more transparent social media research efforts. Our findings will shed light on whether Twitter provides a promising data source for garnering patient perspective data about psoriasis treatment decisions. The data will also help to determine whether Twitter might serve as a potential outreach platform for raising awareness of psoriasis and treatment options among patients and for implementing related health interventions.

Methods

Study Type

This is a qualitative study that will analyze user-generated posts about psoriasis from the social network Twitter.

Data Source

Twitter posts in English containing terms related to psoriasis will be obtained for the time period from February 1, 2016, to October 31, 2018. To access public Twitter user data, we will use Symplur Signals [49], a health care social media analytics company that maintains the largest publicly available database of health care and disease-related conversations with the globally recognized Healthcare Hashtag Project. Symplur Signals extracts data from the Twitter REST API (representational state transfer application programming interface) and makes it available to researchers; it is commonly used in peer-reviewed research [50-54]. Symplur Signals data are updated daily and easily sortable by social media user type (eg, patient, physician, health care organization), location and time zone, language, disease/health interests, and Twitter message content. The location of the users (limited to users within the United States) will be determined using a mapped location filter as defined by Gnip Inc, a social media data provider, and based on the Profile Geo 2.0 algorithm [55]. That algorithm uses a number of data points to determine a user's location including the self-reported bio location in the Twitter user profile and geotracking data if available. We extracted data from Twitter through the Symplur Signals user interface, searching for the keyword and hashtags listed in Multimedia Appendix 1. The data were provided in an Excel (Microsoft Corp) file, which we further analyzed on local university computers.

Search Filters

We will use a framework for data collection, quality assessment, and reporting standards as well as for developing search filters for social media data as previously suggested by Kim et al [56]. The root terms we will use to collect the sample of tweets are listed in Multimedia Appendix 1. These terms can appear in the post or in an accompanying hashtag, for example, "psoriasis" or #PsoriasisChat. We will select keywords and hashtags based on expert knowledge (clinicians, social media experts) and use a systematic search of topic-related language based on data in Symplur Signals.

Data Cleaning and Debiasing

The following types of irrelevant tweets will be excluded: retweets (ie, messages shared by Twitter users that other users composed) and non-English language tweets identified using the Liu method. Liu et al [57] developed and evaluated a web-based language identification tool called langid.py that uses natural language processing techniques and assists with text categorization in specific languages. They showed that the tool maintains consistently high accuracy. Furthermore, we will use the program Botometer (formerly BotOrNot) to identify Twitter accounts by social bots or commercial groups that could possibly influence the results and introduce bias [58,59]. Automated accounts on Twitter created by industry groups and private companies promote specific ideas or products and, thus, influence discussions. Botometer is a publicly available service launched in 2014 and includes more than 1000 variables to assess the extent to which a Twitter account exhibits characteristics of social bots [60]. Variables include the account network (ie, diffusion patterns), user data (ie, metadata), friends (ie, account's contacts), tweet rate, and sentiment and content of the account messages. The classification system generates a score that determines the likelihood of any one account being a social bot. Davis et al [60] demonstrated that the program scores a detection accuracy above 95%. If an account is identified as a social bot, that account and any tweets produced

from that account will be removed from our dataset so we can focus on analyzing patient's perspectives.

Data Privacy and Confidentiality

All analyses will adhere to the terms and conditions, terms of use, and privacy policies of Twitter. We will further abide by University of Southern California (USC) institutional review board (IRB) regulations and the USC Privacy of Personal Information policy.

All data will be entered into a computer and database that is password protected. The study data will be collected using the system Research Electronic Data Capture at USC, which is a secure, web-based app designed to support data capture for research studies. Provision of data to the IRB, National Institutes of Health (NIH), and FDA is facilitated by this database system.

Any identifying and personal health information will be redacted from the dataset by the coders. Information that might identify a contributor's identity will be redacted from any report developed to share the findings, and any Twitter posts we include in publications will be paraphrased to protect the privacy of the users.

Data Analysis

We will use a standard coding approach for characterizing the Twitter messages and users. Two independent team members will be responsible for coding based on a set of a priori classifiers listed in Multimedia Appendix 2 and 3. Information available in a user's Twitter profile (ie, username, description, avatar image) will be used to characterize the user of the Twitter account who generated the post to determine if the individual is a psoriasis patient (Multimedia Appendix 3). In other words, we will characterize a Twitter user as a psoriasis patient if they specifically mention being a patient in their description or previous tweets. We will further code the person's gender and race/ethnicity (White person versus person of color) if the Twitter profile contains sufficient information to do so.

We will then code the Twitter messages from psoriasis patients (Multimedia Appendix 2). Individual Twitter posts will be classified as posts originating from these patients either if the user who authored the message was already classified as a psoriasis patient through examination of their Twitter profile or if the post mentioned psoriasis in the first person (eg, "Haven't felt myself lately. Asked my doc about an alternative treatment plan today.") We will analyze the messages from these patients to identify the health issues and concerns they express (Multimedia Appendix 2).

Cohen kappa will be calculated for each code category to assess interrater reliability [61,62]. Once we establish concordance in the coder's classification with Cohen kappa greater than .80 for each coding category, the remaining data will be divided between the two coders. The project principal investigators will help to establish consensus in instances where coders disagree.

Statistical Analysis

This study will rely on public, anonymized data and adhere to the terms and conditions, terms of use, and privacy policies of Twitter. The proposed work received IRB approval from the authors' university.

We will use descriptive statistics to analyze the data and identify the most prevalent topics in the Twitter content. Units of analysis will be unique terms in posts as well as the number of Twitter messages and users (ie, patients). We will describe the patient characteristics focusing on gender and race/ethnicity, as displayed on Twitter. For each tweet theme analysis, we will present findings in a confusion matrix where the diagonal line indicates the prevalence of a topic and the off-diagonal lines indicate topic overlap. The number of posts containing 2 or more topics would be found at the intersection of the matrix for these topics. Representative examples of tweets within each category will be selected to illustrate additional themes and will be shown as paraphrased quotes to protect users' privacy.

Risk Analysis

The described work presents minimal risk research. We will use public user data from the social network Twitter. Patient identifiers do not apply. Identifiable information such as human subjects' names and Twitter handles will not be included in the analysis dataset.

Dissemination of Study Findings

The authors plan to publish the study findings in a peer-reviewed journal and at topic-related conferences (to be determined at a later date). All listed authors and/or contributors are compliant with guidelines outlined by the International Committee of Medical Journal Editors for author inclusion in a published work.

Results

Study approval was obtained from the IRB at USC (protocol HS-18-00867). Data extraction and cleaning are complete. For the time period from February 1, 2016, to October 31, 2018, we obtained 95,040 Twitter posts containing terms related to psoriasis from users in the United States published in English. After removing duplicates, retweets, and non-English tweets, we found that 75.51% (52,301/69,264) of the psoriasis-related posts were sent by commercial or bot-like accounts, while 16,963 posts were noncommercial and will be included in the analysis to determine the patient perspective (see Multimedia Appendix 4 for detailed data extraction and cleaning flow diagram). Analysis was completed in Summer 2020.

Discussion

Limitations

This exploratory pilot study is limited to Twitter conversations from people who use words and hashtags related to psoriasis in their Twitter posts. As a result, we will only include those patients' posts in the dataset who are familiar with the term "psoriasis" and not include posts from patients who might talk about their disease experience on Twitter but don't include any of these words.

The generalizability of the study is somewhat limited, because Twitter messages from locations outside of the United States

and messages in other, non-English languages will not be included. We also recognize that this type of social media research favors those with internet access and could, therefore, lead to potential bias in the research data. Twitter users tend to be younger (38% are aged 18 to 29 years), college graduates (32%), and located in urban areas (26%) [17].

Practical Significance

If successful, our findings will shed light on whether Twitter provides a promising data source for garnering patients' perspectives about psoriasis treatment decisions. The data will also help to determine whether Twitter might serve as a potential outreach platform for raising awareness of psoriasis and treatment options among patients and implementing related health interventions. This protocol paper provides a detailed description of a social media research project including the process of data extraction, cleaning, and analysis. It is our goal to contribute to the development of more transparent social media research efforts.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Keywords and hashtags to assess attitudes toward treatment among patients with psoriasis on Twitter. The selection is based on data from Symplur Signals.
[PDF File (Adobe PDF File), 83 KB - resprot_v10i2e13731_app1.pdf]

Multimedia Appendix 2
Code categories to identify main themes in Twitter posts related to psoriasis.
[PDF File (Adobe PDF File), 71 KB - resprot_v10i2e13731_app2.pdf]

Multimedia Appendix 3
Code categories to classify Twitter users.
[PDF File (Adobe PDF File), 59 KB - resprot_v10i2e13731_app3.pdf]

Multimedia Appendix 4
Data extraction and cleaning flow diagram.
[PDF File (Adobe PDF File), 53 KB - resprot_v10i2e13731_app4.pdf]

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Abbreviations

FDA: US Food and Drug Administration
IRB: institutional review board
NIH: National Institutes of Health
PGHD: patient-generated health data
REST API: representational state transfer application programming interface
USC: University of Southern California

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Protocol

Investigating the Ethical and Data Governance Issues of Artificial Intelligence in Surgery: Protocol for a Delphi Study

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Abstract

Background: The rapid uptake of digital technology into the operating room has the potential to improve patient outcomes, increase efficiency of the use of operating rooms, and allow surgeons to progress quickly up learning curves. These technologies are, however, dependent on huge amounts of data, and the consequences of their mismanagement are significant. While the field of artificial intelligence ethics is able to provide a broad framework for those designing and implementing these technologies into the operating room, there is a need to determine and address the ethical and data governance challenges of using digital technology in this unique environment.

Objective: The objectives of this study are to define the term digital surgery and gain expert consensus on the key ethical and data governance issues, barriers, and future research goals of the use of artificial intelligence in surgery.

Methods: Experts from the fields of surgery, ethics and law, policy, artificial intelligence, and industry will be invited to participate in a 4-round consensus Delphi exercise. In the first round, participants will supply free-text responses across 4 key domains: ethics, data governance, barriers, and future research goals. They will also be asked to provide their understanding of the term digital surgery. In subsequent rounds, statements will be grouped, and participants will be asked to rate the importance of each issue on a 9-point Likert scale ranging from 1 (not at all important) to 9 (critically important). Consensus is defined a priori as a score of 7 to 9 by 70% of respondents and 1 to 3 by less than 30% of respondents. A final online meeting round will be held to discuss inclusion of statements and draft a consensus document.

Results: Full ethical approval has been obtained for the study by the local research ethics committee at Imperial College, London (20IC6136). We anticipate round 1 to commence in January 2021.

Conclusions: The results of this study will define the term digital surgery, identify the key issues and barriers, and shape future research in this area.

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KEYWORDS

artificial intelligence; digital surgery; Delphi; ethics; data governance; digital technology; operating room; surgery

Introduction

The emergence of huge datasets ranging from imaging, sensors, and electronic medical records has resulted in the rapid uptake of artificially intelligent technology across health care [1]. The operating room is no exception; it incorporates digital technologies ranging from augmented reality systems [2] to next generation robotics [3]. The hope of this armory of technology at the surgeon's disposal is for more efficient, safe, and precise surgery that will in turn improve patient outcomes, lead to more efficient utility of operating theaters, and allow surgeons to progress rapidly up learning curves. Driven by the

promise of such rich rewards, uptake in digital technology in the operating theater has been rapid, and this has been further accelerated by the emergence of COVID-19, which has seen widespread adoption of digital technology across health care [4].

However, incorporation of this technology into the operating room is not without risk. Digital systems are inherently dependent on data to function, and the accessing, sharing, and use of huge amounts of potentially sensitive personalized data pose significant risk. Lessons can be learned from the failure of implementation of digital technologies across health care that have been widely reported in the media [5,6]. The risks of mismanagement of these large datasets are often overlooked in the pursuit of furthering efficiency. Therefore, when failures do occur, the net result is the reduction of public trust and ultimately the hindering of development of these technologies. It is therefore vital that we address the key ethical and data governance issues of the transformation into a digital operating room.

We can seek guidance from the implementation of artificial intelligence (AI) across different industries. The field of AI ethics is a response to the potential harms that AI systems can cause such as bias and discrimination, invasion of privacy, and poor-quality outcomes. AI ethics can be defined as "a set of values, principles, and techniques that employ widely accepted standards of right and wrong to guide moral conduct in the development and use of AI technologies" [7]. The 4 key pillars named by the Alan Turing Institute concerning the design and use of AI systems are fairness, accountability, sustainability, and transparency.

While this provides a basis for clinicians and technologists to adhere to for surgical AI systems, the operating room is a unique environment that poses its own specific challenges. Surgical AI systems must contend with issues of consent if future digital systems are dependent on opaque algorithms. There is also the issue not only of privacy of patients but of future surgical teams who will be potentially under scrutiny for every action they take. Questions around litigation and liability are, to date, untested. Finally, not only will the digital operating room be dependent on data, but it has the potential to become a priceless data pipeline leading to issues of data ownership and the potential consequences of commercial partnerships. There is now a critical need to address these ethical and data regulation issues in this digital surgery era.

The objectives of this study are to conduct a Delphi exercise to determine opinions and gain consensus on the key ethical and data regulation issues concerning the use of AI in surgery. Through this process, we will define the term digital surgery and its components and develop a consensus-based list of issues, barriers, and future research goals from a variety of stakeholders across digital surgery.

Methods

Justification for Study Design

Delphi exercises have been used widely across health care to determine consensus across a wide variety of issues, and their merits are amplified in areas where there is uncertainty or limited knowledge [8,9]. It is an iterative process of sequential questionnaires designed to combine expert opinion into group consensus [10]. A series of questionnaires are answered and submitted. Following each round of questionnaires, participants receive a summary of the entire panel's answers from the previous round and are asked to repeat the questionnaire. Participants are encouraged to review the panel responses and revise their own responses and through this process converge toward consensus.

The Delphi technique has several key advantages over face-to-face roundtable discussions. It allows all panelists to be heard equally without domination of a single voice. The feedback mechanism, where results of the panel are returned to participants, also permits participants to change their minds easily having reviewed the views of the rest of the panel [11,12]. Most importantly, however, the Delphi technique has gained popularity for practical reasons: it allows experts to participate all over the world without restriction and therefore is a pragmatic and cost-effective means of gaining consensus.

The Delphi technique, however, is not without criticism. It is reliant on the continued participation of panelists through the rounds of the exercise. As such, Delphi exercises may suffer from a decline in response rate, and this has been a frequent criticism of the Delphi technique [13]. Therefore, efforts must be made to encourage continued participation to prevent attrition bias. In addition, criticisms have been made concerning the reliability of the Delphi technique. Critics have argued there is no guarantee the same results will be obtained should the same information be presented to 2 different panels of experts [13]. It is therefore important to ensure that the panel consists of a broad and diverse representation of experts. Despite these criticisms, however, the Delphi technique continues to be a popular, easy, and low-cost means of determining consensus.

Moreover, the Delphi methodology has been shown to be effective in areas of research where there is uncertainty or little knowledge [13]. There has been, to our knowledge, little work performed in this area. The Delphi methodology is not only a tool for gaining consensus but is also an effective means for idea generation. Novel ideas can subsequently be fed back to the panelists, which will encourage further ideas to be synthesized.

Finally, participation in the Delphi process has been shown to be a highly motivating experience for participants. The feedback mechanism can also be a stimulating process for those engaging in the Delphi process [9]. We hope that this will spark future discussion in this relatively unknown field.

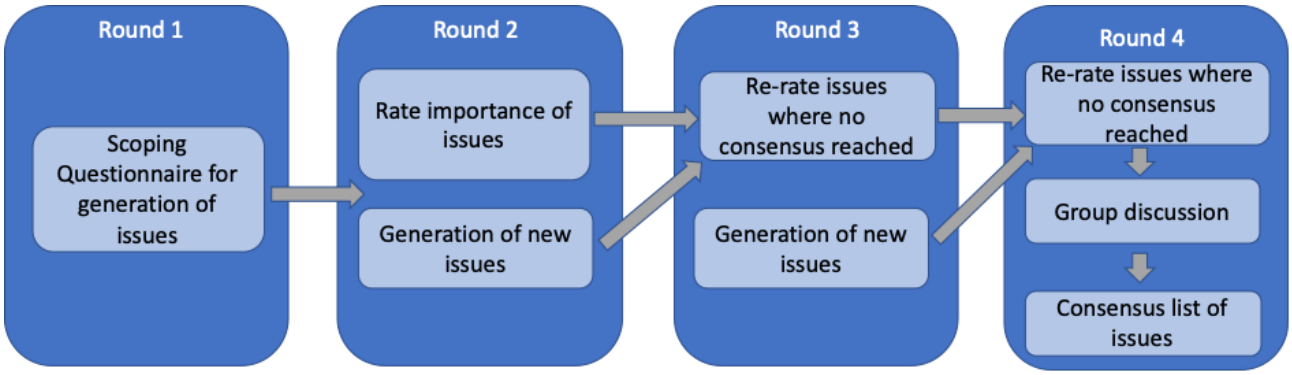
Ethics

Ethical approval for this study was granted by the local research ethics committee at Imperial College, London (20IC6136). All participants will be required to provide informed consent to take part at the start of the online questionnaire. Data will be handled in accordance with UK data protection regulations.

Structure

The Delphi exercise will consist of 3 online questionnaire rounds and a final live online consensus meeting (Figure 1). Round 1 will consist of an online scoping questionnaire, rounds 2 and 3 will consist of online questionnaires where statements will be rated, and round 4 will take the form of a live online meeting delivered through videoconferencing software. Online questionnaire rounds will be undertaken through Qualtrics software (Qualtrics) and will be active for periods of up to 4 weeks. Those who do not complete the questionnaire will be sent a reminder email weekly.

Figure 1. Structure of the Delphi exercise.



All invited participants will receive a personalized invitation to participate via email. This will include an explanatory statement about the Delphi exercise, why they have been chosen, and a link to the questionnaire. Participants will be encouraged to complete all rounds, as attrition bias can lead to overestimation of the degree of consensus in the final results [11]. Strategies that we will employ to prevent attrition bias include sending potential participants a personalized pre-Delphi invitation to participate in the first round and listing only those who complete the entire Delphi process in the final publication.

Participants will be quasi-anonymous for online questionnaire rounds; identities of the participants will not be known to other participants but will be known to the study organizers. Anonymity allows equal opportunity for all participants to provide and react to ideas unbiased by the identities of others [13]. While anonymity cannot be achieved in the final online meeting, the result tally of participant votes will be anonymized.

An initial scoping round will encourage panelists to generate statements for subsequent rounds. These statements will be presented to panelists in the two subsequent rounds where the panelists will vote on the importance of the statements; group discussion of the statements will occur at a final online meeting. Through the 4 rounds of the Delphi, we aim first to gain consensus agreement on the term digital surgery and the key components of digital surgery. Second, we aim to identify high value statements across 4 domains within this theme: ethical issues, data governance issues, barriers, and future research goals.

Selection of International Experts

Due to the broad nature of the subject matter, we aim to recruit experts across multiple sectors: clinical, ethics and law, policy, AI, and industry. These are all key stakeholders in the development and implementation of digital surgery, and involvement of all these sectors is vital to gain a representative view of the key issues. We identified experts as those with national and international profiles in their respective fields, authors of impactful research in the literature, major digital technology companies, and experts recommended by peers. There are no strict exclusion criteria. All individuals identified or recommended by peers as suitable to participate in the Delphi exercise will be sent an initial personalized pre-Delphi invitation email requesting participants to express their interest.

A sample size calculation dependent on statistical power to generate a number of participants required was not calculated. Because the Delphi exercise is dependent more upon gaining a representative view across multiple disciplines, there is no consensus on the minimum number of participants required [12]. We aim to recruit a minimum sample size of 20 across these varying areas, which has been shown to provide reliable and effective judgement [14].

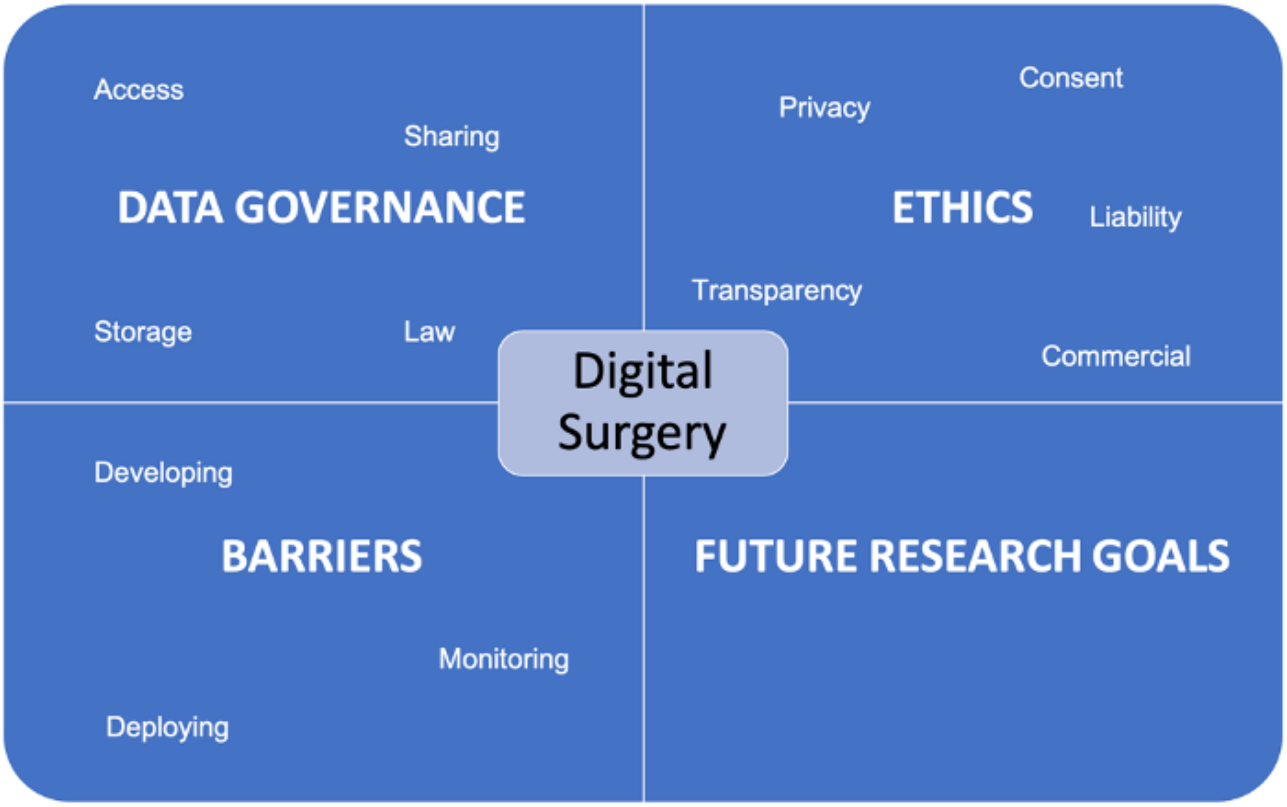
Round 1

The initial round of the Delphi exercise acts to generate ideas to discover issues relating to the topic of study. It is therefore vital to ask open questions in this round and not impose the study team's views on the participants thereby introducing bias into the study. Providing a list of potential issues to study participants may subconsciously emphasize the significance of certain issues favorable to the study team rather than those important to the experts undertaking the Delphi exercise [11].

In the first round, we ask participants open questions across 4 key domains: data governance, ethics, barriers, and future research goals. In addition, participants will be asked their understanding of the term digital surgery.

To facilitate responses, each domain will be further divided into areas we have identified from the literature (Figure 2). We believe this will give more structure and guidance in their free-text answers. In addition, participants will be free to suggest additional issues that may not be covered by our questions.

Figure 2. Key domains of round 1.



Laypeople with no technical expertise in any of the associated fields will also be invited to participate in round 1. A version of the questionnaire, understandable to the general public, will be presented to a broad sample of the public. The statements generated by the public will also be presented to the expert panel in round 2.

Rounds 2 and 3

Only those who complete all previous rounds will be invited to participate in subsequent rounds of the Delphi exercise. Statements from round 1 will be grouped according to common themes and presented to participants alongside statements generated from laypeople with no technical expertise. In both of these online questionnaire rounds, participants will be asked to rank the importance of items according to a 9-point Likert scale, where 1 indicates not important and 9 indicates critical. Issue scoring: 1 to 3 indicates the issue is of little importance, 4 to 6 indicate an issue is important but not critical, and 7 to 9 indicates the issue is critically important. There is no standardized definition of consensus in Delphi exercises. Therefore, we have elected to define consensus as being where the issue is scored 7 to 9 by 70% of respondents and 1 to 3 by less than 30% of respondents, a popular approach used in Delphi exercises [15]. Statements that fail to reach the threshold of consensus will be put forward to the next round of the Delphi consensus process. Participants will also be encouraged to contribute further statements during each of these rounds.

Round 4

Only participants who have completed round 3 will be invited to participate in round 4. This final consensus meeting will consist of the study team alongside all participants who have completed all previous rounds. The use of a final online consensus meeting was chosen as it facilitates expert interaction in the final round and allows participants to justify their viewpoints and seek further clarification on statements; this has been thought to improve on the original Delphi method [16]. The primary objective of this online meeting is to develop a consensual draft of statements from the Delphi exercise. The meeting will be structured around the nominal group technique, a highly structured group interaction framework [17]. After initial introduction and an explanation of the aims of the meeting, the results of round 3 will be presented to the participants alongside summary descriptive statistics. All nonconsensus statements and newly generated statements from round 3 will first be put forward for voting on the same Likert scale. The definition of consensus will be as per the previous round. All panelist responses will be analyzed together.

Members of the meeting will then be asked to discuss the inclusion and exclusion of statements generated from the entire voting process. Participants will also be encouraged to clarify or further discuss any statements generated. The meeting will be facilitated by members of the study team to ensure all members of the meeting have an equal opportunity to express their views and the discussion is not dominated by a single member. The final consensus statement will be distributed to all those who complete the full Delphi exercise for final approval. Key methodological criteria for the study is detailed in Table 1.

Table 1. Key methodological criteria for reporting of Delphi studies as per Diamond et al [18].

Criteria	Response
Objective	
Does the Delphi study aim to address consensus or to quantify level of agreement?	Consensus
Participants	
How will participants be selected or excluded?	Experts will be from the fields of surgery, artificial intelligence, policy, ethics, and industry. Laypeople will also be asked to respond to a nontechnical version of the scoping questionnaire
Methodology	
Level of anonymity	Anonymous to other panel members in online questionnaire rounds
A priori definition of consensus	Between 7 and 9 on a 9-point Likert scale of importance by 70% of respondents and between 1 and 3 by less than 30% of respondents
Criteria used to determine when to stop the Delphi in the absence of consensus?	4 rounds will be conducted in total

Results

Infrastructure support for this research was provided by the National Institute for Health Research Imperial Biomedical Research Center. We anticipate round 1 to commence in January 2021 and all Delphi rounds to be completed by Fall 2021. We expect that the study will be published in a peer-reviewed journal and presented at national and international conferences.

Discussion

Summary

While the popularity of the use of AI in surgery has increased, there is still a relative paucity of knowledge of the ethical and data governance issues concerning its use. The Delphi exercise described in this paper aims to determine the key issues to be addressed and therefore shape the direction of future research. We hope this work will increase awareness of these issues across all key stakeholders in digital surgery with the ultimate goal of creating not only efficient but ethical surgical AI.

Strengths and Limitations

The strengths of this study center around the involvement of participants across multiple areas of expertise. This Delphi exercise aims to capture the representative views across clinicians who may use these digital technologies; technologists creating them; and experts in ethics, policy, and law who are concerned with the regulations governing them. We will also include the views of laypeople with no expertise in the fields. It is important to understand the views of the public as digital technology in the operating room is ultimately developed for patient benefit, and therefore public acceptability is of paramount importance. While we aim to recruit participants with an active interest in this field, the study is limited by the willingness of those invited to participate. As such, while we aim to capture a representative sample of all those involved in digital surgery, the views of the experts who participate in the Delphi may differ from those who decline to participate. In addition, we acknowledge that due to the international scope of this study, the use of a final online meeting may limit the attendance of panelists from differing time zones. We believe this is outweighed, however, by the benefits of a live online meeting that will allow clarification and debate of statements. The hosting of two separate meetings to facilitate differing time zones can also be considered should this be required.

Conclusion

This paper describes the protocol of a Delphi consensus exercise that will aim to define the term digital surgery and identify the key ethical and data governance issues, barriers, and future research goals of the use of AI in surgery. The results of this study will shape future research in this area.

Authors' Contributions

KL and FMI substantially contributed to discussion of content, wrote the article, and reviewed and edited the manuscript before submission. SP and JK substantially contributed to discussion of content and reviewed and edited the manuscript before submission.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence

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Protocol

Usability, Perceived Usefulness, and Shared Decision-Making Features of the AFib 2gether Mobile App: Protocol for a Single-Arm Intervention Study

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Abstract

Background: The Centers for Disease Control and Prevention has estimated that atrial fibrillation (AF) affects between 2.7 million and 6.1 million people in the United States. Those who have AF tend to have a much higher stroke risk than others. Although most individuals with AF benefit from anticoagulation (AC) therapy, a significant majority are hesitant to start it. To add, providers often struggle in helping patients negotiate the decision to start AC therapy. To assist in the communication between patients and providers regarding preferences and knowledge about AC therapy, different strategies are being used to try and solve this problem. In this research study, we will have patients and providers utilize the AFib 2gether app with hopes that it will create a platform for shared decision making regarding the prevention of stroke in patients with AF receiving AC therapy.

Objective: The aim of our study is to measure several outcomes related to encounters between patients and their cardiology providers where AFib 2gether is used. These outcomes include usability and perceived usefulness of the app from the perspective of patients and providers. In addition, we will assess the extent and nature of shared decision making.

Methods: Eligible patients and providers will evaluate the AFib 2gether mobile app for usability and perceived usefulness in facilitating shared decision making regarding understanding the patient's risk of stroke and whether or not to start AC therapy. Both patients and providers will review the app and complete multiple questionnaires about the usability and perceived usefulness of the mobile app in a clinical setting. We will also audio-record a subset of encounters to assess for evidence of shared decision making.

Results: Enrollment in the AFib 2gether shared decision-making study is still ongoing for both patients and providers. The first participant enrolled on November 22, 2019. Analysis and publishing of results are expected to be completed in spring 2021.

Conclusions: The AFib 2gether app emerged from a desire to increase the ability of patients and providers to engage in shared decision making around understanding the risk of stroke and AC therapy. We anticipate that the AFib 2gether mobile app will facilitate patient discussion with their cardiologist and other providers. Additionally, we hope the study will help us identify barriers that providers face when placing patients on AC therapy. We aim to demonstrate the usability and perceived usefulness of the app with a future goal of testing the value of our approach in a larger sample of patients and providers at multiple medical centers across the country.

Trial Registration: ClinicalTrials.gov NCT04118270; https://clinicaltrials.gov/ct2/show/NCT04118270

International Registered Report Identifier (IRRID): DERR1-10.2196/21986

(JMIR Res Protoc 2021;10(2):e21986) doi:10.2196/21986

KEYWORDS

shared decision making; mobile health; stroke risk; anticoagulation risk; anticoagulation education; atrial fibrillation; anticoagulation therapy; anticoagulation; atrial flutter; mobile phone

Introduction

Atrial fibrillation (AF) and atrial flutter occur in epidemic proportions in the United States [1-4]. The Centers for Disease Control and Prevention estimates that AF affects between 2.7 million and 6.1 million people in the United States [5]. Anticoagulation (AC) is the mainstay of therapy, but many patients are reluctant to start taking anticoagulants [6]. Patients who have a diagnosis of AF generally have a higher risk of stroke than the general population [7]. Even among those who do start AC therapy, many do not persist with the treatment after bleeding or other setbacks. Providers also struggle with balancing the risks and benefits of AC therapy. Being able to determine an optimal decision for each patient is a valuable goal in stroke prevention. Shared decision making has been recommended by the American Heart Association (AHA) and other professional societies as a way to arrive at an optimal decision, but the usability and perceived usefulness of conducting shared decision making via an app visit are unclear [8].

Conducting shared decision-making visits will require several changes from standard provider-patient interactions. Shared decision-making visits will help patients and providers make the best choice in therapy that will fit into a patient's life. Firstly, providers do not always draw attention to the fact that there is a decision to be made and may make the decision for the patient without soliciting the patient's preferences. Secondly, providers do not always inquire about the patient's preferred treatment approach, which can create a barrier for shared decision making. It is also possible that providers may not be knowledgeable or confident in managing AF patients with the most recently published guidelines and the advent of direct oral AC therapy (ie, modern AF management). Conducting AF management through a shared decision-making process may help in overcoming the above limitations. Currently, it is unknown how best to operationalize shared decision making around AC therapy for AF.

Shared decision-making tools can help patients make informed decisions with less conflict [9]. The AFib 2gether mobile app, which was developed by Pfizer Inc in consultation with a cardiologist (DM), is one potential approach for operationalizing shared decision making around AC therapy for AF. The app can provide a platform for a patient to determine their risk of stroke and identify items for discussion at an upcoming visit with their provider. The app was designed to support collaboration during patient visits, which allows for the app to provide a high-level overview of AF and AC therapy and to prepare patients to have the tools needed to ask questions of their providers. The provider can review the answers given by the patient's app as well as any questions the patient solicited in the app for discussion prior to the visit. The goal is that this interaction will help the patient make a more informed decision by helping them become more engaged in their health status and improve their stroke prevention management related to AF.

We have not previously tested the app with patients and providers for usability and perceived usefulness for clinical encounters. Therefore, we describe herein our protocol for testing the app in a clinical setting, including measurement of the usability of the app and its usefulness during clinical appointments between patients with AF, who are not currently prescribed AC therapy, and their cardiology providers. We also propose a measurement of the extent and nature of shared decision making that occurs through audio-recording the encounters facilitated by our app.

Methods

Study Aims

The aim of the AFib 2gether research study is to measure the usability and perceived usefulness of the shared decision-making mobile app AFib 2gether from the perspective of patients and providers. We will also measure patient AC status by chart review 6 months after their shared decision-making visit to see if patients started AC therapy. Finally, we will assess the extent and nature of shared decision making through a review of audio-recordings of the patient encounters with their providers.

Study Population

Setting

This study will take place at the cardiology practice of an academic, tertiary care health system in central Massachusetts.

Providers

We will enroll up to 20 cardiology providers practicing at the University of Massachusetts (UMass) Memorial Healthcare System in the Ambulatory Care Center (ACC) Cardiology Clinic.

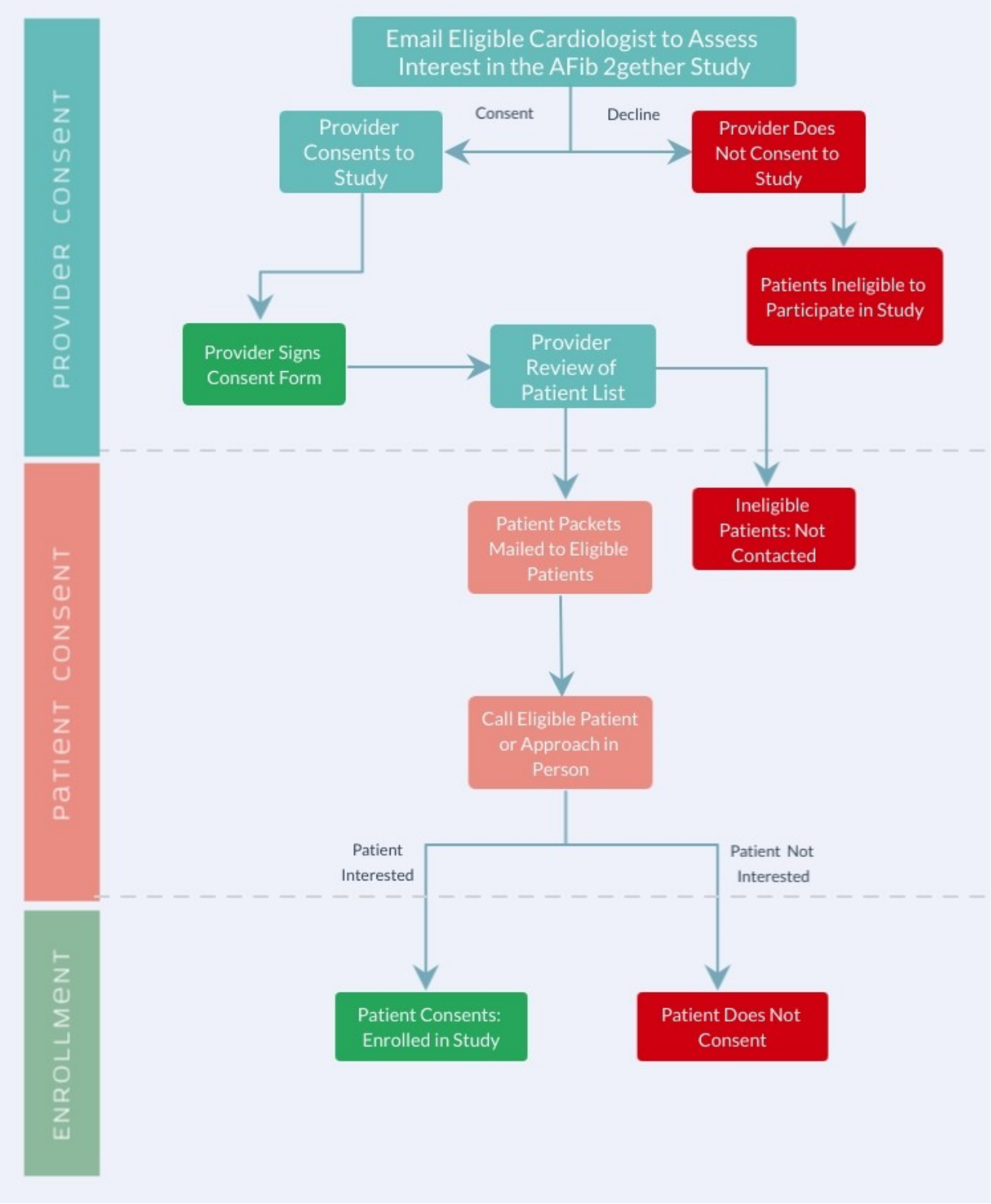
Patients

We will enroll up to 60 patients who are not receiving AC therapy, with each provider contributing up to 6 AF patients with elevated stroke risk. Recruitment will be restricted to patients aged 18 years and older. To identify patients, we will use a diagnostic concept grouper within our electronic health record (EHR) system that follows our inclusion criteria consistent with AF. Subsequently, patients will be filtered to retain those patients with CHA_2DS_2-VASc stroke risk scores of 2 or greater [8] who were not on AC therapy and had an upcoming cardiology visit in the next 3 months. The CHA_2DS_2-VASc score assigns 1 point for congestive heart failure, hypertension, age 65 to 74 years, diabetes mellitus, vascular disease history, and female sex. The score assigns 2 points for age greater than 75 years and for previous stroke or transient ischemic attack history.

The following participants will be excluded: patients that have a WATCHMAN device or have had left atrial appendage closure surgery, patients in hospice or for whom life expectancy is less than 6 months, and patients with bleeding episodes or falls with

injury 4 weeks prior to their cardiology appointment. Additionally, patients with preferred languages other than English will be excluded from the study because the app AFib 2gether is only available in English. Patients will be excluded from the study if they are members of vulnerable populations (ie, pregnant women and prisoners). The eligibility process is outlined (see Figure 1) to represent how patient eligibility will be verified before patients consent to participate in the study.

Figure 1. Overview of the provider and patient eligibility process for consent and enrollment in the study.



Study Procedures

Screening and Recruitment

A custom query developed by the information technology department at our institution will be used to identify eligible patients who have encounters with consenting cardiology providers in the upcoming 3 months. A manual review of patients' charts will be conducted to confirm that a patient was not receiving AC therapy (eg, from an outside provider, sometimes documented in scanned notes as opposed to structured variables).

The research assistant (RA) will start recruiting providers who had 3 or more patients that fit the study inclusion criteria. Each provider will then receive a study inquiry email from the RA to see if they are interested in participating in the study. If the provider agrees, they will sign the consent form and a letter will be mailed to their patients. Once enrolled, providers will receive a link to the secure REDCap (Research Electronic Data Capture)-based survey [10] to self-administer a questionnaire (see Multimedia Appendix 1) about their knowledge regarding AF management.

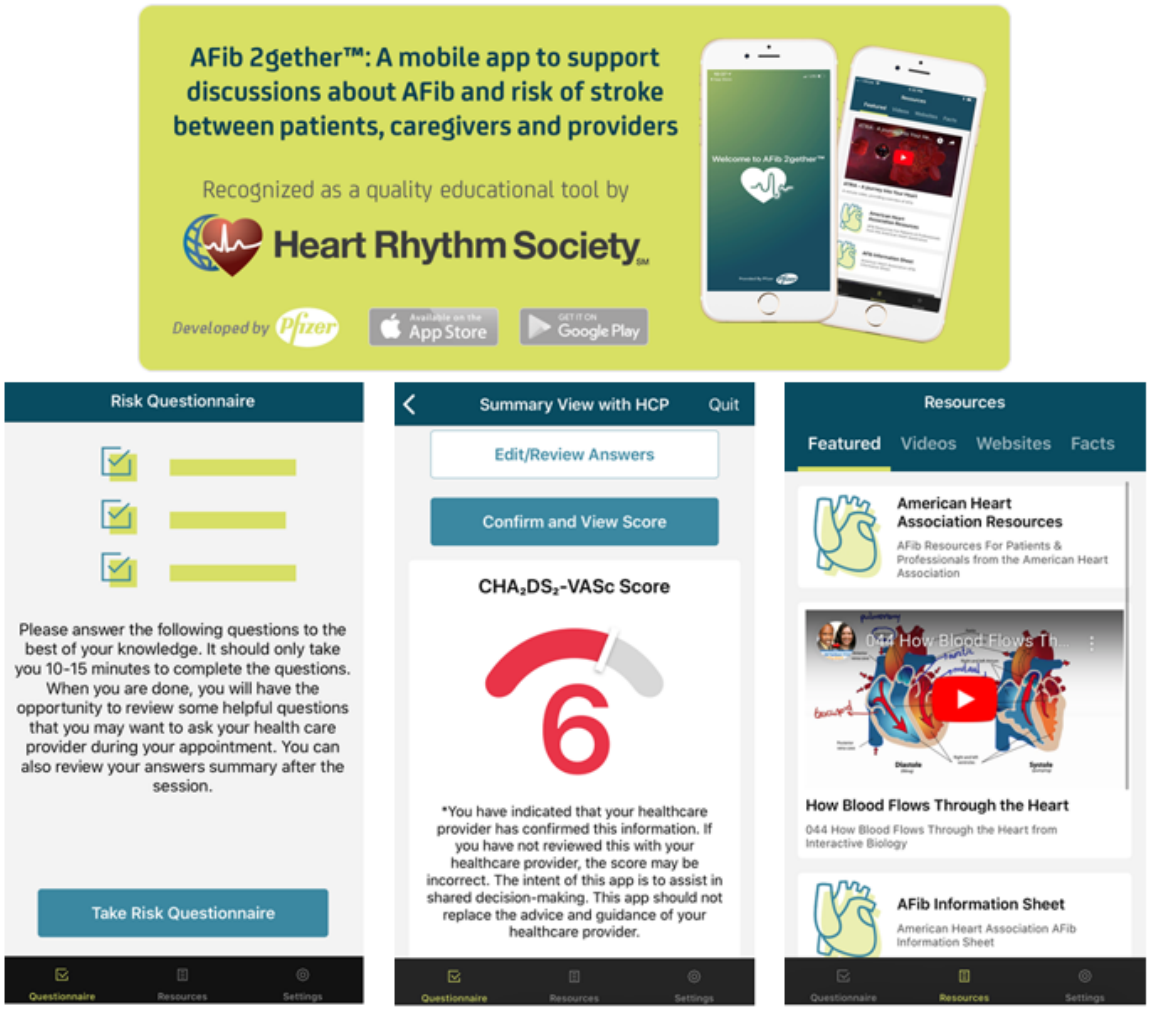
Additionally, letters signed by the patient's cardiology provider along with a fact sheet and Health Insurance Portability and Accountability Act (HIPAA) authorization form will be mailed to each eligible patient 1 to 2 weeks prior to the patient's appointment. Approximately 5 days later, the RA will call patients for a follow-up to gauge interest in participating in the study. For patients who scheduled a visit within 1 week of the appointment date, messages with study recruitment and consent materials will be sent to the patients as attachments using the Epic patient portal. Subsequently, patients will be called in the next 1 to 2 days to obtain consent. For patients who did not respond to either of these mechanisms or for patients that were scheduled within 24 hours of their appointment, our Institutional Research Board approved the RA to meet and recruit patients, as feasible, in the waiting room of the cardiology clinic prior to the patient visits.

Intervention and App Description

Once a patient has provided informed consent to participate, we will ask them to download the AFib 2gether mobile app onto their personal smartphone or a family member's smartphone or to use the study device for in-person visits. AFib 2gether is a mobile app that may be helpful to foster a shared decision-making discussion between patients and providers. The AFib 2gether app may help increase a patient's understanding of their risk of stroke due to AF through the personalized stroke risk calculator, information sheets, videos, website links, and facts in the app (see Figure 2). In addition, the app allows patients to select questions about AF and their stroke risk score to discuss with their health care providers. The goal of the app is to improve patient understanding; it stands in distinction to other apps related to assisting providers with choosing a particular anticoagulant.

For patients recruited at the time of their office visit, the RA will offer the study smartphone, an Android OS smartphone, for patient use with the AFib 2gether app predownloaded on the device or will assist the patient in downloading the app onto their personal device. Next, the RA will instruct the patient to put in a study-specific code for the app. Once the patient puts in the study code, the patient will be able to consent to the app's terms and conditions. Once the patient has agreed to the app's terms and conditions, the patient may then answer questions on the app to determine their knowledge of their stroke risk score. The questions include whether the patient has ever had heart failure, hypertension, diabetes, stroke, vascular disease, or previous stroke and what their age and gender are. Once the participant answers the questions, the app will display their categories for stroke risk and will allow the participant to select up to three questions from a list of 13 commonly asked questions that they may want to discuss with their provider during their visit based on their risk assessment. Examples of the types of questions a participant could choose are as follows: Would you like to know more about your condition? What is the cost of AC therapy? and What are the benefits of going on AC therapy to avoid stroke? The participant will be given the option to type in any additional questions they may have that were not listed in the app. Lastly, the patient's risk factors and questions will then be sent via email to the provider as a PDF document to review prior to their appointment.

Figure 2. Advertisement of the AFib 2gether app in the Heart Rhythm Society's patient toolkit with screenshots of sections of the app.



Data Collection

The RA will administer a modified version of the Mobile App Rating Scale (MARS) for the purpose of assessing usability (see Multimedia Appendix 2) [11]. The MARS is a validated survey that can be used to assess health apps [11]. The modified questionnaire includes functionality and aesthetics domains that are similar to the original. We will not include items from the engagement and entertainment or information domains. We will include one item from the app subjectivity quality domain, which is the overall star rating of the app. This followed recent evidence suggesting the validity of scoring each domain separately [12]. The RA will wait with the participant until their visit with the provider begins. Once the cardiology provider is ready to begin the visit, the RA will then turn on and place the encrypted recorder—the Olympus DS-7000 (OM Digital Solutions)—in the room. At this point, the RA will prompt the provider to review the questions posed by the patient and then step outside the room and allow the visit to take place without any further scripting.

At the end of the visit, the RA will collect the voice recorder and administer questionnaires to both the patient and provider related to the perceived usefulness of the app following the technology acceptance model (TAM) [13,14]. Although we did also consider the unified theory of acceptance and use of technology 2 (UTAUT2), which unifies the eight theories including the TAM, we selected the TAM as our theoretical construct given its applicability to individual patients following other examples in the literature. Accordingly, we will administer a questionnaire assessing the patient perceived usefulness of the mobile app (see Multimedia Appendix 3). For providers, we will administer a questionnaire assessing the provider perceived usefulness of the mobile app (see Multimedia Appendix 4).

Once the patient completes their appointment and questionnaires, the RA will give the patient a US $25 Amazon gift card for participating in the study. Providers will be compensated with a US $200 Amazon gift card after they complete all study activities.

The UMass Medical School approved our protocol, including data collection and incentive procedures.

Modified Study Procedures for COVID-19

During periods when in-person recruitment is not permissible due to COVID-19 restrictions, we will utilize remote recruitment and consenting processes. For remote patient recruitment, the same provider letter will be used, but the fact sheet and HIPAA authorization will be modified to remove information about the audio-recording. We will not replace audio-recording with another method of objectively measuring the extent and type of shared decision making that occurs. The original HIPAA authorization form's wet signature will be replaced with a process of acknowledgment to disclose protected health information through the process of agreeing to participate in the study and phone interview.

Primary Outcomes

Usability

We will group items in the MARS into three domains for functionality, aesthetics, and overall quality; they will receive a rating of number of stars out of 5.

Perceived Usefulness

Perceived usefulness will be calculated for patients and providers based on a custom set of questions derived from the TAM. More specifically, we will examine their distribution similar to how we described the usability outcome. We collected usefulness data on a 5-point Likert scale for simplicity's sake, in contrast to the traditional 7-point Likert scale used in TAM or UTAUT2 literature. In addition, timing will be recorded for each of the components of the shared decision-making encounter. The distribution of time required for each activity will be reviewed.

Shared Decision Making

We will also assess for elements of shared decision making, including multiple themes covered in established instruments [15]. These will include a mention that options are available, evidence that the provider shared stroke and bleeding risk with the patient, and, most notably, evidence of patient involvement in the discussion.

Secondary Outcome: Anticoagulation Start

The RA will review each patient's medical record in our institution's EHR system, Epic, to see if the patient started AC therapy within these 6 months.

Patient and Provider Characteristics

Patient Demographics

Through electronic capture from the data repository associated with our institution's EHR system, we will collect age, sex, race, and ethnicity information.

Comorbidities

From our EHR system, we will also collect the CHA_2DS_2-VASc scores using our previously validated algorithm. From manual chart review, we will also collect information about why the patient did not previously receive AC therapy, including potential responses, such as *low AF burden*, *the patient refused*, *fall risk*, and *concomitant aspirin use*.

Provider Factors

Through information available from our credentialing office, we will collect provider age and years in practice in addition to provider credentials (ie, MD versus NP or PA).

Provider Knowledge

We will measure provider AC therapy decision-making confidence in several areas, including applying guidelines from the ACC, the AHA, and the Heart Rhythm Society and assessing antithrombotic therapy, using CHA_2DS_2-VASc scores to access stroke risk, among others. Response options will include *somewhat confident*, *moderately confident*, and *very confident*.

Analysis

For each domain of usability of the app (ie, MARS items), we will calculate the mean and standard deviation. For perceived usefulness, we will group patients into consolidated ordinal categories based on the Likert response format. We will then assess for trends in associations and examine associations between patient characteristics and usability and perceived usefulness. Where feasible, given low sample size, we will also calculate *t* tests or chi-square tests for determining statistical significance. We will perform all analyses in SAS 9.4 (SAS Institute Inc) [16]. The UMass Medical School Institutional Review Board approved our protocol.

Results

This study was registered at ClinicalTrials.gov (NCT04118270). Enrollment in the AFib 2gether shared decision-making study is still ongoing for both patients and providers. The first participant enrolled on November 22, 2019. Analysis and publishing of results are expected to be completed in spring 2021.

Discussion

We have developed a protocol to measure the usability and perceived usefulness of a mobile app to facilitate shared decision making for patients with AF not currently receiving AC therapy. We also describe the administration of a separate provider survey that will allow us to measure the association between provider knowledge and each of these outcomes. Our protocol provides flexibility to recruit patients during the COVID-19 pandemic or other circumstances where face-to-face interaction is not possible and where telehealth virtual engagement strategies are implemented.

With the fast-growing use of online sources for accessing health information throughout society, a shared decision-making app or tool for clinical settings has a great potential for impact. Man-Song-Hing et al developed a decision aid based on a risk stratification scheme that helped patients and providers make informed decisions about whether to use warfarin compared with aspirin for patients with AF [17]. More patients in the intervention group (n=138, 99%) were able to make definite choices regarding antithrombotic therapy compared with those in the control group (n=139, 94%; *P*=.02). More recently, Kunneman et al tested a shared decision-making tool that provided individualized risk estimates of stroke in various AC

therapy options [18]. Although they did not find a significant effect on treatment decisions, more clinicians were satisfied with the encounter in the intervention arm compared with the standard arm. Neither of the two studies specifically studied the usability or perceived usefulness of their shared decision-making tool [17,18].

Overall, there are advantages and disadvantages to using mobile health apps to conduct shared decision making. Some of the potential advantages of using a mobile app for shared decision making include patient empowerment, encouragement of patient participation in medical decision making, and increased overall satisfaction [19]. However, we need to balance this against the potential to increase the anxiety of patients, security concerns, and lack of accessibility in lower-income areas. The AFib 2gether app provides a convenient and comfortable way for patients to identify concerns they have about initiating or resuming AC therapy. The AFib 2gether app provides an updated and accurate shared decision-making tool that is readily available to patients and providers through both Google Play and the Apple App Store, for Android phones and iPhones, respectively. The AFib 2gether app will provide the tools to patients and providers to help them make informed decisions about the best treatment options for the patients. Users of the app can refer to multiple reliable educational videos, websites, and facts about AF, stroke, and AC therapy.

We acknowledge multiple limitations to our work. Firstly, the sample size of both the provider and patient populations are too small to make any firm conclusions about clinical outcomes, such as initiating AC therapy. Therefore, we restricted the scope of the proposed study to verify the usability and perceived usefulness of the AFib 2gether mobile app, as well as the extent and nature of shared decision making with the use of the app. Secondly, we did not have a control population against which to compare our intervention. In the future, we plan to increase the sample size and conduct a randomized controlled trial powered to find a difference in AC therapy starts. Thirdly, some patients downloaded and explored the app at home prior to the visit, whereas others, such as those without smartphones, only reviewed it in the waiting room of the office. We invited the latter patients to arrive 30 minutes prior to their visit in order to adequately evaluate the app. Nonetheless, we acknowledge the variability in usability that might be reported for a patient who reviewed the app without time constraints at home compared to a patient who only reviewed the app in the waiting room. In the future, with a greater sample size, we plan to measure the discrete effect of the intervention in each situation. Fourthly, we also acknowledge that prompting by the RA may have made the app appear more useful than it would have appeared with no prompting. Given that we are still making minor modifications to enhance the app, we anticipate being able to replace the manual prompting with an automated text message alert reminding providers to review patient responses. Lastly, a final limitation is that the patients who agree to participate likely represent a healthier, more technologically proficient, and potentially more educated population. We did not collect specific information to gauge patient technology proficiency, so we cannot compare our population with others. Future assessment of technology proficiency would help us to understand the representativeness of the population exposed to the app versus the general AF population.

In conclusion, we have described the protocol for assessing the usability and perceived usefulness of a mobile app to facilitate shared decision making concerning AC therapy in patients with AF and elevated stroke risk. The AFib 2gether app-based intervention improves on other shared decision-making interventions by leveraging a convenient platform (ie, the cell phone app) and soliciting items for discussion and review before the patient-provider visit. Although we will not be able to confirm the ability of the app to demonstrate a significant increase in AC therapy starts, our study will lay the groundwork for future efforts to conduct a multicenter, randomized clinical trial that will be able to elucidate the impact of our mobile app on clinical outcomes. With the latter road paved, we anticipate generating significant interest among other researchers developing app-based interventions to facilitate shared decision making for AC therapy in AF and similarly challenging treatment decisions.

Acknowledgments

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Conflicts of Interest

AK received sponsored research support from Pfizer Inc for this project and has received similar support in the past from both Bristol-Myers Squibb and Pfizer Inc. DM receives sponsored research support from Bristol Myers Squibb, Boehringer Ingelheim, Pfizer Inc, Biotronik, and Philips Healthcare and has consulted for Bristol Myers Squibb, FlexCon, Samsung, Philips, and Pfizer Inc. DM has equity in Mobile Sense Technologies, LLC. AA, AH, DM, KM, and AK are employees of the Department of Medicine, UMass Medical School, Worcester, Massachusetts, which received financial support from Pfizer Inc in connection with this research. CP, KM, and RHD are full-time employees of Pfizer Inc.

Multimedia Appendix 1
Assessment of provider knowledge and therapeutic approaches for reducing stroke risk in patients with nonvalvular atrial fibrillation.
[PDF File (Adobe PDF File), 172 KB - resprot_v10i2e21986_app1.pdf]

Multimedia Appendix 2
Provider and patient usability of the mobile app.
[DOCX File , 15 KB - resprot_v10i2e21986_app2.docx]

Multimedia Appendix 3
Questionnaire assessing the patient perceived usefulness of the mobile app.
[DOCX File , 12 KB - resprot_v10i2e21986_app3.docx]

Multimedia Appendix 4
Questionnaire assessing the provider perceived usefulness of the mobile app.
[DOCX File , 12 KB - resprot_v10i2e21986_app4.docx]

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Abbreviations

AC: anticoagulation
ACC: Ambulatory Care Center
AF: atrial fibrillation
AHA: American Heart Association
CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, vascular disease, age 65-74 years, sex category
EHR: electronic health record
HIPAA: Health Insurance Portability and Accountability Act
MARS: Mobile App Rating Scale
RA: research assistant
REDCap: Research Electronic Data Capture
TAM: technology acceptance model
UMass: University of Massachusetts
UTAUT2: unified theory of acceptance and use of technology 2

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Protocol

Clinical and Epidemiological Characteristics of Postdischarge Patients With COVID-19 in Tehran, Iran: Protocol for a Prospective Cohort Study (Tele-COVID-19 Study)

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Abstract

Background: COVID-19 was declared a pandemic on March 11, 2020. Given that the severe shortage of hospital beds has led to early discharge and insufficient patient education on home care routines and isolation protocols, the close follow-up of patients and their immediate relatives is an integral part of transitioning from hospital care to home care for patients with COVID-19.

Objective: We designed the Tele-COVID-19 prospective cohort to follow-up with COVID-19 patients in Tehran, Iran, and improve health care delivery and the recording of postdischarge patients' clinical profiles.

Methods: All adult patients who were admitted to the COVID-19 wards of teaching hospitals in Tehran, Iran were eligible to participate in this cohort study. At baseline, patients were recruited from 4 major hospitals from March 9, 2020 to May 20, 2020. Telephone follow-ups, which were led by volunteer medical students, were conducted on postdischarge days 1-3, 5, 7, 10, and 14. We collected data on a range of sociodemographic, epidemiological, and clinical characteristics by using a standard questionnaire.

Results: Of the 950 patients with confirmed COVID-19 who were approached, 823 (response rate: 86.6%) consented and were enrolled into the cohort. Of the 823 participants, 449 (54.5%) were male. The mean age of participants was 50.1 years (SD 12.6

years). During the initial data collection phase, more than 5000 phone calls were made and over 577 reports of critical patients who were in need of urgent medical attention were recorded.

Conclusions: The Tele-COVID-19 cohort will provide patients with sufficient education on home care and isolation, and medical advice on care and the proper use of drugs. In addition, by preventing unnecessary hospital returns and providing information on household SARS-CoV-2 transmission as early as possible, this cohort will help with effective disease management in resource-limited settings.

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KEYWORDS

cohort studies; COVID-19; health care delivery; Iran; medical education; telemedicine

Introduction

The COVID-19 disease, which is caused by the SARS-CoV-2 virus, was declared a pandemic on March 11, 2020. Based on the existing evidence, the risk of infection appears to be relatively low for the general population. However, older people, immunocompromised people, and those with underlying health conditions, such as cardiovascular diseases, are at an elevated risk of morbidity and mortality [1]. As of December 11, 2020, 71,088,688 patients with confirmed COVID-19 and 1,595,096 deaths have been reported across the globe [2]. To date, effective treatment options for COVID-19 are unavailable. However, more than 2500 trials and studies are being conducted worldwide to develop and evaluate different therapeutic options for COVID-19 [3]. Implementing swift, community-centered preventive measures, providing timely diagnoses, treatments, contact tracing services, and methods for the successful isolation of patients at home, and reducing the household transmission of the virus among infected patients' close contacts have been at the core of recommended strategies for combating the disease [4-6].

Despite the extensive worldwide efforts for controlling the pandemic, the constantly rising patient load and limited personal protective equipment supplies have overwhelmed health care systems across the globe. However, the toll of the COVID-19 pandemic has been heavier for low- and middle-income settings, wherein health care systems are already underfunded, understaffed, and overstretched. Iran is one of the countries that was hit the hardest by the COVID-19 outbreak. The first patient with confirmed COVID-19 in Iran was reported on February 19, 2020 in the city of Qom, which is 200 km away from Tehran, the capital city of Iran. As of December 11, 2020, 1,092,407 patients with confirmed COVID-19 and 51,727 deaths have been reported in the country [7]. Iran's initial response to the pandemic included physical distancing control policies that aimed to minimize close contact within communities, as well as individual-level restrictions (eg, quarantine and isolation) and community-level restrictions (eg, educational and recreational facility closures, nonessential business closures, and the cancellation of public/mass/crowded gatherings). Nevertheless, economic sanctions, inadequate financial and human resources, inefficient leadership, and limited hospital capacities for the rapidly growing number of patients with COVID-19 who require hospitalization have created real and considerable challenges for controlling the epidemic [8-10]. As >98% of the population has access to mobile or landline phones [11], a cost-effective method for reducing the community transmission of SARS-CoV-2 and managing the influx of patients with COVID-19 in Iran's hospitals could be managing discharged patients or patients with noncritical conditions via routine telephone follow-ups. Telemedicine has been proposed as an effective approach for responding to health emergencies. A telemedicine approach may ensure that the limited number of hospital beds are occupied by the people who need them most, and provide patients and their families with access to medical care, without unnecessary referrals to health care facilities [12,13]. Therefore, we designed a prospective cohort study (ie, the Tele-COVID-19 study) to follow-up with patients with COVID-19 who have been discharged from teaching hospitals in Tehran, to assess the overall spread of SARS-CoV-2 in the community. The specific objectives of the Tele-COVID-19 study are as follows: (1) conduct telephone-based follow-ups with patients who were admitted to the coronavirus emergency departments of certain hospitals in Tehran; (2) precisely monitor postdischarge patients' signs and clinical symptoms; (3) provide patients with sufficient education on home care and isolation principles, and medical advice on care and the proper use of drugs; (4) prevent unnecessary hospital returns and provide timely information on the in-household transmission of SARS-CoV-2; and (5) refer postdischarge patients with critical conditions to the emergency department in a timely manner, and facilitate patient readmission when necessary. Herein, we present the overall characteristics of the Tele-COVID-19 cohort and the preliminary baseline characteristics of the first-round patients who were recruited into the cohort.

Methods

Study Design

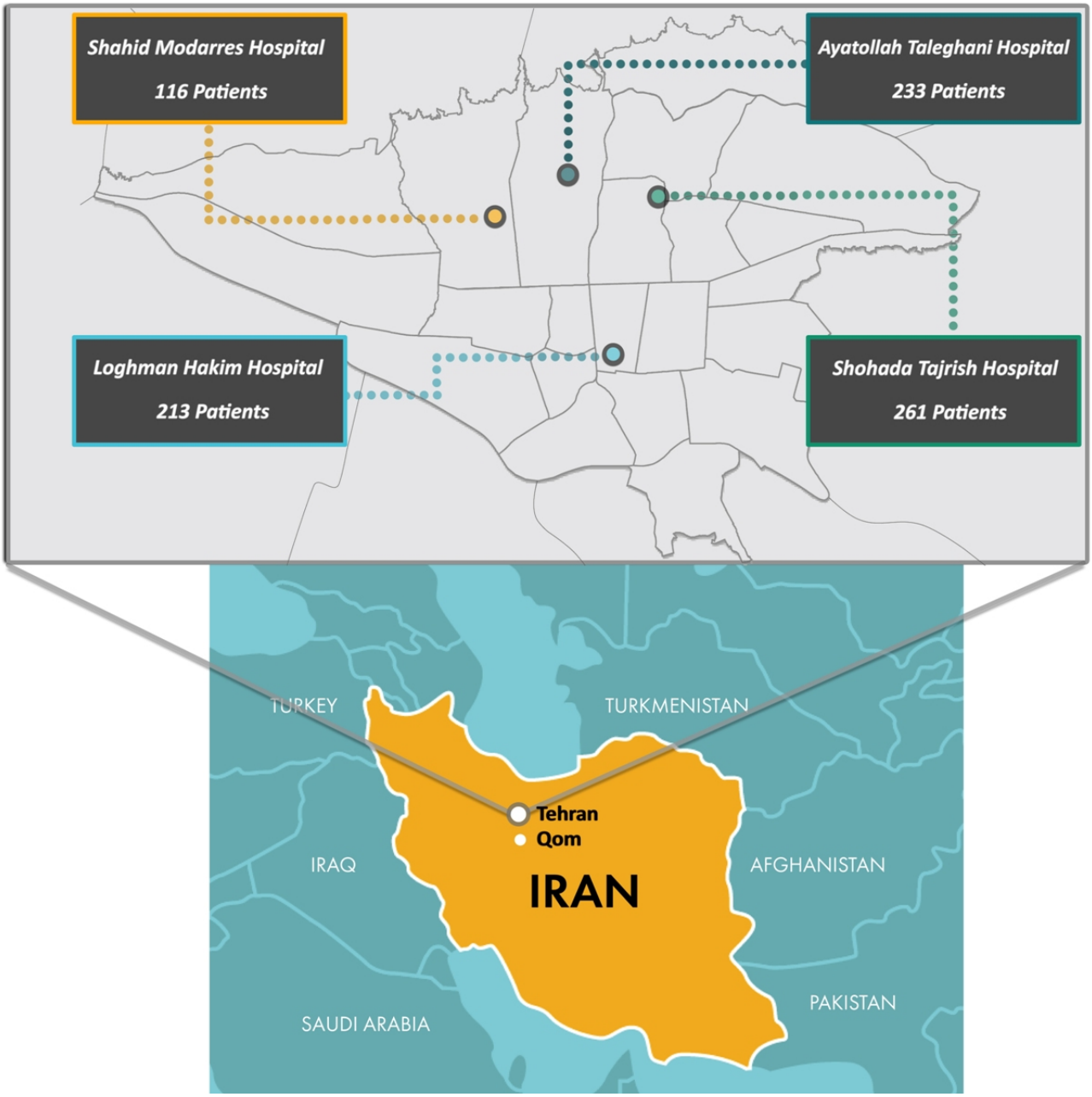
The Tele-COVID-19 study is a prospective cohort study that was designed to follow-up with postdischarge patients with COVID-19 for a 2-week period in Tehran, Iran. At baseline, data collection was completed by a medical student volunteer group, which was established on February 22, 2020 under the supervision of clinical professors [14]. Baseline data collection was conducted from March 9, 2020 to May 20, 2020. Given the prospective nature of the cohort, a top-up sample of participants will be included in the sampling frame during subsequent waves of data collection. Due to the emerging nature of SARS-CoV-2, a prospective sample size was not calculated. Additionally,

because the recruitment of patients depends on the spread of COVID-19 in Tehran, there is no specific end date for recruitment at this point in time.

Setting

In total, 4 major teaching hospitals in Tehran (ie, Shohada Tajrish Hospital, Ayatollah Taleghani Hospital, Shahid Modarres Hospital, and Loghman Hakim Hospital) were included at baseline. Collectively, these hospitals have 1652 beds, 136 primary care clinics, more than 100 specialties, and over 3000 employees. Of these 4 hospitals, 3 are located in the northern districts of Tehran and 1 is located in the southern district (Figure 1).

Figure 1. Hospitals included in the first phase of recruitment for the Tele-COVID-19 cohort.



Eligibility Criteria

Eligible participants were hospitalized adults (ie, aged >18 years) with COVID-19. Patients who tested positive for SARS-CoV-2 infection in polymerase chain reaction tests, and those who were treated and discharged from COVID-19 wards were recruited into the cohort. Participants were excluded if their contact information was wrong or missing. All patients who did not respond to follow-up phone calls or declined to provide consent were also excluded. Participants were briefed about this study's aims and objectives via in-person discussions in the hospital and postdischarge phone calls. All participants provided verbal consent, and each patient received a unique national identification code to avoid potential biases that could arise from patients who went to several other health care facilities postdischarge.

Data Collection

At baseline, telephone follow-ups, which were led by volunteer medical students, were conducted on postdischarge days 1-3,

5, 7, 10, and 14, in accordance with a predetermined protocol and under the supervision of clinical professors. The calls were made to patients' cell phones or landline phones from 10 AM to 4 PM. In the case of a nonresponse, calls were repeated 3 times at 2-hour intervals until the end of the calling time. Patients were excluded if they could not be reached by the end of the day. The first round of interviews was conducted by medical clerks. If a patient was assessed to have a concerning or critical condition, a follow-up phone call was made by a senior medical intern after consulting clinical professors for further assessment. Data were recorded on a secure and password-protected web-based platform. Each medical clerk signed a nondisclosure agreement before the enrollment period, to ensure that data remained secure and confidential. Medical clerks could only observe the data that they themselves collected; they could not observe the data that other team members collected. By the end of each patient's 14-day follow-up period, all data were extracted from the web-based platform and stored on a password-protected external hard drive.

Data were collected by using a pilot-tested, comprehensive COVID-19 risk assessment questionnaire. The development of the questionnaire was informed by the Center for Disease Control and Prevention and the national guidelines of the Ministry of Health and Medical Education, and included the following areas: sociodemographic information (eg, age and sex), a history of potential exposure to SARS-CoV-2 (eg, a travel history to China or the city of Qom and a history of exposure to patients with COVID-19), signs and clinical symptoms (eg, fever, dry cough, dyspnea, nausea, and diarrhea), a medical history of underlying conditions (eg, a history of diabetes, cardiovascular disorders, chronic lung disease, chronic renal disease, and immunodeficiency), habitual history (eg, current smoker, former smoker, and nonsmoker), prescribed drugs at postdischarge (eg, hydroxychloroquine and lopinavir/ritonavir), a history of non-COVID-19–related medications (eg, nonsteroidal anti-inflammatory drugs and statin), and household information on close contacts (eg, high-risk household contacts and household transmissions).

Interview Process

Interviewers were enrolled if they were fourth-year to seventh-year medical students and registered in their respective medical schools at the time of interviews. There were 2 main groups of interviewers, as follows: (1) medical clerks (ie, those in their fourth and fifth years of training) and (2) medical interns (ie, those in their sixth and seventh years of training). Under the supervision of clinical professors, medical interns were mentored by faculty staff. Medical interns also helped with supervising the medical clerks. All interviewers completed a 40-hour crash course. The educational topics in the course were tailored toward COVID-19–related prevention, care, and treatment. The topics included methods for taking a complete history, methods for conducting complete physical examinations, essential practices for COVID-19, guidance on precautionary measures for providing home care and isolating patients and other household members, and the assessment of high-risk conditions (ie, interviewers were given a referral guide for each medical condition). Data collection procedures were pilot-tested with patients through role play to ensure that data were collected consistently. During the phone calls, patients and their household members were educated on home care procedures and isolation guidelines. All clinical signs and symptoms were closely examined and recorded. Treatment regimens and procedures were adjusted accordingly, and patients were instructed to stay at home or return to the emergency room if they or their household members exhibited critical symptoms.

Statistical Analysis

Data entries were double-checked and cleaned by using STATA version 15 (StataCorp LLC). For the purposes of this prospective cohort study, descriptive statistics, including relative frequencies for categorical variables and means and standard deviations for quantitative variables, were reported. However, for the purposes of future studies that derive data from our cohort, associations will be examined by using appropriate regression analyses.

Ethics

The study protocol was reviewed and approved by the ethics committee of the Shahid Beheshti University of Medical Sciences (Ethics approval reference number: IR.SBMU.RETECH.REC.1399.114).

Results

Of the 950 patients with confirmed COVID-19 who were approached at the initial phase of the Tele-COVID-19 study, 823 (86.6%) consented and were successfully enrolled in this study. Of the 823 participants, 261 (31.7%) were from Shohada Tajrish Hospital, 213 (25.9%) were from Loghman Hakim Hospital, 233 (28.3%) were from Ayatollah Taleghani Hospital, and 116 (14.1%) were from Shahid Modarres Hospital. The baseline characteristics of the enrolled patients are presented in Table 1.

Of the 823 participants, 449 (54.5%) were male. The mean age of participants was 50.1 years (SD 12.6 years). Overall, 65 (65/821, 7.9%) participants were health care workers, and 19 (19/821, 2.3%) participants reported that they travelled to known epicenters of COVID-19 within the previous 14 days of the interview. A total of 471 (471/818, 57.6%) reported that they were exposed to a patient with COVID-19 within the past 14 days of the interview. A total of 701 (701/814, 86.2%) patients visited a hospital due to suspicious signs and symptoms, and 59 (59/814, 7.2%) patients sought medical attention due to being exposed to people with probable COVID-19. Overall, 167 (167/811, 20.6%) were current/former smokers. Most patients did not have any underlying diseases (372/676, 55%), and only 25 (25/818, 3.1%) were immunodeficient. The mean length of hospitalization was 5.23 days (SD 4 days).

Detailed data on baseline clinical symptoms was available for 676 patients. Among the baseline clinical symptoms, the 3 most common symptoms were cough (466/676, 68.9%), respiratory distress (394/676, 58.3%), and fever (364/676, 53.8%). Only a small proportion of patients (29/676, 4.3%) had severe conditions (ie, admitted to an intensive care unit or had an oxygen saturation level of <90%). Most patients reported that they would be able to self-isolate at postdischarge (565/676, 83.5%).

Table 1. Baseline characteristics of patients with COVID-19 from the Tele-COVID-19 cohort in Tehran, Iran.

Characteristics	Value
Number of patients from each hospital (N=823), n (%)[a]	
Loghman Hakim Hospital	213 (25.9)
Shohada Tajrish Hospital	261 (31.7)
Shahid Modarres Hospital	116 (14.1)
Ayatollah Taleghani Hospital	233 (28.3)
Sex (N=823), n (%)[a]	
Male	449 (54.6)
Female	374 (45.4)
Age (years; N=823), mean (SD)	50.1 (12.6)
Health care worker (N=821), n (%)[a]	
Yes	65 (7.9)
No	756 (92.1)
Travel history in the previous 14 days (N=821),n (%)[a]	
China	1 (0.1)
Qom province	10 (1.2)
Gilan province	8 (0.9)
No travel history	802 (97.6)
Exposure to patients with confirmed COVID-19 in the previous 14 days (N=818), n (%)[a]	
Yes	176 (21.5)
No	642 (78.5)
Reason for hospital visit (N=814), n (%)[a]	
Suspicious clinical signs and symptoms	701 (86.2)
Exposure to a probable COVID-19 patient	59 (7.2)
Other	54 (6.6)
Smoking history (N=811), n (%)[a]	
Current smoker	77 (9.5)
Former smoker	90 (11.1)
Nonsmoker	644 (79.4)
Chronic respiratory conditions[b] (N=818), n (%)[a]	
Yes	81 (9.9)
No	737 (90.1)
Diabetes mellitus (N=820), n (%)[a]	
Yes	159 (19.4)
No	661 (80.6)
Cardiovascular conditions (N=817), n (%)[a]	
Yes	181 (22.2)
No	636 (77.8)
Chronic renal conditions (N=821), n (%)[a]	
Yes	57 (6.9)
No	764 (93.1)

Characteristics	Value
Chronic liver conditions (N=821), n (%)[a]	
Yes	23 (2.8)
No	798 (97.2)
Immunodeficiency (N=818), n (%)[a]	
Yes	25 (3.1)
No	793 (96.9)
Underlying neurological conditions[c] (N=819), n (%)[a]	
Yes	52 (6.5)
No	767 (93.5)
Number of hospitalization days, mean (SD)	5.32 (4)
Clinical signs and symptoms (N=676), n (%)[a]	
Fever	364 (53.8)
Chills	327 (48.4)
Myalgia	225 (33.3)
Headache	306 (45.3)
Cough	466 (68.9)
Respiratory distress	394 (58.3)
Nausea and vomiting	270 (39.9)
Diarrhea	239 (35.4)
Loss of appetite	289 (42.8)
Loss of weight	69 (10.2)
Abdominal pain	144 (21.3)
Anosmia	127 (18.8)
Ageusia	134 (19.8)
Rhinorrhea	117 (7.9)
Sore throat	171 (17.3)
Consciousness alterations	95 (14.1)
COVID-19 severity[d] (N=676), n (%)[a]	
Mild to moderate	647 (95.7%)
Severe	29 (4.3%)

[a]Percentages are rounded to 1 decimal point.

[b]Chronic respiratory conditions include asthma, emphysema, and chronic obstructive pulmonary disease.

[c]Underlying medical conditions include chronic neurological diseases and neurodevelopmental/intellectual disability.

[d]Severe cases included people who were admitted to the intensive care unit or had an oxygen saturation level of <90%.

During the initial data collection phase, more than 5000 phone calls were made. Overall, 577 reports were recorded in the daily critical case report sheets. Patients with critical conditions were directly followed by medical interns and clinical professors for more specific medical care. Patients with serious conditions (n=69) were referred to the emergency department, in accordance with hospital staff recommendations. Of these 69 patients, 40 (58%) were rehospitalized. Patients with minor conditions who primarily intended to revisit a hospital were successfully managed over the phone, leading to the prevention of unnecessary hospital visits (296/823, 36%). A total of 60 (60/823, 7.3%) patients who reported that they were experiencing adverse reactions to medications were managed through phone calls.

Discussion

Principal Findings

The Tele-COVID-19 cohort provided a platform for effectively following up with patients with COVID-19 after hospitalization. Our prospective cohort study presents a cost-effective way of

managing postdischarge patients with COVID-19 and supporting them and their family members on their path to full recovery. The Tele-COVID-19 cohort was designed and run by a group of volunteer medical students, who successfully followed up with 823 postdischarge patients with COVID-19 during the baseline wave of this study. Given the burden of COVID-19 on health care systems in resource-limited settings such as Iran, telephone-based follow-up studies that involve medical students may not only enhance patient care, but also enhance medical education for medical students, who are often left out of the COVID-19 response due to concerns about limited personal protective equipment resources and students' safety [15]. Early, postdischarge telephone follow-up calls have previously been shown to improve patients' health outcomes and reduce their chances of readmission or critical condition development in the first month after discharge [16-19].

Limitations

We acknowledge that our study has several limitations that are common among studies of a similar nature. First, our nonrandom sample of participants from major hospitals in Tehran may not be generalizable to patients with COVID-19 in other parts of Tehran or Iran. However, it is likely that the characteristics of the participants who were recruited into our cohort are not considerably different from those of patients from other Tehran hospitals that were not included in our study. Second, participants' self-reported responses with regard to potential risk factors or underlying comorbidities are prone to social desirability and reporting biases. Third, we did not collect any data on the mental health profiles of patients. This could be considered for future waves of data collection. Fourth, most patients in our cohort (647/676, 95.7%) exhibited mild or moderate COVID-19 symptoms. Furthermore, these patients had no adverse underlying conditions. Therefore, these patients do not provide a complete clinical picture of severe COVID-19 in Tehran hospitals.

Conclusions

The Tele-COVID-19 cohort is a unique, student-led cohort that could provide an effective platform for improving our evolving understanding of COVID-19 care and treatment in Iran. Such cohort studies assist the medical community by reducing the number of medical complications among people who are recovering from COVID-19, improving our understanding of the clinical course of the disease, identifying potential drug interactions and the adverse effects of pharmacotherapies, reducing the household transmission and secondary attack rates of SARS-CoV-2, referring discharged patients with critical conditions to the emergency department in a timely manner, reducing patients' anxiety, and preventing unnecessary hospital visits. Moreover, cohorts like the Tele-COVID-19 cohort provide a cost-effective and rapidly implementable platform for improving our understanding of COVID-19 in resource-limited settings.

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Authors' Contributions

All authors contributed to the development of the cohort. LJK and MV prepared the first draft of the manuscript under the supervision of MK. All authors reviewed, revised, and approved the final manuscript draft.

Conflicts of Interest

None declared.

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Protocol

Improving Assessment, Diagnosis, and Management of Urinary Incontinence and Lower Urinary Tract Symptoms on Acute and Rehabilitation Wards That Admit Adult Patients: Protocol for a Before-and-After Implementation Study

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Abstract

Background: Urinary incontinence (UI) and lower urinary tract symptoms (LUTS) are commonly experienced by adult patients in hospitals (inpatients). Although peak bodies recommend that health services have systems for optimal UI and LUTS care, they are often not delivered. For example, results from the 2017 Australian National Stroke Audit Acute Services indicated that of the one-third of acute stroke inpatients with UI, only 18% received a management plan. In the 2018 Australian National Stroke Audit Rehabilitation Services, half of the 41% of patients with UI received a management plan. There is little reporting of effective inpatient interventions to systematically deliver optimal UI/LUTS care.

Objective: This study aims to determine whether our UI/LUTS practice-change package is feasible and effective for delivering optimal UI/LUTS care in an inpatient setting. The package includes our intervention that has been synthesized from the best-available evidence on UI/LUTS care and a theoretically informed implementation strategy targeting identified barriers and enablers. The package is targeted at clinicians working in the participating wards.

Methods: This is a pragmatic, real-world, before- and after-implementation study conducted at 12 hospitals (15 wards: 7/15, 47% metropolitan, 8/15, 53% regional) in Australia. Data will be collected at 3 time points: before implementation (T_0), immediately after the 6-month implementation period (T_1), and again after a 6-month maintenance period (T_2). We will undertake medical record audits to determine any change in the proportion of inpatients receiving optimal UI/LUTS care, including assessment, diagnosis, and management plans. Potential economic implications (cost and consequences) for hospitals implementing our intervention will be determined.

Results: This study was approved by the Hunter New England Human Research Ethics Committee (HNEHREC Reference No. 18/10/17/4.02). Preimplementation data collection (T_0) was completed in March 2020. As of November 2020, 87% (13/15) wards have completed implementation and are undertaking postimplementation data collection (T_1).

Conclusions: Our practice-change package is designed to reduce the current inpatient UI/LUTS evidence-based practice gap, such as those identified through national stroke audits. This study has been designed to provide clinicians, managers, and policy makers with the evidence needed to assess the potential benefit of further wide-scale implementation of our practice-change package.

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KEYWORDS

urinary incontinence; lower urinary tract symptoms; inpatient; practice-gap; practice improvement; protocol

Introduction

Background

Urinary incontinence (UI) and lower urinary tract symptoms (LUTS) are commonly experienced by adults admitted to hospitals, also referred to as inpatients, and contribute to the complexity and cost of providing care to these individuals. UI types include functional, neurogenic, stress, overflow, continuous, urgency, and mixed UI [1,2]. LUTS include acute and chronic urinary retention, frequency, urgency, and nocturia [1,2]. Surprisingly, data on the prevalence of UI and LUTS in adult inpatients are limited. However, these conditions have been reported to range from 10% to 45% of patients receiving acute and subacute care in hospitals [3-5]. The often-taboo subject of UI is significantly associated with poorer patient outcomes, including urinary tract or urinary catheter–associated infections [6,7], incontinence-associated pressure injury [8], falls [9], and pain associated with these conditions [6,7]. People with UI are twice as likely to experience depression and are more often socially isolated [6,7,10]. UI is associated with increased carer stress and is a main reason for carers feeling unable to continue in the carer role, leading to residential care admissions [11]. Although UI and LUTS are often complex and not always curable, with appropriate clinical care, symptoms can be managed and complications can be avoided.

International and Australian clinical practice guidelines provide recommendations for optimal care for UI and LUTS, based on the current, albeit limited research evidence [1,12-16]. Stroke is an example where UI and LUTS care has been included in condition-specific guideline recommendations [17-19]. Australian stroke guideline recommendations for optimal care are that all people poststroke are screened for continence issues and that those with symptoms receive an assessment, diagnosis, and a tailored inpatient and postdischarge management plan [17]. In the 2017 National Stroke Audit Acute Services, of the one-third of inpatients with UI, only 18% received a management plan [20]. In the 2018 National Stroke Audit Rehabilitation Services, of the 41% of inpatients who had UI, 52% had a documented management plan [21]. These results indicate an evidence-practice gap in current inpatient UI/LUTS care.

Although peak bodies recommend that health services have systems for optimal UI and LUTS care [1,15,17], there is little reporting of effective inpatient interventions to systematically deliver this care, as demonstrated in stroke care. In a recent Cochrane review, it was identified that there was limited evidence for the effectiveness of UI interventions poststroke

[6]. The review included 20 trials (with 1338 participants, reporting 21 comparisons), with the authors reporting that the risk of bias was impossible to judge for many of the included studies because of poor reporting. The authors call for more robust multicenter trials.

As part of our formative quality improvement research [22], in 2009-2010, we translated high-level UI and LUTS guideline recommendations into an intervention that presents clear, concise, and explicit optimal inpatient care in a user-friendly format [23]. We collaborated with health service clinicians and managers from 3 rehabilitation services in the Hunter Region, Australia, to synthesize the best-available evidence into our Structured urinary Continence Assessment and Management Plan (SCAMP) intervention that was specifically designed for inpatients poststroke in metropolitan rehabilitation units [22]. Our SCAMP intervention consists of (1) a 4-page clinical decision support tool guiding comprehensive UI and LUTS assessment, diagnosis, and management; (2) the associated clinical practice guideline; and (3) supporting web-based education modules [22]. Stroke clinicians using the SCAMP intervention identified that it has the potential to be applicable across a range of hospitals in different health districts, for inpatients with a range of diagnoses including stroke, and across the phases of inpatient care.

Aim

The aim of this study is to determine if the implementation of our SCAMP intervention is feasible and effective across this range of clinical scenarios.

Research Questions

Primary

Does the implementation of our SCAMP intervention increase the proportion of inpatients with UI/ LUTS who have an individually tailored UI/ LUTS management plan?

Secondary

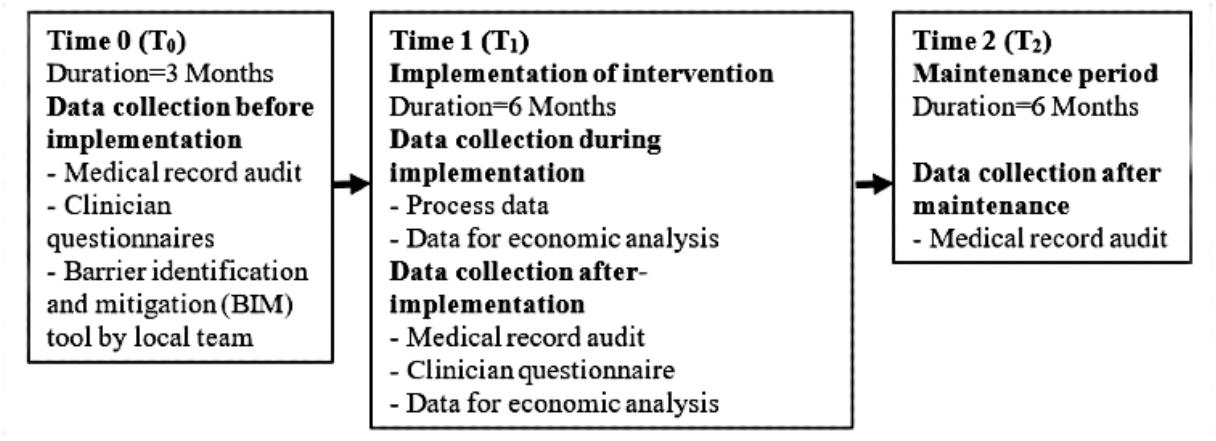
1. Does the implementation of our SCAMP intervention increase the proportion of:
   - Inpatients with UI/LUTS who have an assessment and diagnosis of types of UI/LUTS?
   - Inpatients with UI/LUTS and their caregivers who are involved in the development of the management plan?
   - Clinicians who rate their knowledge, skills, and confidence in identifying the types of UI/LUTS and assessing, diagnosing, and managing UI/LUTS as good or very good?
2. Does the implementation of our SCAMP intervention reduce in-hospital complication rates associated with UI/LUTS or urinary catheterization?
3. Are any improvements in the above outcomes maintained at 12 months after implementation begins?
4. What are the potential economic implications (cost and consequences) for hospitals implementing our SCAMP intervention?

Methods

Design

This will be a pragmatic, real-world, before- and after-implementation study conducted at 12 hospitals. Data will be collected at 3 time points: before implementation (T_0), immediately after the 6-month implementation period (T_1), and again after a 6-month maintenance period (T_2; Figure 1). Data will be collected from medical record audits and clinician questionnaires. An economic evaluation from the perspective of hospitals will be conducted. We will report our primary findings according to the Standards for Reporting Implementation Studies (StaRI) [24,25].

Figure 1. Study design and data collection timeframes.



Target Sites

Eleven hospitals in New South Wales (NSW) and 1 in Queensland, Australia, participated in our study. The hospitals are located in 4 health service districts. The hospitals were a convenience sample. Ten of the hospitals are located in 2 Local Health Districts that form part of the NSW Regional Health Partners, a Centre for Innovation in Regional Health (accredited by the National Health and Medical Research Council). Lead clinicians from the other 2 hospitals heard about our SCAMP intervention at conference presentations and approached the lead author about adopting the intervention.

Fifteen wards where patients after stroke are admitted are participating (Table 1). In Australia, people after stroke are cared for on wards that admit people with a range of conditions.

This care may be provided in a stroke unit embedded in the ward or as part of the general ward population. This study was instigated by stroke clinicians who identified UI/LUTS inpatient care needed to be improved on their ward for people after stroke and potentially for other inpatient populations. To be eligible to participate, key ward clinicians and managers had to identify that UI/LUTS care was an issue for their ward and that they were willing to commit resources toward improving optimal UI and LUTS care by implementing the SCAMP intervention. The characteristics of each ward are outlined in Table 1. A total of 47% (7/15) of the wards are in 4 hospitals in 2 major cities, and the other 53% (8/15) wards are in 8 hospitals in inner regional locations [26]. The wards included 43% (7/15) rehabilitation wards, 27% (4/15) acute medical wards with an embedded stroke unit, 13% (2/15) wards with both acute and rehabilitation inpatients, 7% (1/15) rehabilitation ward with an embedded stroke unit, and 7% (1/15) medical ward. Before commencing the study, the investigators from each ward nominated the target adult inpatient populations from their ward to be included in the study of acute stroke, acute medicine, and/or rehabilitation for any condition, including stroke (Table 1). Clinician representatives from each site have been project team members from the outset (including authors KB, JAD, JS, FM, AS, JB, SO, AB, and SL).

Table 1. Characteristics of the participating wards.

Ward	Ward description	Hospital type and remoteness classification [26]	Previous use of SCAMP[a] intervention	Patient populations included
1.	20-bedded rehabilitation ward	Principal referral or major city	Yes	Rehabilitation
2.	20-bedded rehabilitation ward	Principal referral or major city	No	Rehabilitation
3.	30-bedded rehabilitation ward: • 22 rehabilitation or hospital overflow • 8 neurological	Principal referral or major city	Yes	• Acute medicine • Acute stroke • Rehabilitation
4.	12-bedded ward: • 8 general medicine • 4 acute stroke units	Public acute group A or major city	Yes	• Acute medicine • Acute stroke
5.	30-bedded ward: • 26 general medicine • 4 comprehensive stroke units	Public acute group B or major city	Yes	• Acute medicine • Stroke: acute and rehabilitation
6.	32-bedded ward: • mixed medical and rehabilitation ward	Public acute group B or inner regional	Yes	• Acute stroke • Rehabilitation
7.	32-bedded rehabilitation ward	Public acute group B or major city	No	Rehabilitation
8.	28-bedded general medical ward	Public acute group B or major city	No	• Acute medicine • Acute stroke
9.	22-bedded rehabilitation ward	Public acute group A or inner regional	No	Rehabilitation
10.	28-bedded ward: • 24 general medical • 4 acute stroke unit	Public acute group A or inner regional	Yes	Acute stroke
11.	16-bedded rehabilitation hospital	Rehabilitation or inner regional	No	Rehabilitation
12.	28-bedded ward: • 4 acute stroke units • 8 medical assessment units • 16 respiratory or cardiac units	Public acute group A or inner regional	No	Acute stroke
13.	24-bedded ward: • 20 general rehabilitation • 4 comprehensive stroke units	Public acute group A or inner regional	No	Stroke: acute and rehabilitation
14.	18-bedded hospital: • 8 rehabilitation • 10 general medical	Public acute group C or inner regional	No	Rehabilitation
15.	16-bedded rehabilitation ward	Public acute group A or inner regional	No	Rehabilitation

[a]SCAMP: Structured urinary Continence Assessment and Management Plan.

Target Population

The population targeted by our practice-change package is clinicians (full time, part time, and casual) employed in each participating ward (including nurses, Nurse Unit managers, physiotherapists, occupational therapists, speech pathologists, social workers, and doctors). Participating clinicians are general medical, rehabilitation, or neuroscience clinicians who are not identified as continence or urology specialists. There are no exclusion criteria, as the study is a service improvement initiative, clinicians will not be consented to receive our practice-change package. The unit of analysis is hospital performance, based on patient-level data.

Practice-Change Package (Study Intervention)

Our practice-change package is designed to support clinicians and health services to deliver guideline-recommended UI and LUTS care. It consists of our SCAMP intervention that we will implement using evidence-based implementation strategies.

Intervention

In 2018, we reviewed all 3 components of our SCAMP intervention with experts from stroke, continence, rehabilitation, and urology to ensure that they met the current best-evidence UI and LUTS care for the majority of adult inpatient populations. Our SCAMP intervention consists of the following:

- The 4-page SCAMP decision support tool, which has been approved by the Hunter New England Local Health District Forms Committee
- The associated Clinical Practice Guideline that includes UI Management Flowcharts modified from the International Continence Society flowcharts
- Eight web-based education modules and a local module on how to use the SCAMP decision support tool (a PowerPoint presentation with a voice-over). The web-based modules cover information on normal bladder function, why continence is an issue after stroke, and 6 of the common inpatient UI and LUTS types and are hosted on the Stroke Foundation website [27]

Implementation Strategies

To enhance the success of our SCAMP intervention, we will use evidence-based theoretical approaches for implementation [28,29]. As there is no one all-encompassing theory that guides implementation of a complex multicomponent intervention, we have chosen to use complementary approaches that align best with the various components of the study, including the project design, assessment of the barriers and enablers, systematic planning and development of implementation and sustainability processes, and the evaluation of the project [29]. The Knowledge to Action framework is a process framework that guides implementation [23]. The Theoretical Domains Framework is the determinant framework that will help us identify the constructs that may influence implementation (barriers and facilitators) [30,31]. The evaluation plan is informed by the RE-AIM (reach, effectiveness, adoption, implementation, maintenance) framework [32,33].

Implementation strategies were selected to overcome barriers identified by project team members with experience in implementation science and known barriers to clinicians implementing guideline recommendations identified in the literature [34,35]. Textbox 1 outlines the planned implementation strategies to support the practice change and how these strategies align with the Expert Recommendations for Implementing Change [36].

To identify ward-specific barriers, local teams will use the Barrier Identification and Mitigation tool [37]. Local teams will observe and ask clinicians about the SCAMP decision support tool and guideline and walk through the process to simulate real ward circumstances. From the data they collect during the identification phase, each team will summarize and prioritize barriers and then develop a local action plan. The practice-change package will be adapted by each site to suit their local context.

Textbox 1. Summary of planned implementation strategies.

- Build a coalition. A coalition has been built that includes 15 wards across 12 hospitals, peak government and nongovernment bodies, and multiple universities.
- Work with educational institutions. Coalition members include institutions that provide tertiary and/or professional development education to the target groups.
- Develop academic partnerships and use data experts. Coalition members include academics from multiple institutions with expertise in implementation science, statistics, health economics, and data management.
- Centralize technical assistance. Sites will be supported by a centralized research team who will provide the evidence-based intervention (Structured urinary Continence Assessment and Management Plan; SCAMP); develop implementation resources in consultation with the team (including education materials and Implementation Training Workshops for site leaders); and evaluation resources (data collection tools, data storage, data analysis, and reporting).
- Access new funding. Sites will be supported to conduct the audits with small grants secured by the research team.
- Identify and prepare champions. Each site will have a local project lead and site champions who will drive the project locally. Leads will be senior clinicians, managers, or educators who have influence over local practice.
- Recruit, designate, and train for leadership. Site leaders will attend 2 training workshops that will include an overview what implementation research is and strategies for implementing evidence-based practice, overcoming barriers, generating sponsorship, communication, and using mixed methods for evaluation.
- Create a learning collaborative. A learning collaborative will be developed where sites learn from and share with each other to improve implementation.
- Develop resource-sharing agreements. Sites will share any implementation resources they develop with other members of the collaborative. This will be facilitated by a shared cloud–based repository.
- Organize clinician implementation team meetings and provide ongoing consultations. Project team members from each site will meet at 2 implementation workshops plus monthly teleconferences for education, consultation, and collaboration.
- Identify barriers and facilitators. Local sites will use the Behaviour Identification and Mitigation tool [37] to develop a local implementation plan.
- Tailor strategies and promote adaptability to meet local needs. Local implementation plans will tailor the implementation strategy and adapt the intervention to suit local needs.
- Distribute educational materials. Local sites will facilitate staff undertaking the education modules that inform the SCAMP decision support tool.
- Conduct educational meetings. Sites will conduct local education meetings to educate staff.
- Change record systems. The SCAMP decision support tool will be implemented at all sites. Paper or electronic versions will be used based on local needs.
- Audit and provide feedback. Before-implementation audit data will be fed back to each site.
- Remind clinicians. A poster display of different continence types and possible management solutions will be made available to all sites.

Outcomes

Our primary outcome is the change (T_1-T_0) in the proportion of inpatients who have an individually tailored UI/LUTS management plan. This will be determined via a medical record audit.

Our secondary research outcomes are:

1. The change (T_1-T_0) in proportion of:
   a. Inpatients with UI/LUTS who have an assessment and diagnosis of types of UI/LUTS, determined via a medical record audit
   b. Inpatients with UI/LUTS and their carers who are involved in the development of the management plan, determined via a medical record audit
   c. Clinicians who rate their knowledge, skills, and confidence in identifying the types of UI/LUTS and in assessing, diagnosing, and managing UI/LUTS as good or very good, determined via a clinician questionnaire
2. The change in in-hospital complication rates associated with UI/LUTS or urinary catheterization, determined via medical record audit (T_1-T_0)
3. The change in the aforementioned outcome measures at 12 months after implementation begins (T_2-T_0, T_2-T_1)
4. The potential economic implications for hospitals implementing our SCAMP intervention, determined using a cost-consequences analysis method

Data Collection Procedures

Data will be collected at 3 time points (Figure 1): before implementation (T_0), after a 6-month implementation period (T_1), and after a 6-month maintenance period (T_2). Before-implementation data will be used to tailor the intervention to each ward.

Medical Record Audit

Records of adults aged ≥18 years with the ward-nominated conditions who are discharged from each participating ward will be included. To reduce selection bias, we will include

consecutive records of patients discharged from each ward for each month of the 3-month data collection period.

Screening

Records will be screened to determine if the patient had UI/LUTS, including an indwelling urinary catheter, during their stay on the participating ward. During screening, we will extract data, including demographic, characteristic information, continence status, and how the UI/LUTS status was determined. Patients will be excluded from the full medical record audit if they are determined to have had no UI/LUTS during admission to the participating ward—deemed palliative/at the end of life and died during their admission or were discharged with this care type. People deemed to be at the end of life will be excluded as their management goals for UI/LUTS are usually different from those receiving acute and rehabilitative treatment. Patients who have an unexpected death, for example, cardiac arrest, during admission will be included.

Audits

Medical record audits of patients with UI/LUTS, including those with an indwelling urinary catheter, will be performed for 15 records for each month or until all patients discharged during that month have been screened, whichever occurs first. The medical record audit tool is based on questions in the Australian Stroke Foundation National Audits [20,38,39] and the content of the SCAMP decision support tool. The medical record audit tool was designed by KB and DM, piloted and refined by the project team members, including KB, J Dunne, JS, FM, AS, JB, SO, AB, KP, and SL, who will be performing the audits. The authors then examined the tool for face validity. Medical record audits will be conducted at each hospital by the project team members from that hospital and other local clinicians with legitimate access to the medical records, as per local health service requirements for patient privacy and confidentiality. A web-based medical record audit data dictionary is available. Information regarding assessment, diagnosis, management, complications, level of disability, and the presence of comorbidities relevant to UI/LUTS will be extracted. Study data will be extracted into and managed using the REDCap electronic data capture tool [40], hosted on a secure server at the Hunter Medical Research Institute, NSW.

Clinician Questionnaire

Our web-based clinician questionnaire is aligned with 13 of the 14 domains of the Theoretical Domains Framework [31] of behavior change. The optimism domain was not included as we perceived an overlap with the emotions, beliefs about consequences, beliefs about capability, and goals domain questions. Selecting domains to include in a questionnaire is in keeping with other studies that have used the Theoretical Domains Framework [31,41].

The target population for our intervention will be approached via email or in person by their site project team members and invited to complete a deidentified web-based questionnaire. Local site project team members will not have access to individual participant results. Demographic data will include age range, profession, and years of clinical experience. The clinician questionnaire was designed by authors KB, JD, and DM.

Process Evaluation

Measures will be collected to assess the process and fidelity of the implementation of the intervention. Spot check audits will be conducted by site members of the research team and site champions to identify any local issues with completing the SCAMP decision support tool. This information will inform local strategies to address the identified issues. We will also record the attendance for ward education sessions and the project team implementation workshops, the monthly project team meetings, the number and availability of identified champions throughout, the number and types of resources generated and reminder activities conducted, the number of audit and feedback sessions conducted, and any local changes made to the SCAMP intervention [42].

Economic Evaluation

As there are multiple potential benefits and the cost impacts are unclear from the perspective of the hospitals, we will undertake an exploratory assessment of resource use and costs and present these as a cost-consequences analysis [43]. We will obtain data on the costs of implementing the package (including staff training) and the direct health costs attributable to eligible patients across each study time period for the management of UI/LUTS, and report any potential cost offsets related to the practice-change package. Costs will be valued based on the reference year 2019. Data sources will include screening log and patient-level data from the medical record audits, hospital finance department data, research literature, expert opinion, and project management or administrative data. Costs and outcomes (ie, proportion of inpatients with an individually tailored UI/LUTS management plan and complication rates associated with UI/LUTS or urinary catheterization) will be presented to provide context for the changes in costs relative to the benefits to aid in the future translational potential of this package. All individual health and nonhealth effects of the intervention, including various cost items, will be reported as summary measures, for example, point estimates with a measure of variability (*Data Analysis* section).

Sample Size and Power Calculations

For the primary outcome, 15 consecutive medical record audits per site per month (ie, a pooled sample of 675 audits anticipated per data collection period) will provide >90% power to detect a 10% absolute increase (from before intervention) in the proportion of incontinent patients with a continence management plan (type 1 error rate of 5%). This calculation conservatively assumes that 20% of patients in acute and 50% of rehabilitation sites have a plan before intervention (based on the Australian Stroke Foundation National Audit results for included sites [20,39]).

Data Analysis

The before-intervention group, after-intervention group, and maintenance period group results will be presented with descriptive statistics, including site, clinician, and medical record data for characteristics and demographics. No individual will be identifiable. All results will be presented as aggregated

summary measures, with their variance depending on the distribution of the data (eg, mean and standard deviation, medians, and interquartile range). Groups will be compared with respect to change, from baseline (T_0) to immediately postintervention period (T_1) and from baseline to maintenance period (T_2) using mixed effects logistic regression models, with a random intercept for site, and fixed effect for period. Results are presented as odds ratios with 95% CI and *P* values.

Study Discontinuation

There are no criteria for study discontinuation as it is not anticipated that there are any events that would warrant discontinuation of this study. Any unforeseen adverse events will be reported to the Hunter New England Human Research Ethics Committee (the primary approval committee) and advice sought out regarding the required action. Any deviations from this original protocol will be reported in our study outcomes papers.

Results

Preimplementation data collection (T_0) was completed in March 2020. As of November 2020, 87% (13/15) wards have completed implementation and are undertaking postimplementation data collection (T_1).

Discussion

Our practice-change package is designed to reduce the current inpatient UI/LUTS care evidence-practice gap. We will contribute to the implementation research literature by demonstrating the potential impact of using a clinically applicable, evidence-based intervention that has been informed by the knowledge translation theory to optimize uptake in hospitals. We will describe the resources and costs associated with implementing the SCAMP intervention via a cost-consequences economic analysis. Our cost consequence analysis will provide an opportunity to pilot instruments used to collect economic data, such as resource use and clinical outcomes [43]. This analysis will be essential for establishing the benefit of scaling up the practice-change package. This study has been designed to provide clinicians, managers, and policy makers with the evidence needed to assess the potential benefit of further, wide-scale implementation of our practice-change package. We will report our findings according to the StaRI [24,25]. This will ensure that our practice-change package can be replicated in other clinical sites and in future research.

The results from this study will provide evidence to whether our UI/LUTS practice-change package is effective in supporting clinicians and health services deliver optimal care. To ensure that our practice-change package is evidence-based, clinically relevant, and applicable, it has been developed from the outset with our team of inpatient clinicians and managers, clinician researchers, and academics with experience in implementation science. To increase the generalizability and potential scalability of our practice-change package, we are testing it in a range of clinical scenarios and across the phases of inpatient care for people with a range of diagnoses, including stroke, admitted to metropolitan and regional hospitals in 4 health districts in 2 Australian states. It may also be applicable to other health conditions where providing optimal UI and LUTS care is challenging.

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This study was approved by the Hunter New England Human Research Ethics Committee (HNEHREC reference no. 18/10/17/4.02) and co-registered with the University of Newcastle Human Research Ethics Committee (UON HREC reference no. H-2020-0083). The authors would like to acknowledge the following: the project team members who are not listed as authors: Hunter Stroke Service—Annalese Johnson; Port Macquarie—Emily Saul, Michelle Coad, Jeremy Mulder; Ryde Hospital—Soo Cho, Virginia Mapurazi, Helen Wheat; Coffs Harbour—Helen King; Rockhampton—Sandy Greensill; Wauchope—Catherine Williams; NSW Agency for Clinical Innovation—Kate Jackson (Stroke Network) and Louise Sellars (Rehabilitation Network); Monash University—Joosup Kim and Garveeta Sookram for assistance with the economic evaluation plan; and Hunter Stroke Service—Monique Hourn and Hunter Medical Research Institute—Alix Hall for assistance with Redcap.

Louise-Anne Jordan, who led the initial development of the SCAMP intervention in 2008 and played an integral part in this study protocol, sadly passed away in November 2019. The authors recognize her contributions, leading to her posthumous authorship.

Authors' Contributions

DM, KB, DC, and JD led the overall development of the research protocol and DM led the development of the manuscript. L-AJ and M Pollack contributed to the development of the rationale and background for the protocol. JAD, JS, FM, AS, JB, SO, AB, KP, SL, MP, and KH contributed to the development of the protocol, intervention, and implementation support strategies. DM, KB, DC, and JD contributed to the development of data collection methods. DC contributed to the development of data collection

methods and analysis specific to economic analysis. CO contributed to the study design, sample size calculation, and data analysis plan. JW provided the overall guidance for the proposed conduct. All authors have read and approved the final manuscript.

Conflicts of Interest

This project forms the basis of author KB's PhD Candidature (University of Newcastle, NSW, Australia).

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Abbreviations

LUTS: lower urinary tract symptom
NSW: New South Wales
SCAMP: Structured urinary Continence Assessment and Management Plan
StaRI: Standards for Reporting Implementation Studies
T_0: before implementation
T_1: immediately after the 6-month implementation period
T_2: after a 6-month maintenance period
UI: urinary incontinence

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Protocol

Prospective Associations Between Fixed-Term Contract Positions and Mental Illness Rates in Denmark's General Workforce: Protocol for a Cohort Study

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Abstract

Background: In 2018, 14% of employees in the European Union had fixed-term contracts. Fixed-term contract positions are often less secure than permanent contract positions. Perceived job insecurity has been associated with increased rates of mental ill health. However, the association between fixed-term contract positions and mental ill health is uncertain. A recent review concluded that the quality of most existing studies is low and that the results of the few studies with high quality are contradictory.

Objective: This study aims to estimate the incidence rate ratios (RRs) of psychotropic drug use and psychiatric hospital treatment. These ratios will be considered, first, in relation to the contrast *fixed-term versus permanent contract* and, second, to *fixed-term contract versus unemployment*.

Methods: Interview data with baseline information on employment status from the Danish Labor Force Surveys in the years 2001-2013 will be linked to data from national registers. Participants will be followed up for up to 5 years after the interview. Poisson regression will be used to estimate incidence RRs for psychiatric hospital treatment for mood, anxiety, or stress-related disorders and redeemed prescriptions for psychotropic drugs, as a function of employment status at baseline. The following contrasts will be considered: full-time temporary employment versus full-time permanent employment and temporary employment (regardless of weekly working hours) versus unemployment. The analyses will be controlled for a series of possible confounders. People who have received sickness benefits, have received social security cash benefits, have redeemed a prescription for psychotropic drugs, or have received psychiatric hospital treatment for a mental disorder sometime during a 1-year period preceding baseline will be excluded from the study. The study will include approximately 134,000 participants (13,000 unemployed, 106,000 with permanent contracts, and 15,000 with fixed-term contracts). We expect to find approximately 16,400 incident cases of redeemed prescriptions of psychotropic drugs and 2150 incident cases of psychiatric hospital treatment for mood, anxiety, or stress-related disorders.

Results: We expect the analyses to be completed by the end of 2021 and the results to be published in mid-2022.

Conclusions: The statistical power of the study will be large enough to test the hypothesis of a prospective association between fixed-term contract positions and mental illness in the general workforce of Denmark.

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KEYWORDS

cohort study; fixed-term employment; fixed term contract; unemployment; psychotropic drugs; psychiatric hospital treatment

Introduction

Background

Mental health problems are the most frequent single cause of disability benefits in the Organization for Economic Co-operation and Development (OECD) [1]. In Denmark, mental health problems account for almost half of all new applications for disability benefits [1].

The prevalence of temporary employment contracts in the European Union (EU) has been quite stable since 2005 [2]. Approximately 14% of employees (27 million persons) in the EU had a fixed-term contract in 2018 [3]. The total cost of mental health illness in the EU-28 nations was estimated to be approximately 600 billion euros in 2015, which corresponds to 4.1% combined gross domestic product of the 28 nations [4]. It has been hypothesized that some cases of mental health illness may be due to insecure employment contracts [5]. The main reason for suspecting a link between fixed-term contracts and mental health problems is that perceived job insecurity has been associated with an increased prevalence of depression, anxiety, emotional exhaustion, life satisfaction, and psychological well-being [6] as well as an increased risk of developing depressive symptoms [7]. In addition, employees in fixed-term contracts often have less influence on workplace decisions than employees with permanent contracts [8,9]. Furthermore, a low decision latitude has been associated with an increased risk of developing clinical depression [10].

However, it is still not clear whether fixed-term contracts pose a risk for poor mental health. A review by Hünefeld and Köper [5] considered 84 estimated associations between fixed-term versus permanent contract and mental health. Statistical significance was reported in 40% of the included studies, but only half of the significant associations were positive. Moreover, a recent systematic review and meta-analysis of studies on fixed-term versus permanent contracts and mental health problems concluded (1) that the quality of most existing studies was low and (2) that the results of the few studies with sufficient quality were contradictory [11].

The association between unemployment and mental health disorders has been robustly researched and published. There is a consensus that people who are unemployed are at increased risk of developing mental health problems and that employees with mental health problems are at increased risk of becoming unemployed [12]. A substantial reason for the association between unemployment and mental illness is attributed to the mental distress of chronic financial insecurity [7]. From this perspective, it has been hypothesized that the anticipation of a job loss can be detrimental to mental health as unemployment itself [7]. Recently, a meta-analysis was carried out to estimate the relative risk of developing depression as a function of unemployment and self-perceived job insecurity [7]. The study included results from 20 cohort studies, of which 14 compared the risk among unemployed with the risk among employees, whereas 6 compared the risk among employees with perceived job insecurity with that among other employees. The odds ratio for the contrast *unemployment versus employment* was estimated to be 1.19 (95% CI 1.11-1.28), whereas the odds ratio for "secure versus unsecure employment" was estimated to be 1.29 (95% CI 1.06-1.57).

Objectives

This project aims to estimate the incidence rate ratios (RRs) of psychotropic drug usage and psychiatric hospital treatment. These ratios will be considered in relation to the contrast "fixed-term versus permanent contract" and to "fixed-term contract (regardless of weekly working hours) versus unemployment" among the general population of Denmark. The second analysis will be performed to elucidate the hypothesis of Kim and von dem Knesebeck [7], which states that the anticipation of a possible job loss can be as detrimental for the mental health as unemployment itself.

People may work part time due to health issues or because they are not able to find a full-time job. They may also have chosen to work part time, for example, for furthering their education, caring for a parent or child, or engaging in hobbies or sports activities. The reason for excluding part-time workers in the first analysis is that a participant may have chosen to work part time due to ill health. The reason for not excluding part-time workers in the second analysis is that our data do not permit differentiation between part-time and full-time unemployment.

Job insecurity and unemployment have been associated with an increased risk of mental distress from chronic financial insecurity, which in turn has been associated with an increased risk of mental illness [13-15]. It is reasonable to believe that most people are financially more secure in a fixed-term contract position than they are in a state of unemployment. From this viewpoint, we expect the risk of developing mental health illnesses to be higher among unemployed people than among employees with a fixed-term contract. Likewise, we expect the risk to be higher among employees with a fixed-term contract than among employees with a permanent contract.

Methods

Ethics Approval

The study will comply with The Act on Processing of Personal Data, Denmark (Act No. 429 of May 31, 2000), which implements the European Union Directive 95/46/EC on the protection of individuals. The data usage was approved by the Danish Data Protection Agency (file number 2001-54-0180). The ethical and legal aspects of the project were approved by Statistics Denmark, accounting for 704291. In Denmark, register studies, which do not include medical procedures, are not part of the ethical committee system.

Data Sources

All residents of Denmark have access to tax-financed health care. The educational system is generally tax financed. The so-called flexicurity model provides an income safety net for the unemployed, with unemployment insurance benefits for members of unemployment insurance funds. The residents of Denmark are also entitled to maternity and paternity benefits, sickness-absence benefits, disability benefits, and if needed, social security cash benefits. Person-based data on health care services and redeemed prescriptions of medicine and welfare

benefits payments are collected and reported in national registers, with unique personal identification numbers, which are assigned to all residents of Denmark [16].

This study will be based on baseline data on employment status from the Danish Labor Force Survey (DLFS) 2001-2013 and follow-up data on health from a series of registers, which cover the entire population of Denmark. The following registers will be used: the Central Person Register (CPR) [17], the Employment Classification Module (ECM) [18], the Danish Education Registers [19], the Danish Family Income Register [20], the Danish Register for Evaluation of Marginalization (DREAM) [21], the Psychiatric Central Research Register [22], and the National Prescription Register [23]. Linkage will be based on participants' personal identification numbers. The data sources and information to be included are listed in Table 1.

Table 1. The data sources of the project.

Data source	Type of data source	Information to be included in the present project
The Danish Labor Force Survey [24]	Survey data obtained from interviews on random samples of the population of Denmark	Date of the interview, employment status, type of employment contract, and nighttime work
The Central Person Register [17]	National register, which covers all residents of Denmark	Gender, age, date of migration, and date of death
The Employment Classification Module [18]	National register, which covers all residents of Denmark	Industry sector
The Danish Education Registers [19]	National register, which covers all residents of Denmark	Educational level
The Danish Family Income Register [20]	National register, which covers all residents of Denmark	Equalized disposable family income
The Danish Register for Evaluation of Marginalisation [21]	National register, which covers all residents of Denmark	Date of welfare benefits payment and type of welfare benefits payment
The Psychiatric Central Research Register [22]	National register, which covers all residents of Denmark	Date of hospital contact and principal diagnosis (ICD-10[a] code)
The National Prescription Register [23]	National register, which covers all residents of Denmark	Date of redeemed prescription and type of medicine (ATC[b]-code)

[a]ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

[b]ATC: Anatomical Therapeutic Chemical Classification System.

DLFS is based on quarterly random samples of 15- to 74-year-old residents of Denmark, with systematic oversampling of unemployed people. Each participant is invited to be interviewed 4 times over the course of a year and a half. The purpose of the interviews is to collect person-based information on inter alia, labor market attachment, type of contract, and working hours [24]. Among those invited for the DFLS, the response rate decreased over time from 70% in 2002 to 53% in 2013 [25]. The CPR contains, inter alia, information on gender, addresses, and dates of birth, death, and migrations for every person who is or has been a resident of Denmark sometime between 1968 and the present time. The ECM contains annual, person-based information on, inter alia, the socio-economic status, occupation, and industry of the residents of Denmark. The Danish Education Registers contain person-based information on, inter alia, a person's highest educational attainment. The Danish Family Income Register contains information on household income. DREAM contains weekly, person-based information on social transfer payments (welfare benefits payments) such as maternity and paternity benefits, sickness-absence benefits, unemployment benefits, social security cash benefits, and state educational grants. DREAM has existed since 1991 and covers all residents of Denmark. The weekly benefits data are recorded if the person has been on a benefit for 1 or more days of the week. However, as only 1 type of social transfer payment can be registered per week, types of benefits are prioritized in the case of data overlap. The above-mentioned social transfer payments are prioritized in the order listed, that is, maternity and paternity benefits have higher priority than sickness-absence benefits, which in turn have higher priority than unemployment benefits, etc. The Psychiatric Central Research Register contains person-based information on inpatients, outpatients, and emergency ward visits in all psychiatric hospital departments in Denmark. The National Prescription Register contains person-based data on all redeemed prescriptions at pharmacies in Denmark.

This study has access to the data on Anatomical Therapeutic Chemical Classification System (ATC) codes [26] from the National Prescription Register for the time period 2000-2014 and International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes [27] from the Psychiatric Central Research Register for the time period 1995-2017.

Clinical Endpoints

RRs will be examined for the following endpoints:

- Redeemed prescriptions for any type of psychotropic medicine, that is, drugs in the ATC-code category N05 (psycholeptica) or N06 (psychoanaleptica)

- Psychiatric hospital treatment with mood, anxiety, or stress-related disorder (ICD-10: F30–F41 or F43) as the principal diagnosis

The following mental disorders are included in the above case definition:

- F30 Manic episode
- F31 Bipolar affective disorder
- F32 Depressive episode
- F33 Recurrent depressive disorder
- F34 Persistent mood (affective) disorders
- F38 Other mood (affective) disorders
- F39 Unspecified mood (affective) disorder
- F40 Phobic anxiety disorders
- F41 Other anxiety disorders
- F43 Reaction to severe stress and adjustment disorders

Exposure

The following exposure categories will be considered: *unemployed but actively searching for a job and ready to start working within 14 days*, *employed on a fixed-term contract position*, and *employed on a permanent contract*. The categories are based on the DLFS-questionnaire [18].

Covariates

The literature suggests that estimated risks of mental health depend on gender [28,29], age [30-32], calendar year [33], education level [34], and income [35-38]. Moreover, it has been shown that the birth of a child may result in maternal [39] and paternal [40] postpartum depression.

The following covariates will therefore be regarded in all analyses: gender, age, calendar time of the interview, education level (at the end of the calendar year preceding the interview), equivalent disposable family income (in the calendar year preceding the interview), and maternity or paternity benefits (in the 1-year period preceding the interview).

In addition to the above, the following covariates will be regarded in the analyses of differences between employees with fixed-term and permanent contracts: main industry (in the calendar year preceding the interview), unemployment benefits (in the 1-year period preceding the interview), state educational grants (in the 1-year period preceding the interview), and nighttime work (at the time of the interview). We control for industry, as a previous study has found significant industry-related inequalities in the rate of mood disorders among employees in the general working population of Denmark [41]. We control for unemployment benefits and state educational grants in the 1-year period preceding the interview, as we believe that people's attitudes toward fixed-term and permanent contracts may depend on their previous labor market attachment. We control for nighttime work because it has been shown that the prevalence of psychotropic drug usage in Denmark is greater among shift workers than among workers without shift work [42].

The variables will be operationalized as follows:

Gender

Gender is classified into male or female as registered in the CPR.

Age

In this study, we will not have access to the exact dates of birth, but we will have access to information about the birth year of the participants, that is, we will know what their integer age was at the very beginning and at the very end of a calendar year. To form baseline age categories, the participants who were interviewed before July 1 in a given calendar year will be assigned the integer age they had at the beginning of that year, whereas the participants who were interviewed after June 30 will be assigned the integer age they would have at the end of the calendar year. The participants will thereafter be divided into 10-year age groups (20-29,…50-59 years), and the age group will be treated as a categorical variable.

Calendar Time of the Interview

The calendar years of the interviews will be treated as a categorical variable and divided into the following categories: 2001-2003, 2004-2006, 2007-2009, and 2010-2013.

Educational Level (at the End of the Calendar Year Preceding the Interview)

A person's highest attained education is registered and classified with a 2-digit code in the Danish Education Registers [19]. In this study, it will be divided as follows (Table 2) into the categories low, medium, high, and unstated.

Table 2. Classification of education levels.

The present project	The Danish Education Registers
Low	• 10 Primary and lower secondary education
Medium	• 20 Upper secondary education • 30 Basic vocational education • 35 Qualifying vocational education • 40 Short-term tertiary education
High	• 50 Medium-term tertiary education • 60 Bachelor's degree • 70 Master's degree or equivalent tertiary education level • 80 Doctoral degree or equivalent tertiary education level
Unstated	• Unstated

Equivalized Disposable Family Income (in the Calendar Year Preceding the Interview)

The equivalent disposable income is the total income of a household, after tax and other deductions, which is available for spending or saving, divided by the number of household members converted into equalized adults; household members are equalized or made equivalent by weighting each according to their age, using the so-called modified OECD equivalence scale (cited from Eurostat [43]).

The equivalent disposable income is calculated in 3 steps (cited from Eurostat [43]):

- All monetary incomes received from any source by each member of a household are added up. These include income from work, investment, and social benefits, as well as any other household income; taxes and social contributions that have been paid are deducted from this sum.
- To reflect differences in household size and composition, the total (net) household income is divided by the number of 'equivalent adults,' using a standard (equivalence) scale: the modified OECD scale. This scale gives a weight to all members of the household (and then adds these up to arrive at the equivalized household size): 1.0 to the first adult, 0.5 to the second and each subsequent person aged 14 and over, and 0.3 to each child aged under 14.
- Finally, the resulting figure is called the equivalent disposable income and is attributed equally to each member of the household.

This study will treat the equivalent disposable family income as a categorical variable, divided into low, medium, and high in accordance with calendar-year specific sample tertiles. The tertiles will be based on all DLFS responders who were 20 to 59 years old and employed at the time of the interview.

Main Industry (in the Calendar Year Preceding the Interview)

The industries will be divided into 10 groups, as shown in Table 3. The industrial codes are based on the industrial classification DB93 [44] in 1999-2002, DB03 [45] in 2002-2007, and DB07 [46] in the calendar years 2008-2013.

Table 3. Industrial groups coded according to the classifications DB93, DB03, and DB07, respectively.

Industrial group	Code according to		
	DB93	DB03	DB07
Agriculture, forestry, hunting, and fishing	A+B	A+B	A
Manufacturing, mining, and quarrying	C+D	C+D	B+C
Construction	F	F	F
Wholesale and retail trade and repair of motor vehicles and motorcycles	G	G	G
Transporting and storage	I	I	H
Accommodation and food service activities	H	H	I
Human health and social work activities	N	N	Q
Other	E, J, K, L, M, O, P, Q	E, J, K, L, M, O, P, Q	D, E, J, K, L, M, N, O, P, R, S, T, U
Unstated	X	Missing	Missing

Unemployment Benefits (in the One-Year Period Preceding the Interview)

This variable is equal to 1 if the participant, according to DREAM, received unemployment benefits (DREAM codes: 111-115, 121-126, 211-219, 231, 232, and 299) at least once during the 1-year period preceding the DLFS interview. Otherwise, it is equal to 0.

Maternity or Paternity Benefits (in the One-Yar Period Preceding the Interview)

This variable is equal to 1 if the participant, according to DREAM, received maternity or paternity benefits (DREAM code: 881) at least once during the 1-year period preceding the DLFS interview. Otherwise, it is equal to 0.

State Educational Grants (in the One-Year Period Preceding the Interview)

This variable is equal to 1 if the participant, according to DREAM, received state educational grant payments (DREAM codes: 651, 652, and 661) at least once during the 1-year period preceding the DLFS interview. Otherwise, it is equal to 0.

Nighttime Work

In the DLFS interview, the participants were asked whether they worked at night during the last 4 weeks. In this study, nighttime work will be treated as a categorical variable in accordance with the 3 response categories *Yes, regularly*, *Yes, occasionally*, and *No*.

Follow-Up

The study will be based on data that already exist. The included participants of the DLFS will be followed by national registers. The follow-up in the register data will start on the date when 6 weeks would have passed since the first DLFS interview and end on the date when any of the following events occur: 5 years pass since the date of the start of the follow-up, the participant emigrates, the participant dies, the participant meets the clinical endpoint of the analysis, or the study period ends. The end of the study period was set at the end of the calendar years 2014

and 2017 for redeemed prescriptions of psychotropic drugs and psychiatric hospital treatments, respectively. Person-years at risk will be calculated for each of the included participants. Participants who die or emigrate during the follow-up will be censored at the time of the event. That is, they will participate with person-years at risk until the time of death or emigration.

Inclusion Criteria

The primary analyses will be based on data from the participants' first interview in the time period 2001-2013. In the comparisons between employees with a full-time fixed-term versus a full-time permanent contract, we will require inclusion criteria 1-6 fulfilled (see below). In the comparisons between employees with a fixed-term contract (regardless of weekly working hours) versus unemployed people, we will require that criteria 1-4 and criteria 7 are fulfilled.

Inclusion criteria:

1. The participants were aged between 20 and 59 years at the time of the interview.
2. They did not receive any social transfer payments other than holiday allowance (DREAM code: 121), unemployment benefits (DREAM codes: 111-115, 122-126, 211-219, 231, 232, 299), maternity or paternity benefits (DREAM code: 881), or state educational grants (DREAM codes: 651, 652, 661) during the one-year period preceding the interview.
3. They did not receive any psychiatric hospital treatment with mental disorders (ICD-10: F01–F99) as the principal diagnosis during a 1-year period preceding the start of follow-up.
4. They did not redeem any prescription for psychotropic drugs (ATC: N05–N06) during a 1-year period preceding the start of follow-up.
5. They were employees, according to the interview.
6. They usually worked ≥32 h a week, according to the interview.
7. They were either unemployed but actively searching for a job and ready to start working within 14 days or employed with a fixed-term contract at the time of the interview.

Moreover, it is necessary that the concerned DLFS–based exposure variables and covariates are nonmissing.

Primary Statistical Analysis

Poisson regression will be used to estimate incidence RRs for psychiatric hospital treatment for mood, anxiety, or stress-related disorders and redeemed prescriptions for psychotropic drugs, as a function of employment status at baseline. The following contrasts will be considered: (1) Full-time fixed-term contract versus full-time permanent contract and (2) fixed-term contract (regardless of weekly working hours) versus unemployment. All analyses will be controlled for age, sex, disposable family income, educational level, calendar year of the interview, and reception of maternity or paternity benefits sometime during a 1-year period preceding baseline. The RRs for the contrast *fixed-term versus permanent contract* will, in addition to the above, be controlled for baseline industry group and nighttime work as well as reception of unemployment benefits and state study grants, sometime during a 1-year period preceding baseline. The logarithm of person-years at risk will be used as an offset. Likelihood ratio tests will be used to test first for main effects and then for effects of interaction with gender, age, and education level. We test for interactions, as it has been suggested that the strength of adverse health effects of fixed-term contracts depends on gender [47], age [48], and education level [49].

The main effects will be tested both for psychiatric hospital treatments and redeemed prescriptions for psychotropic drugs. The interaction effects will only be tested for redeemed prescriptions for psychotropic drugs. A Bonferroni correction will be used to adjust for multiple testing. We want the overall significance level to be less than or equal to 0.05. Hence, each of the 10 tests will be conducted at a significance level of 0.005. RRs for main effects will be estimated and presented with 99.5% CI. Moreover, the RRs for redeemed prescriptions for psychotropic drugs will be stratified (and presented with 99.5% CI) by gender, age, and educational level.

Power Calculations

Under the null hypothesis, we expected to find approximately 29 new cases of psychotropic drug usage and 3.4 new cases of psychiatric hospital treatment for mood, anxiety, or stress-related disorders per 1000 person-years at risk [50]. If we assume that approximately 15% of the otherwise eligible participants will be excluded due to exclusion criteria 1-4, the total number of expected cases in the concerned exposure categories will be approximately as shown in Table 4.

Table 4. The total number of expected cases in the concerned exposure categories.

Exposure category	Expected number of eligible participants	Expected number of psychotropic drug cases	Expected number of psychiatric hospital cases
Fixed-term full-time contract	10,600	1300	170
Permanent full-time contract	106,000	13,000	1700
Fixed-term contract (regardless of weekly working hours)	15,000	1800	240
Unemployment	13,000	1600	210

On the basis of the expected number of cases, the Poisson distribution, the Gauss propagation of error formulas, and the central limit theorem, we estimated the statistical power of the planned significance tests. The statistical powers for the main effects are given in Figures 1 and 2, for incident use of psychotropic drugs and psychiatric hospital treatment for mood, anxiety, or stress-related disorders, respectively, as a function of the underlying RR.

Figure 1. Power to detect main effects of fixed-term contracts on the rates of new cases of psychotropic drug use, as a function of underlying rate ratios (α=.005).

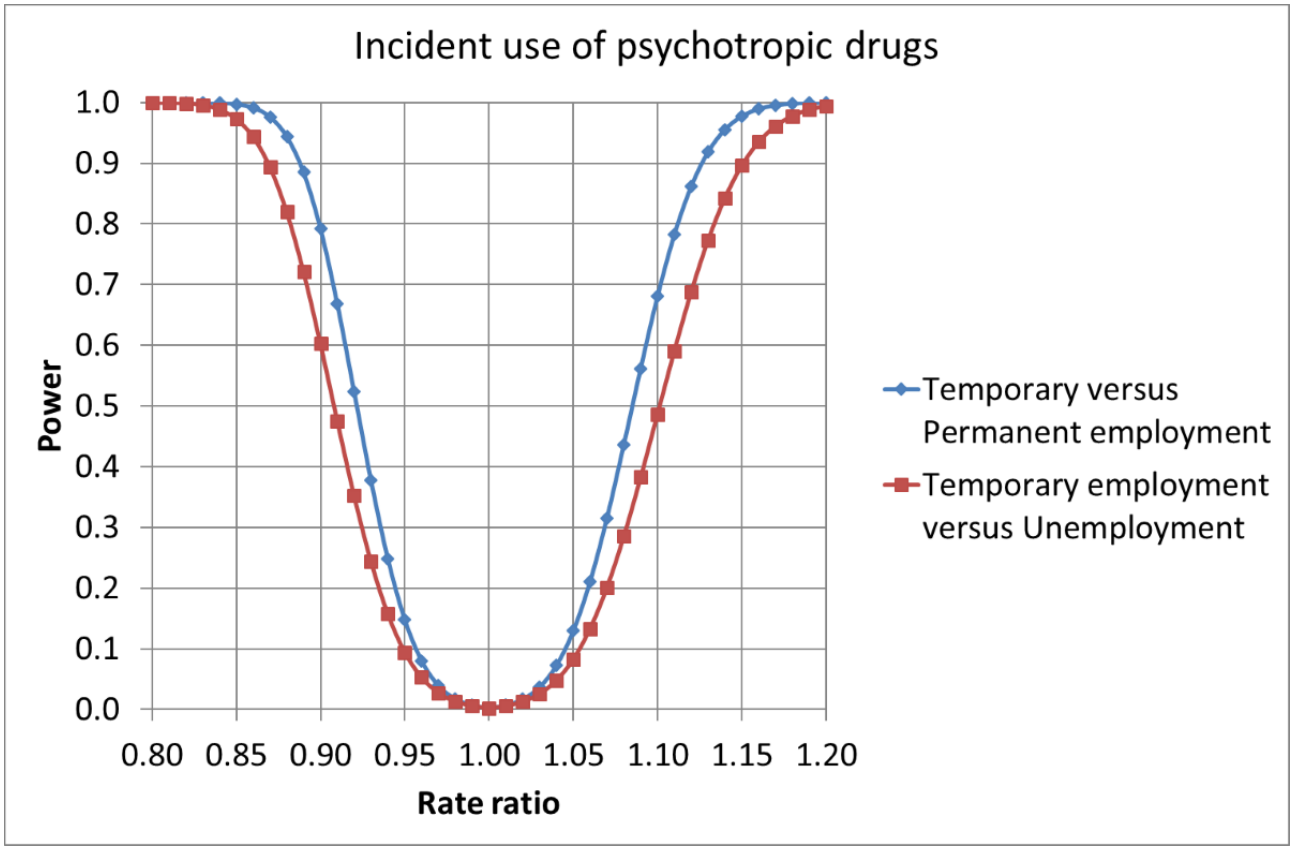
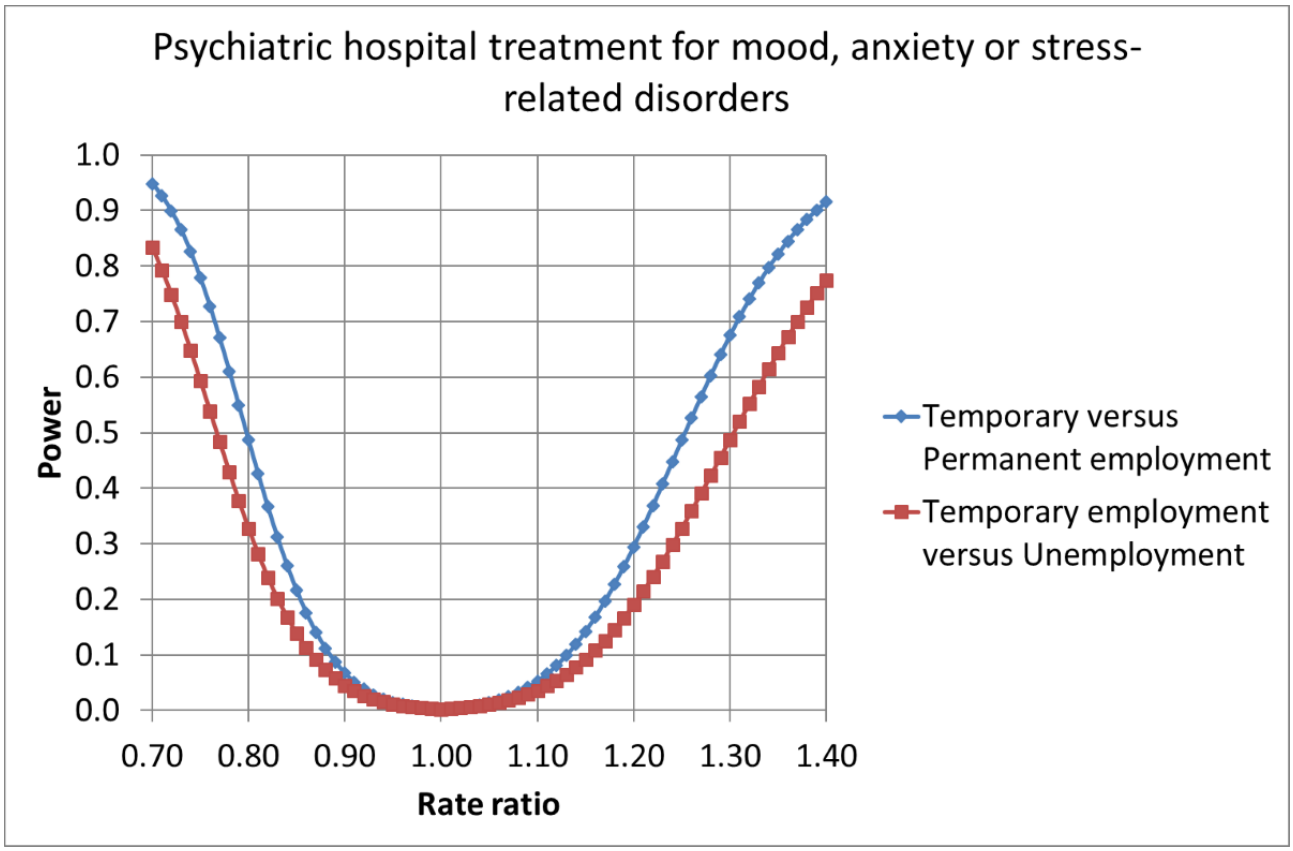


Figure 2. Power to detect main effects of fixed-term contracts on the rates of new cases of psychiatric hospital treatment for mood, anxiety, or stress-related disorders, as a function of underlying rate ratios (α=.005).



The statistical powers to detect interaction effects were estimated in relation to the Cohen w [51], where w=0.1 is defined as a small effect, w=0.3 is defined as a medium effect, and w=0.5 is defined as a large effect. On the basis of the expected number of cases, test specific degrees of freedom, and the noncentral chi-square distribution, we estimated that the power to detect a small effect (w=0.1) is greater than 0.98 in each of the planned interaction tests of this project.

The calculations indicate that the power is sufficiently large to test both the main and interaction effects of fixed-term contracts on the incidence of psychotropic drug usage. The powers to detect effects of fixed-term contracts on the incidence of psychiatric hospital treatment for mood, anxiety, or stress-related disorders (Figure 2) are, however, quite low, and this needs to be taken into account when the results are evaluated.

Sensitivity Analyses

We will conduct 6 sensitivity analyses. The endpoint of the sensitivity analyses will be redeemed prescriptions of psychotropic drugs. Interaction effects will be disregarded. RRs will be estimated and presented with 99.5% CI. The RRs and their associated confidence intervals will not be regarded as statistical significance tests. However, they may strengthen, weaken, or invalidate the statistical conclusions of the primary analyses.

Sensitivity Analysis 1: Exclusion of All Cases that Occurred Within 5 Years Preceding the Start of Follow-Up

The primary analysis will exclude all people who received psychiatric hospital treatment or redeemed a prescription for psychotropic drugs sometime during a 1-year period before the start of the follow-up. Hence, no known current cases of psychiatric treatment will be included in the follow-up. It is, however, possible that people who received treatment more than 1 year before the follow-up will influence the analysis. To shed some light on this issue, we will conduct a sensitivity analysis in which we will exclude all people who received psychiatric hospital treatment or redeemed a prescription for psychotropic drugs sometime during a 5-year period before the start of the follow-up. This sensitivity analysis will be based on data from the participants' first interview in the period 2005-2013. Moreover, it will only include people who lived in Denmark throughout the concerned 5-year period. The statistical models and inclusion criteria will otherwise be the same as in the primary analysis. The interpretation of results will include the fact that approximately 20% of the population experiences mental health problems during their lifespan due to different causes; so the analysis may be overcontrolling.

Sensitivity Analysis 2: Relapse Rate Ratios

At this point, it is useful to further elucidate (/examine) the possible influence of former cases of psychiatric treatment on the association between fixed-term contract and psychotropic drug usage. To this end, we will estimate relapse RRs among the participants who were excluded from the first sensitivity analysis due to psychiatric hospital treatment or redeemed prescription for psychotropic drugs sometime between 1 and 5 years before the start of follow-up.

Current cases, that is, people who received treatment sometime during a 1-year period before the start of follow-up will still be excluded. The statistical models will otherwise be the same as in sensitivity analysis 1.

Sensitivity Analysis 3: Long-term Exposure Versus Exposure at a Single Time Point

In the primary analysis, we regard the contrasts *full-time fixed-term contract versus full-time permanent contract* and *fixed-term contract versus unemployment* with the exposure categories defined at a single time point (the first interview). We want to know whether the strength of the concerned associations will increase if we base the exposure categories on more than one interview and only include people who belong to the same exposure category in all of their interview rounds. In other words, we want to know whether the strength of the associations will increase if we base the contrasts on *long-term exposure* instead of *exposure at a single time point*. To shed some light on this issue, we will conduct a sensitivity analysis in which we will only include people who (1) participated in more than one interview, (2) were aged between 20 and 59 years during their last interview, and (3) belonged to the same exposure category in all of their interview rounds. The follow-up of the included participants will commence 6 weeks after their last interview. The statistical models and inclusion criteria will otherwise be the same as in the primary analysis.

Sensitivity Analysis 4: Minimally Adjusted Rate Ratios

In the primary analyses, we will exclude all people who received sickness benefits or social security cash benefits during a 1-year period before the baseline interview. Moreover, we control for disposable family income as well as a series of other covariates. It is possible that the rigorous inclusion criteria and the many control variables will lead to overly conservative estimates. Therefore, we will conduct a sensitivity analysis in which we will (1) remove the second of the inclusion criteria listed in the method section and (2) remove all control variables except for gender, age, and education. The methods will otherwise be the same as in the primary analyses.

Sensitivity Analysis 5: Reason for Being on a Fixed-Term Contract

All EU-Labor Force Survey participants with a fixed-term contract are asked for the reason of having a fixed-term contract. Their answers are categorized as follows:

- It is a contract covering a period of training (apprentices, trainees, research assistants, etc)
- Person could not find a permanent job
- Person did not want a permanent job
- It is a contract for a probationary period

We want to know whether the risk of developing mental health illnesses among employees with a fixed-term contract depends on the reason for being on a fixed-term contract. To answer this question, we will estimate incidence RRs for redeemed prescriptions of psychotropic drugs as a function of the reason for being on a fixed-term contract.

Participants who did not want a permanent job (category 3) will serve as the reference group. We will include all employees on

fixed-term contracts, who fulfilled inclusion criteria 1-5, as listed in the method section. The analyses will initially be conducted only with full-time employees (≥32 h a week) and then with all employees regardless of weekly working hours. The analyses will be controlled for all variables given in the *Covariate* section. The statistical model and follow-up periods will be the same as in the primary analysis.

Sensitivity Analysis 6: Stratification by Industry Sector

We know that the prevalence of fixed-term contracts in the Nordic countries depends on the industry sector [52], and that the rates of mood disorders in the general working population of Denmark depend on the industry sector [41]. It is possible that the effect of fixed-term contract positions on mental health illnesses also depends on the industry. Therefore, we conduct a sensitivity analysis in which we will stratify the results of the comparison between employees with a fixed-term and a permanent contract by the industry sector. The industries are grouped as shown in Table 3. The inclusion criteria and covariates will be the same as in the primary analysis.

Reasons why the association between fixed-term contracts and mental health illnesses might depend on industry could be, first, that chances for reemployment may depend on the industry sector and, second, that expectations regarding a fixed-term versus permanent contract may depend on the industry.

Another reason for stratifying by the industry sector is that the social partners might be interested in seeing the association between fixed-term contracts and mental health illnesses in their own industry sector.

Possible Confounding From Smoking, Being Overweight, and Obesity: a Feasibility Study

Studies have suggested that smoking habits [53,54] and being overweight [55] predict depression. It has been estimated that the risk ratio of new-onset depression is 1.46 (95% CI 1.03-2.07) for smokers versus nonsmokers [53], 1.08 (95% CI 1.02-1.14) for overweight versus normal weight, and 1.57 (95% CI 1.23-2.01) for obesity versus normal weight [55]. The DLFS does not contain any information about smoking habits and body weights of the participants. Therefore, we cannot control for these factors in the analyses. However, we have access to some collateral data, which we have used to estimate to what extent and in what direction the RRs of the present project are likely to be influenced by differences in distributions of body mass index and smoking habits. The collateral data were gathered from a survey on work and health in a random sample of the Danish population in 2005. The response rate of the survey was 62% [56]. In this study protocol, we have used the survey data to estimate the prevalence of smoking, being overweight, and obesity among 20-59-year-old people in Denmark, stratified by the exposure categories of interest to this study. The crude prevalence is given in Table 5, whereas prevalence that is standardized for age, gender, and education is given in Table 6. The total sample of 20- to 59-year-old people was used as the standard population.

Table 5. Crude percentages of current smokers, people with moderate overweight (25≤BMI<30), and people with obesity (BMI≥30), by exposure category, in a random sample of 20- to 59-year-old people in Denmark, 2005.

Exposure category	Current smoker, n (%)	25≤BMI<30, n (%)	BMI≥30, n (%)
Fixed-term full-time contract (n=748)	221 (29.5)	231 (30.9)	72 (9.6)
Permanent full-time contract (n=8016)	2438 (30.4)	2859 (35.7)	834 (10.4)
Fixed-term contract (regardless of weekly working hours; n=908)	281 (30.9)	267 (29.4)	77 (8.5)
Unemployment (n=393)	141 (35.9)	123 (31.3)	54 (13.7)

Table 6. Age (10-year classes), gender and education (low, medium, and high) standardized percentages of current smokers, people with moderate overweight (25≤BMI<30), and people with obesity (BMI≥30), by exposure category, in a random sample of 20- to 59-year-old people in Denmark, 2005.

Exposure category	Current smoker, % (95% CI)	25≤BMI<30, % (95% CI)	BMI≥30, % (95% CI)
Fixed-term full-time contract	31.8 (28.4-35.6)	33.0 (29.6-36.8)	10.6 (8.5-13.3)
Permanent full-time contract	30.4 (29.4-31.4)	34.3 (33.3-35.3)	10.1 (9.5-10.8)
Fixed-term contract (regardless of weekly working hours)	33.3 (30.1-36.8)	32.5 (29.4-35.9)	9.5 (7.6-11.9)
Unemployment	36.5 (32.1-41.4)	31.9 (27.4-37.1)	14.1 (11.0-18.2)

Table 6 suggests that the standardized prevalence among people with fixed-term full-time contracts are very similar to those among people with permanent full-time contracts. We note, however, that the estimated prevalence of smoking and obesity is greater among the unemployed than among the employees on fixed-term contracts. We want a rough estimate of the effect that such differences may have on the RR of mental health illnesses among employees on fixed-term contracts versus unemployed in our target population. Therefore, we have estimated the expected RR between these exposure categories under the assumption that the groups are equal in all respects other than smoking and BMI distribution and that an RR for depression can be used as a proxy for the RR of mental health illnesses. We used the following equation:

where RR_1=1.08 is the estimated rate ratio for depression among people in the category 25≤BMI<30 versus BMI<25, RR_2=1.57 is the estimated rate ratio for depression among people in the category BMI≥30 versus BMI<25, and RR_3=1.46 is the estimated rate ratio for depression among smokers versus nonsmokers. The parameters p_1, p_2, and p_3 are the standardized sample prevalences of overweight, obesity, and smoking, respectively, among people with fixed-term contracts (cf. Table 6). The parameters q_1, q_2, and q_3 are the corresponding prevalence among the unemployed people (cf. Table 6).

The calculation yielded an estimated rate ratio of 0.96. This means that a failure to control for overweight, obesity, and smoking in this project is expected to bias the estimated rate ratio for mental health illnesses among fixed-term versus unemployed people downward with a factor of 0.96.

Results

We expect the analyses to be completed by the end of 2021 and the results to be published mid-2022.

Discussion

This study protocol contains a statistical analysis plan for a research project aimed at estimating prospective associations between fixed-term contracts and mental health illness in the general population of Denmark. As all covariates, outcome variables, inclusion criteria, statistical models, and significance levels are completely defined, published, and peer-reviewed before we link the exposure data of the project to its outcome data, we minimized the risk of hindsight bias.

A major strength of the project is that the data material is large enough to afford sufficient statistical power to detect important associations between fixed-term contracts and incident use of psychotropic medication. Another strength is that the outcome variables as well as the censoring variables (death and emigration) will be ascertained through national registers, which cover the entire population of Denmark. The study is weakened by the low response rate in the DLFS, which makes the representativeness of the participants questionable. Another weakness is the lack of data on lifestyle factors.

Studies have shown that the prevalence of depression tends to be higher among migrants than in the general population [57]. Studies of the general working population in Sweden [58] and Spain [59] have shown that immigrants are more likely to be on a fixed-term work contract. A survey of the general workforce in Canada found that newcomer immigrants (within the first 5 years) were on fixed-term contracts more often than natives [60]. Due to the comparability with Sweden and Canada, we expect the figures to be similar in Denmark. The response rate in questionnaire surveys among ethnic minorities in general is relatively low [61,62]; for example, half among non-Western immigrants compared with Danes [53]. The background to this study is the DLFS; thus, the issue of ethnicity cannot be addressed, as there are relatively few with immigrant background answering the survey.

Finally, it should be noted that the results of the study may not be fully transferable to other countries. Due to the relatively low employment protection in Denmark combined with a comprehensive income safety net for the unemployed, the so-called flexicurity model, it can be hypothesized that this may result in fewer fixed-term contracts in Denmark compared with other European countries [63].

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Conflicts of Interest

None declared.

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Abbreviations

ATC: Anatomical Therapeutic Chemical Classification System
CPR: Central Person Register
DLFS: Danish Labor Force Survey
DREAM: Danish Register for Evaluation of Marginalization
ECM: Employment Classification Module
EU: European Union
ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision
OECD: Organization for Economic Co-operation and Development
RR: rate ratio

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Protocol

Cardiomyocyte Injury Following Acute Ischemic Stroke: Protocol for a Prospective Observational Cohort Study

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Abstract

Background: Elevated cardiac troponin, which indicates cardiomyocyte injury, is common after acute ischemic stroke and is associated with poor functional outcome. Myocardial injury is part of a broad spectrum of cardiac complications that may occur after acute ischemic stroke. Previous studies have shown that in most patients, the underlying mechanism of stroke-associated myocardial injury may not be a concomitant acute coronary syndrome. Evidence from animal research and clinical and neuroimaging studies suggest that functional and structural alterations in the central autonomic network leading to stress-mediated neurocardiogenic injury may be a key underlying mechanism (ie, stroke-heart syndrome). However, the exact pathophysiological cascade remains unclear, and the diagnostic and therapeutic implications are unknown.

Objective: The aim of this CORONA-IS (Cardiomyocyte injury following Acute Ischemic Stroke) study is to quantify autonomic dysfunction and to decipher downstream cardiac mechanisms leading to myocardial injury after acute ischemic stroke.

Methods: In this prospective, observational, single-center cohort study, 300 patients with acute ischemic stroke, confirmed via cerebral magnetic resonance imaging (MRI) and presenting within 48 hours of symptom onset, will be recruited during in-hospital stay. On the basis of high-sensitivity cardiac troponin levels and corresponding to the fourth universal definition of myocardial infarction, 3 groups are defined (ie, no myocardial injury [no cardiac troponin elevation], chronic myocardial injury [stable elevation], and acute myocardial injury [dynamic rise/fall pattern]). Each group will include approximately 100 patients. Study patients will receive routine diagnostic care. In addition, they will receive 3 Tesla cardiovascular MRI and transthoracic echocardiography within 5 days of symptom onset to provide myocardial tissue characterization and assess cardiac function, 20-min high-resolution electrocardiogram for analysis of cardiac autonomic function, and extensive biobanking. A follow-up for cardiovascular events will be conducted 3 and 12 months after inclusion.

Results: After a 4-month pilot phase, recruitment began in April 2019. We estimate a recruitment period of approximately 3 years to include 300 patients with a complete cardiovascular MRI protocol.

Conclusions: Stroke-associated myocardial injury is a common and relevant complication. Our study has the potential to provide a better mechanistic understanding of heart and brain interactions in the setting of acute stroke. Thus, it is essential to develop algorithms for recognizing patients at risk and to refine diagnostic and therapeutic procedures.

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International Registered Report Identifier (IRRID): DERR1-10.2196/24186

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KEYWORDS

ischemic stroke; troponin T; myocardial ischemia; myocardial injury; stroke-heart syndrome; cardiac imaging techniques; magnetic resonance imaging; Takotsubo syndrome; autonomic nervous system

Introduction

Background

Elevated cardiac troponin (cTn), which is a sign of myocardial injury, frequently occurs in the early phase after an acute ischemic stroke (AIS) and is associated with poor functional outcome, especially increased mortality [1,2]. Using high-sensitivity assays, cTn is detectable in more than 90% of stroke patients; 30%-60% have at least one cTn above the assay-specific 99th percentile upper reference limit (URL) [2,3]. Approximately 5%-20% show a rise/fall pattern indicating acute myocardial injury according to the fourth universal definition of myocardial infarction (MI) [4]. In the latter group, acute coronary syndrome has to be suspected [4-6]. Following the American guidelines (American Heart Association/American Stroke Association), it is specifically recommended to measure cTn in stroke patients [7,8]. However, recommendations on how to deal with elevated cTn in the context of AIS remain vague [8]. Furthermore, expert consensus documents on practical considerations on the clinical use of cTn list ischemic stroke as one of the illnesses that leads to clinical uncertainty in the context of interpretation of elevated cTn [9].

The phenomenon of acute brain injuries (including an ischemic stroke and intracranial hemorrhage) leading to cardiac complications, including elevated cardiac enzymes, is known for a long time. In reference to AIS, it has recently been described as stroke-heart syndrome (SHS) [10-13]. However, the exact pathophysiologic background of myocardial injury (ie, cTn elevation) after stroke is not entirely understood [13,14]. Several hypotheses have been discussed. Besides concomitant acute MI caused by atherothrombotic coronary artery disease (type 1 MI), situations of oxygen supply/demand mismatch have to be considered as underlying reasons. For example, tachyarrhythmia, hypotension/shock, anemia, or respiratory failure, which are frequently seen in stroke patients, can lead to a demand ischemia [4,15]. Furthermore, systemic conditions such as sepsis or chronic kidney disease may cause or facilitate myocardial injury [16].

In the TRELAS (Troponin Elevation in Acute Ischemic Stroke) study, patients with AIS with markedly elevated cTn were significantly less likely to have a corresponding culprit lesion on coronary angiography when compared with age- and sex-matched patients with non-ST elevation acute coronary syndrome (ACS; showing no significant difference in the degree of cTn elevation) [17]. Together with the finding that half of the patients with AIS with markedly elevated cTn had no coronary artery disease at all, this implies that alternative mechanisms beyond ACS may play an important role [17]. This is supported by animal research and clinical and neuroimaging studies, suggesting that stroke-associated myocardial injury may originate from structural and/or functional interference within the central autonomic nervous system (CAN) with an overshooting sympathetic response [18-20]. On a cellular basis, it is assumed that excessive catecholamine and cortisol levels lead to an increased sarcoplasmic calcium influx with a consecutive hypercontraction of the sarcomeres, electrical instability, and metabolic and oxidative stress. Consequently, these pathological mechanisms can induce a contraction band necrosis and interstitial inflammatory reaction [12,21]. In summary, elevated troponin levels are frequent, and the underlying pathologies can be manifold, ranging from concomitant type 1 MI, demand ischemia, and chronic structural cardiac disease to systemic conditions. However, especially in situations with acute cTn elevation after AIS, the CAN seems to play an important role in the development of myocardial injury not only by triggering direct myocardial toxicity but also by facilitating situations of demand ischemia [13,14,22]. Nonetheless, the exact cascade of events remains mostly unclear, and when it comes to diagnostic procedures and treatment of affected patients, therapeutic options lack good scientific evidence [8].

Objective

The aim of the Cardiomyocyte injury following Acute Ischemic Stroke (CORONA-IS) study is to gain mechanistic insights into stroke-associated myocardial injury. We intend to provide a detailed characterization of (1) myocardial tissue; (2) myocardial, ventricular, and atrial function; and (3) associated autonomic dysfunction by using multimodal diagnostic measures.

Methods

Study Design

The CORONA-IS study is an investigator-initiated, prospective, observational, single-center cohort study that aims to include 300 patients with AIS. In November 2018, the Ethics Committee of the Charité-Universitätsmedizin Berlin, Germany (EA4/123/18), approved the study. All study procedures are carried out in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The study was pre-registered under clinicaltrials.gov, NCT03892226. All

patients with AIS admitted to the hospital within 48 hours of symptom onset are listed in a hospital-based registry as part of an assessment of high-sensitivity cTn (hs-cTn) development in patients with AIS. All study patients have to fulfill the study inclusion criteria listed in Textbox 1, and all participants have to provide written informed consent (for exclusion criteria refer to Textbox 2).

Textbox 1. Inclusion criteria.

- ability to provide informed consent
- age ≥18 years
- diagnosis of acute ischemic stroke and hospital admission within 48 hours of symptom onset
- visible diffusion-weighted imaging lesion in cerebral magnetic resonance imaging
- repeated measurement of high-sensitivity cardiac troponin within 24 hours of admission

Textbox 2. Exclusion criteria.

- pregnancy or breastfeeding
- impaired renal function (estimated glomerular filtration rate <30 ml/min/1.73 m^2)
- contraindications to undergo magnetic resonance imaging (eg, cardiac pacemaker, implantable cardioverter-defibrillator, and cerebral clips)
- persistent or permanent atrial fibrillation (patients with paroxysmal atrial fibrillation will be included if they are in sinus rhythm at admission or during cardiac monitoring of the stroke unit)
- ST-elevation in electrocardiogram fulfilling criteria of myocardial ischemia
- history of cardiac intervention (eg, coronary artery bypass surgery or percutaneous coronary intervention) within the last 4 weeks

Depending on serial measurements of hs-cTn during the acute hospital stay (assay characteristics: hs troponin T, Roche Elecsys, Gen 5; 99th percentile upper reference limit=14 ng/l; 10% coefficients of variation (CV) precision=13 ng/l; limit of detection=5 ng/l) and according to the fourth universal definition of MI, 3 groups are defined (Table 1) [4]. We aim to include 100 patients in each group. The cTn values are based on at least two blood exams: the first one at hospital admission and a control measurement within 24 hours after admission.

Table 1. Definition of the 3 groups based on patients' high-sensitivity cardiac troponin values.

Group	Description	hs-cTn[a] values (URL[b]=14 ng/l)
Group 1	Normal hs-cTn levels	Both hs-cTn levels ≤URL
Group 2	Chronic myocardial injury (elevated but stable cTn levels)	At least one hs-cTn level >URL but *no* rise/fall (>20%) in serial measurements
Group 3	Acute myocardial injury (dynamic elevation)	At least one hs-cTn level >URL *and* rise/fall (>20%) in serial measurements[c]

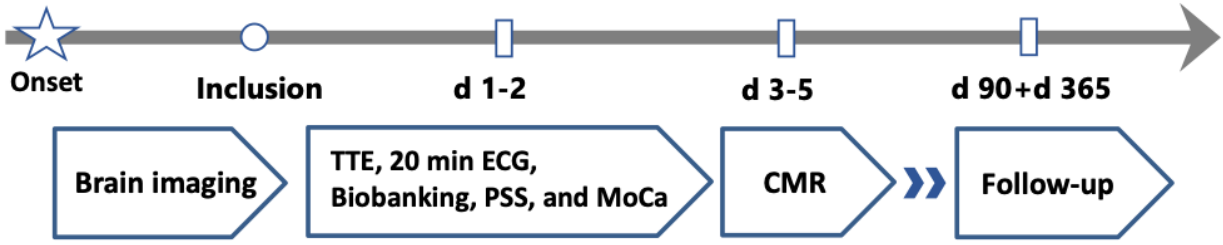
[a]hs-cTn: high-sensitivity cardiac troponin.

[b]URL: upper reference limit (=14 ng/l).

[c]Or initial cTn value ≤URL and second value >URL+increase >50% URL (ie, 7 ng/l).

In addition to routine clinical procedures (refer to the *Baseline Visit* section), study patients receive a baseline assessment, an additional blood draw for biobanking, 3 Tesla (3T) cardiovascular magnetic resonance imaging (CMR), transthoracic echocardiography (TTE), and a 20-min high-resolution electrocardiogram (ECG) for a comprehensive assessment of cardiac autonomic function as well as a questionnaire testing cognitive function and the perception of stress. Furthermore, 3 and 12 months after discharge, patients will be followed up via structured telephone interviews for cardiovascular events and clinical outcomes (Figure 1).

Figure 1. Study procedure of the Cardiomyocyte injury following Acute Ischemic Stroke study. Patients with a confirmed diagnosis of acute ischemic stroke via magnetic resonance imaging within 48 hours of symptom onset are eligible for inclusion. Patients receive a baseline visit, transthoracic echocardiography, 20-min electrocardiogram recording, blood sampling for biobanking, and cognitive testing within the first 2 days after enrolment. 3T cardiovascular magnetic resonance imaging takes place 3-5 days after symptom onset. Telephonic follow-up for cardiovascular events and functional outcomes will be conducted after 3 and 12 months. CMR: cardiovascular magnetic resonance imaging; d: day; ECG: electrocardiogram; MoCA: Motreal-Cognitive-Assessment; PSS: Perceived Stress Scale; TTE: transthoracic echocardiography; y: year.



Participants

Patients with a diagnosis of AIS, defined by a diffusion-weighted imaging lesion on magnetic resonance imaging (MRI), and hospital admission within 48 hours of symptom onset are included in the study. The study is carried out at the Department of Neurology, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany.

Baseline Visit

The baseline assessment of the study patients includes demographics, medical history, medication, and information about the current stroke (time of symptom onset, time of hospital admission, and treatment including thrombolysis or thrombectomy). Stroke severity is classified using the National Institutes of Health Scale Score. The degree of disability is assessed using the modified Rankin Scale score. The presence of chest pain and dyspnea at admission and before the event is documented. Cognitive function and the individual perception of stress will be assessed via 2 questionnaires: Perceived Stress Scale and Montreal-Cognitive-Assessment [23,24]. In addition, the results of routine diagnostic procedures and stroke unit monitoring (eg, vital signs, 12-lead ECG, laboratory results, cerebral computed tomography imaging/MRI, and ultrasound of the brain-supplying arteries) are recorded.

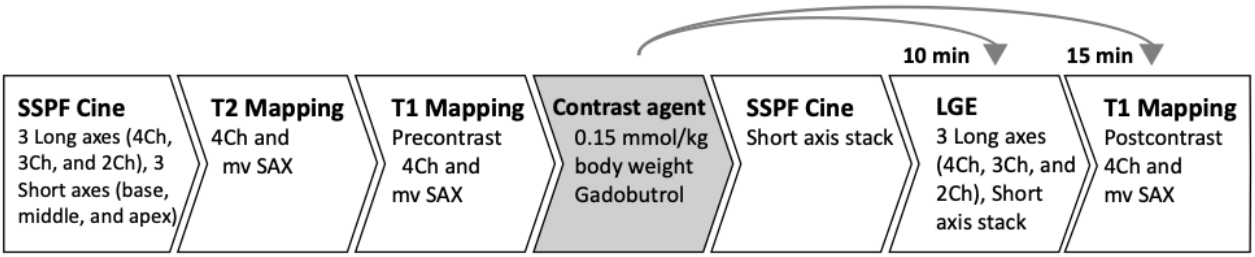
Cardiovascular MRI Protocol

Patients receive a 3T cardiovascular MRI (CMR). The examination is performed on a 3T MR scanner (Siemens Magnetom Prisma fit 3T, Siemens) using ECG for cardiac gating.

The detailed CMR protocol is depicted in Figure 2. Initially, for localizing, a half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence is conducted. Second, to evaluate the morphology and function of the left ventricle (LV) and right ventricle (RV), *steady-state free-precession cine images* (SSFP) are acquired during repeated breath-holds. Data are obtained for 3 long axes (4-chamber [4Ch], 3-chamber [3Ch], and 2-chamber [2Ch] view) and RV (imaging parameters: repetition time [TR] 45.78 ms, echo time [TE] 1.43 ms, flip angle [FA] 80°, and slice thickness 6.0 mm) and short axes stack—after contrast media application—to cover the LV (imaging parameters: TR: 44.80 ms, TE: 1.4 ms, FA: 58°, and slice thickness 7.0 mm, no gap). Furthermore, after cine long axis, 3 cine short axes (base, middle, and apex) are conducted, serving as a base for mapping imaging (imaging parameters: TR: 44.80 ms, TE: 1.4 ms, FA: 58°, and slice thickness: 7.0 mm). Motion-corrected *T2 mapping* is conducted using a fast low-angle shot (FLASH) gradient echo sequence in a 4Ch view and 3 short axis views (SAX) as basal, medial, and apical slices. T2 maps are based on images with T2 preparation times of 0/30/55 ms, slice thickness of 6.0 mm, TR of 251.49 ms, and TE of 1.32 ms.

Postcontrast imaging is performed after intravenous injection of 0.15 mmol/kg body weight Gadobutrol (Gadovist, Bayer Healthcare). *Focal fibrosis imaging* (late gadolinium enhancement [LGE]) is conducted 10 min after Gadobutrol application. LGE imaging is performed using a phase-sensitive inversion recovery sequence (PSIR) in the same slice position as cine imaging (4Ch, 3Ch, and 2Ch view; imaging parameters: TR: 750.0 ms, TE: 1.55 ms, FA: 20°, and slice thickness: 7.0 mm) as well as full coverage of the LV in a short axis package (imaging parameters: TR: 1002.4 ms, TE: 1.24 ms, FA: 55°, and slice thickness: 8.0 mm). TI was adapted to suppress the myocard.

Figure 2. 3T cardiovascular magnetic resonance imaging protocol. Workflow of the cardiovascular magnetic resonance imaging sequences conducted. 2Ch: 2-chamber view; 3Ch: 3-chamber view; 4Ch: 4-chamber view; 3T: 3 Tesla; LGE: late gadolinium enhancement; mv: midventricular; SAX: short axis view; SSPF: steady-state free-precession.



Finally, for further myocardial tissue characterization, motion-corrected *T1 mapping* based on the Modified look-locker inversion recovery technique (MOLLI) using a 3-3-5 pattern is performed before and 15 min after contrast media application in 4Ch view and 3 short axes with basal, medial, and apical slices (imaging parameters: TR: 281.64 ms (4Ch) and 332.67 ms (SAX), TE: 1.12 ms, slice thickness: 6.0 mm, and Generalized Autocalibrating Partial Parallel Acquisition (GRAPPA) acceleration factor: 2).

Pseudonymized CMR data are transferred to the core Lab *AG Kardiale MRT* (Prof Dr J Schulz-Menger) at the Department of Cardiology, Charité Campus Buch (Berlin), for further analysis. Experienced readers (Society for Cardiovascular Magnetic Resonance level III) analyzing the MR data are blinded to the clinical data. The clinical results are provided to the study patient, and in case of pathological findings that require further diagnostics or treatment, the clinical results are provided to the patients' treating physician.

TTE Protocol

Patients undergo TTE on the first day after enrollment. A second TTE for evaluating dynamic changes in cardiac function is attempted on the third to fifth day thereafter. Trained physicians and trained technicians conduct the examination using the ultrasonic device *Vivid T8* (GE Healthcare). The focus of the examination is the left and right ventricular systolic as well as diastolic function and morphology. According to the guidelines of the American Society of Echocardiography, images are acquired using standard views [25]. The TTE protocol includes two-dimensional imaging, M-mode measurements, color Doppler imaging and spectral Doppler imaging (continuous-wave [CW], pulsed-wave [PW], and Doppler tissue imaging [DTI]), as well as strain imaging using a 2D-speckle-tracking technique. Systolic LV function will be defined according to the *recommendations for cardiac chamber quantification by echocardiography in adults* as normal range (left ventricular ejection fraction [LV EF] 52%-72% [male]/54%-74% [female]), mildly abnormal (42%-51% [male]/41%-53% [female]), moderately abnormal (30%-40%), and severely abnormal (<30%) [26]. Values of signs suggesting pathologic RV systolic function are defined as TAPSE (tricuspid annular plane systolic excursion) <17 mm and s' velocity <9.5 cm/s [27]. In addition, diastolic function will be evaluated according to the criteria of the Heart Failure Association of the European Society of Cardiology [28]. An independent rater blinded to clinical information will evaluate the echocardiographic data.

Autonomic ECG Markers

In addition to routine 12-lead ECG at admission and stroke unit monitoring, included patients receive an additional 20-min high-resolution resting ECG during the first day after enrollment using the portable medilog AR4+ device (Schiller AG). The aim is to measure specific autonomic markers periodic repolarization dynamics (PRD) and deceleration capacity (DC), reflecting sympathetic and vagal components of cardiac autonomic function in addition to standard measures of heart rate variability (HRV) in time and frequency domain [29-31]. The 7 electrodes of the high-resolution ECG are applied according to the Frank lead configuration in the 3 orthogonal axes X, Y, and Z. The examination is performed under standardized conditions (supine position, patient is not allowed to talk or change the position during the recording). For analysis, the pseudonymized ECG data are transmitted to the core lab of the academic working group *biosignal analysis* (Prof Dr A Bauer) at the cardiology department of the Medical University of Innsbruck, Austria. Members of the working group analyzing the data are blinded to all clinical information.

Biobanking

The study protocol includes an additional blood examination for biobanking to allow future study of further potential mechanisms. Blood drawing takes place during the first day after enrollment and includes 2 EDTA (for both whole blood and plasma samples), 1 heparin, 1 coagulation sodium citrate, and 1 serum tube. Blood withdrawal, centrifugation, and processing will be conducted by a trained study nurse. Blood samples are transferred to the Central Biomaterial Bank Charité for management and storage. After processing, the stored samples consist of 5.7 mL of EDTA whole blood; 1.5 mL of citrate plasma; and 2 mL of EDTA plasma, heparinized plasma, and serum samples each. These samples will allow measurement of various potential biomarkers of interest. Dependent on further funding, we consider to determine biomarkers of cardiac injury and stress, proinflammatory markers, and markers of endothelial dysfunction (such as N-terminal B-type natriuretic peptide [NT-proBNP], midregional proatrial natriuretic peptide [MRproANP], Copeptin, interleukin-6, interleukin-1β, Soluble suppression of tumorigenicity 2 [sST2], and monocyte chemoattractant protein-1 [MCP-1]). Furthermore, we consider exploring whether patients with signs of stroke-associated

myocardial injury present distinct miRNA-pattern. Finally, the design allows future cooperation with other research groups.

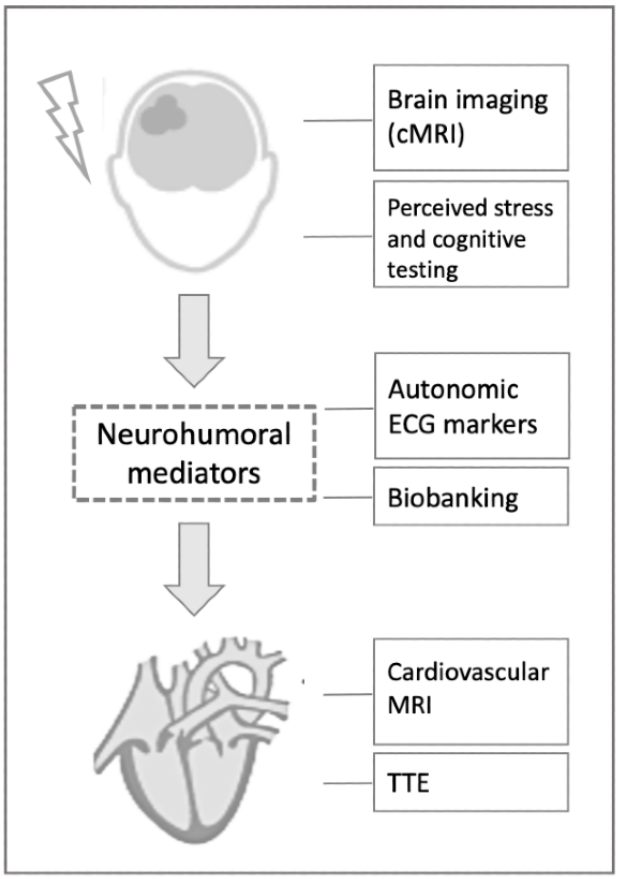
Follow-Up Telephone Interview

A follow-up regarding major cardiovascular events takes place 3 and 12 months after enrollment via telephone interview and is conducted by a trained participant of the research group. A major cardiovascular event is defined as the occurrence of transient ischemic attack and ischemic stroke, intracranial hemorrhage, MI, coronary artery bypass surgery or percutaneous coronary intervention, new atrial fibrillation, hospitalization for heart failure, and death. The functional outcome is assessed using the modified Rankin Scale. In case of death, the date of death is recorded using information from registration offices. In the case of cardiovascular events, medical records will be requested from the treating physician/institution. Furthermore, Charité records will be screened for readmission or further treatment. In case of unclear loss to follow-up, mortality status will be retrieved from the residents' registration office.

Study Outcomes

Our main hypothesis is that the development of stroke-associated myocardial injury in patients with AIS is based on a stroke-related interference in the CAN resulting in myocardial tissue alterations and dysfunction (ie, stroke-induced "myocardial stunning") [13]. Using a systemic and multimodal diagnostic approach, we aim to provide a detailed characterization of myocardial tissue, cardiac function, and autonomic cardiac regulation (Figure 3). Thus, outcome measures are primarily based on cardiac tissue characterization via CMR, functional assessment using TTE and CMR measurements, and values of specific autonomic ECG markers. Textbox 3 shows the detailed outcome measures. In summary, as we assume that patients with stroke-associated myocardial injury show a Takotsubo syndrome (TTS)/stress cardiomyopathy pattern of lesions in the myocardium, we will focus on the presence of wall motion abnormalities together with myocardial edema (T2 mapping) but without corresponding LGE in CMR [32,33]. Left ventricular dysfunction and wall motion abnormalities will be measured via cine imaging in CMR and TTE. As a correlate of chronic myocardial injury, we further assess myocardial fibrosis/scar via LGE, diffuse fibrosis via T1 mapping, and extracellular volume fraction (ECV%) [34]. To facilitate the differentiation between stroke-induced and coronary-mediated myocardial injury, we evaluate typical CMR signs suggesting a recent MI (ie, presence of co-occurring LGE and acute edema in CMR). Infarcted myocardium will be defined as a region with a mean signal intensity >5SDs relative to the remote uninjured myocardium on LGE images [35].

Figure 3. Diagnostic assessment of the Cardiomyocyte injury following Acute Ischemic Stroke study. Illustration of the target points of the multimodal diagnostic workup to provide a thorough phenotyping of patients with stroke-associated myocardial injury. cMRI: cerebral magnetic resonance imaging; ECG: electrocardiogram; MRI: magnetic resonance imaging; TTE: transthoracic echocardiography.



Textbox 3. Study endpoints.

Primary outcome measures

- Frequency of Takotsubo syndrome pattern on cardiovascular magnetic resonance imaging (CMR); consisting of wall motion abnormalities together with myocardial edema (T2 mapping) but without late gadolinium enhancement
- Frequency and extent of myocardial edema
- Frequency of recent myocardial infarction on CMR
- Frequency and extent of ischemic and nonischemic myocardial fibrosis according to late gadolinium enhancement imaging and according to extracellular volume fraction on T1 mapping
- Frequency of left ventricular dysfunction in CMR (ie, ejection fraction and end diastolic left ventricular volume)
- Frequency of impaired left ventricular systolic and diastolic function in the transthoracic echocardiography

Secondary outcome measures

- Frequency of pathologic values of Periodic Repolarization Dynamics (PRDs) and Deceleration Capacity (DC; PRD≥5.75 deg²; DC≤2.5 ms)
- Frequency of values corresponding to *high perceived stress* in the Perceived Stress Scale (values ranging from 27 to 40)
- Frequency of cardiovascular events after 3 and 12 months
- Functional outcome after 3 and 12 months assessed using the modified Rankin Scale.

Sample Size Calculation and Statistical Analysis

Regarding the primary hypothesis and based on the published literature, we expect a rate of acute myocardial edema on T2 mapping in CMR in approximately 15% of patients with acute myocardial injury [17,36]. In the comparison groups with no or chronic myocardial injury, we expect a significantly lower rate (approximately 2%) presenting with acute myocardial edema [37].

To show a significant difference between the groups (two-sided α=.05), a sample size of 48 patients per group is required to reach a power of 80% and 89 patients per group for a power of 90%. Taking into consideration that in previous studies, due to impaired compliance or technical problems, the complete protocol of CMR could be realized only in approximately 85% of the study patients, we aim to include approximately 100-105 patients in each group.

Group comparisons (when comparing between the 3 groups) of the primary and secondary outcome measures (frequencies of specific alterations in CMR, TTE, and ECG) will be conducted using the chi-square test for categorical variables and, in case of continuous variables, using one-way analysis of variance or Kruskal-Wallis test, as appropriate. When comparing 2 groups (group 3 vs group 1 or group 3 vs group 2), Student *t* test will be used to compare continuous data. Logistic regression analyses will be used to calculate odds ratios and 95% CI to examine the association between elevated hs-cTn levels and the presence of specific structural and functional cardiac alterations in CMR and TTE. Multiple regression analyses using backward selection will be used to identify factors associated with certain myocardial alterations or ECG findings.

Results

Screening started in January 2019. After the initial pilot phase, the first patient was enrolled in April 2019. We estimate a recruitment period of approximately 3 years to enroll 300 patients with the complete CMR protocol. At the time of submission, 107 patients had been included. The final results are expected in 2023.

Discussion

Overview

This prospective, observational CORONA-IS study aims to clarify the underlying pathobiology of stroke-associated myocardial injury. The observation that patients with acute, severe neurological events often develop cardiac complications is well known and has been described as SHS or brain-heart syndrome [13]. Although there are strong indicators, suggesting that a stroke-induced dysregulation of the CAN leads to functional and structural cardiac alterations, many aspects of the pathophysiology remain unknown, and so far, no diagnostic or therapeutic algorithms for the treatment of these patients are available. Therefore, the aim of the CORONA-IS study is to explore and clarify the pathway from the brain to the heart, focusing on the crucial role of the autonomic nervous system and the cardiac phenotype.

The first goal is to visualize downstream cardiac mechanisms using CMR and TTE. We expect stroke patients with acute myocardial injury to show a higher rate and a different pattern of myocardial edema than patients with normal cTn. More precisely, we expect a myocardial edema (in T2 mapping in CMR) with wall motion abnormalities but without LGE [36,38]. This combination of edema without LGE is also seen in TTS, a condition that is in turn associated with an increased sympathetic stimulation [39]. TTS typically occurs following an emotionally or physically triggering event, but it can also develop after an acute neurologic illness [40]. In addition, we aim to assess alterations suggesting an acute or recent MI in the different groups. So far, several studies have applied CMR in stroke patients but mostly as part of a diagnostic workup to determine possible cardioembolic etiology in cryptogenic stroke [41-43]. For example, the HEBRAS (HEart and BRain interfaces

in Acute ischemic Stroke) study will determine whether an enhanced diagnostic MRI workup (including CMR) combined with prolonged Holter monitoring will increase the detection rate of pathologic cardiac findings in patients with AIS [44]. To date, myocardial tissue characterization in patients with stroke-associated myocardial injury has not been investigated via CMR.

Besides structural alterations of the myocardium, we further aim to clarify whether patients with AIS and stroke-associated myocardial injury show—especially transient—functional cardiac alterations. Cardiac dysfunctions, including wall motion abnormalities or reduced EF, are often seen in patients with ischemic stroke and other acute severe neurologic conditions [1,45,46]. Regarding our study population, we expect to see higher rates of changes in left ventricular systolic and diastolic functions in patients with dynamic troponin elevation.

The second aim of the study is to investigate the role of CAN in the development of stroke-associated myocardial injury. There are different ways to display the influence of CAN on the cardiovascular system. Invasive diagnostic methods with direct recording of neural activity are not feasible in clinical settings. Noninvasive methods include for instance measurement of baroreceptor sensitivity or HRV. Reduced HRV and impaired baroreceptor sensitivity are associated with higher stroke severity and worse clinical outcomes [47,48]. However, these diagnostic tools represent only the combined sympathetic and parasympathetic influence on the cardiovascular system. There is evidence that increased sympathetic nervous activity can lead to destabilization of the myocardial repolarization phase [49]. In the CORONA-IS study, we will use the novel ECG markers, PRD, and DC. PRD assesses rhythmic modulations of cardiac repolarization in the low-frequency spectral range (≤0.1 Hz) [31,50]. Experimental and clinical evidence suggests that these low-frequency alterations are caused by phasic efferent sympathetic activity. DC is an integral measure of deceleration-related oscillations of the heart rate and primarily reflects parasympathetic activity [51]. PRD alone and in combination with DC have been shown to be a strong and independent predictor of sudden cardiac death in patients with MI [30,31,52]. To date, these markers have not been investigated in patients with AIS. They could provide important information regarding the assumed dysfunction of the CAN causing stroke-associated myocardial injury. It has to be kept in mind that these noninvasive measures can only serve to display an association between altered autonomic cardiac control and the presence of myocardial injury in stroke patients. To show a direct causation, further studies with nonobservational designs will be necessary. As the clinical differentiation between concomitant MI and stroke-associated myocardial injury is difficult, we aim to investigate whether specific biomarkers can help distinguish between both conditions. Therefore, we conduct thorough biobanking to evaluate the role of various potential biomarkers.

Limitations

Some limitations of the study will need to be considered. First, as the aim of CORONA-IS is to investigate patients with stroke-associated myocardial injury (ie, SHS), it is necessary to avoid including patients with clearly coronary-mediated myocardial ischemia. Hence, patients with signs of a concomitant or recent MI (ie, typical alterations in the ECG, such as ST elevations or a new left bundle branch block, as well as a recent coronary artery bypass surgery or percutaneous coronary intervention) will be excluded. Second, as CMR and the assessment of autonomic ECG markers depend on a rhythmic heartbeat, patients with persistent or permanent atrial fibrillation will not be included, even though they may be prone to develop stroke-associated myocardial injury. Third, specific contraindications to undergo CMR (eg, certain metallic implants, claustrophobia, or physiologic constitution such as severe obesity or an inability to stay in the supine position) may lead to an underrepresentation of these patients in the study. To correct for potential selection bias in the final analysis, the screen log of the study will be analyzed at the end of data collection to assess whether the rate of excluded patients due to CMR contraindications differed among the 3 groups. Finally, considering the necessity of giving informed consent to participate in the CORONA-IS trial, patients with large infarctions and aphasia may also be underrepresented.

Conclusions

In summary, the CORONA-IS study aims to provide a deep phenotyping of patients with stroke-associated myocardial injury by using different diagnostic tools, such as 3T CMR, TTE, specific novel autonomic ECG markers, and different blood biomarkers. The goal of this prospective, observational study is to develop a better understanding of the characteristics and the pathophysiology of stroke-associated acute myocardial injury (SHS) to identify patients at risk and improve diagnostic and therapeutic procedures.

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Authors' Contributions

The study is conceived by JS. JS, RG, HS, CN, JSM, and ME contributed to the design. RG, HS, SH, and EB are substantially contributing to the data acquisition. EB and JM contribute substantially to the CMR data analysis. AB created the technique and software of the autonomic ECG marker analysis performed in the study. HS wrote the manuscript and conceived the figures. All

authors contributed to the revision of the manuscript before submission for publication. All authors have read and approved the final manuscript.

Conflicts of Interest

ME received funding from Deutsche Forschungsgemeinschaft under Germany´s Excellence Strategy – EXC-2049 – 390688087, BMBF, DZNE, DZHK, EU, Corona Foundation, and Fondation Leducq. ME reports grants from Bayer and fees paid to the Charité from Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Amgen, GSK, Sanofi, Covidien, Novartis, Pfizer, all outside the submitted work.

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Abbreviations

2Ch: 2 chamber
3T: 3 Tesla
3Ch: 3 chamber
4Ch: 4 chamber
ACS: acute coronary syndrome
AIS: acute ischemic stroke

CAN: central autonomic nervous system
CMR: cardiovascular magnetic resonance imaging
CORONA-IS: Cardiomyocyte injury following Acute Ischemic Stroke
cTn: cardiac troponin
DC: deceleration capacity
ECG: electrocardiogram
EF: ejection fraction
FA: flip angle
HRV: heart rate variability
hs-cTn: high-sensitivity cTn
LGE: late Gadolinium enhancement
LV: left ventricle
MI: myocardial infarction
MRI: magnetic resonance imaging
PRD: periodic repolarization dynamics
RV: right ventricle
SAX: short axis view
SHS: stroke-heart syndrome
TTE: transthoracic echocardiography
TTS: Takotsubo syndrome

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Protocol

Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS) to Improve Collaboration in School Mental Health: Protocol for a Mixed Methods Hybrid Effectiveness-Implementation Study

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Abstract

Background: Public schools in the United States are the main providers of mental health services to children but are often ill equipped to provide quality mental health care, especially in low-income urban communities. Schools often rely on partnerships with community organizations to provide mental health services to students. However, collaboration and communication challenges often hinder implementation of evidence-based mental health strategies. Interventions informed by team science, such as Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS), have the potential to improve treatment implementation and collaboration within schools.

Objective: The objective of this study is to improve communication and collaboration strategies among mental health and school staff by adapting an evidence-based team science intervention for school settings. We present a protocol for a hybrid effectiveness-implementation study to adapt TeamSTEPPS using stakeholder feedback, develop a tailored implementation plan, and pilot the adapted content in eight schools.

Methods: Study participants will be recruited from public and charter schools and agencies overseeing school mental health services in the local metro area. We will characterize current services by conducting a needs assessment including stakeholder interviews, observations, and review of administrative data. Thereafter, we will establish an advisory board to understand challenges and develop possible solutions to guide additional TeamSTEPPS adaptations along with a complementary implementation plan. In aim 3, we will implement the adapted TeamSTEPPS plus tailored implementation strategies in eight schools using a pre-post design. The primary outcome measures include the feasibility and acceptability of the adapted TeamSTEPPS. In addition, self-report measures of interprofessional collaboration and teamwork will be collected from 80 participating mental health and school personnel. School observations will be conducted prior to and at three time points following the intervention along with stakeholder interviews. The analysis plan includes qualitative, quantitative, and mixed methods analysis of feasibility and acceptability, school observations, stakeholder interviews, and administrative data of behavioral health and school outcomes for students receiving mental health services.

Results: Recruitment for the study has begun. Goals for aim 1 are expected to be completed in Spring 2021.

Conclusions: This study utilizes team science to improve interprofessional collaboration among school and mental health staff and contributes broadly to the team science literature by developing and specifying implementation strategies to promote sustainability. Results from this study will provide knowledge about whether interventions to improve school culture and climate can ready both mental health and school systems for implementation of evidence-based mental health practices.

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KEYWORDS

teams; Team Strategies and Tools to Enhance Performance and Patient Safety; school mental health; school health

Introduction

Background

Youth living in poverty experience internalizing and externalizing mental health disorders at considerably higher rates than higher socioeconomic status peers. One in five children living below 100% of the federal poverty level has a mental, behavioral, or developmental disorder [1]. These disproportionately high rates are due in large part to exposure to psychosocial stressors such as community violence and housing insecurity [2,3]. Approximately half of all children with emotional and behavioral disorders receive mental health services [4]; however, rates of service utilization are likely lower among low-income youth [5,6]. Public schools have become the main provider of mental health services to children in the United States and offer a way to increase access for low-income youth [7]. In fact, a 2017-2018 national survey showed that 58% of urban schools provided mental health diagnostic services and 42% provided treatment [8]. However, the primary mission of schools is education, not health care, and many schools are ill equipped to provide quality mental health care to students [9,10].

Due to a lack of internal capacity to adequately meet student mental health needs, districts often have contracts with community agencies for services. A comprehensive national survey found that about half of school districts in the United States had contracts with community organizations for student mental health services, typically provided in school with a combination of school and community staff [11]. Regarding the coordination of mental health activities in schools, about one-third of schools never held interdisciplinary staff meetings, and the most frequent form of coordination was informal communication [11]. Although school-based mental health services fill an unmet need in an accessible context for children, it is unclear whether services are coordinated effectively for maximal positive impact on student outcomes while minimizing burden on schools.

Effective collaboration among interdisciplinary personnel is a necessary yet understudied aspect of providing school-based mental health services. Supporting school-aged children with mental health needs often requires a team of providers, including teaching and nonteaching staff, paraprofessionals, mental health clinicians, case managers, and physicians [12]. Collaboration challenges include limited time and resources, poor communication, and vaguely defined roles [13-18]. For example, mental health teams and teachers may not realize the mutual benefit of receiving each other's input and collaboration on discipline-specific yet shared goals for classroom behavior management or treatment plans. Even when teachers are interested in increasing collaboration and involvement in student mental health [19], specific strategies for facilitating this engagement are lacking. Ineffective teamwork may hinder the quality of services as evidence-based school mental health interventions typically rely on the engagement and coordination of multiple individuals [20].

Team science literature has the potential to inform implementation efforts and improve collaboration within school-based mental health teams [21-23]. One particular team training intervention, Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS) [24,25], has been widely used in health care settings with encouraging outcomes [26,27]. TeamSTEPPS has been associated with improvements in teamwork and communication [26,28], reduced provider burnout [29] and turnover [30], and improved patient outcomes [31]. Core competencies targeted in TeamSTEPPS are leadership, situation monitoring, mutual support, and communication. These competencies represent trainable skills [23], and performance, knowledge, and attitudinal outcomes result from proficiency in these competencies. The curriculum consists of an introductory module and four didactic modules targeting each core competency [23-25]. Defining team skills, demonstrating strategies for improving proficiency in competencies, and identifying tools for overcoming barriers are emphasized [23]. Vignettes and case scenarios reinforce learning. TeamSTEPPS implementation typically occurs as a multiphase process that includes (1) assessment, (2) planning, training, and implementation, and (3) sustainment, though the necessary implementation supports have not been well defined in the literature. Improvements in team skills and behaviors of staff, such as those that have been attributed to TeamSTEPPS [26,28], have the potential to improve culture and climate in schools, which may lead to improved student outcomes [32].

Prior Work

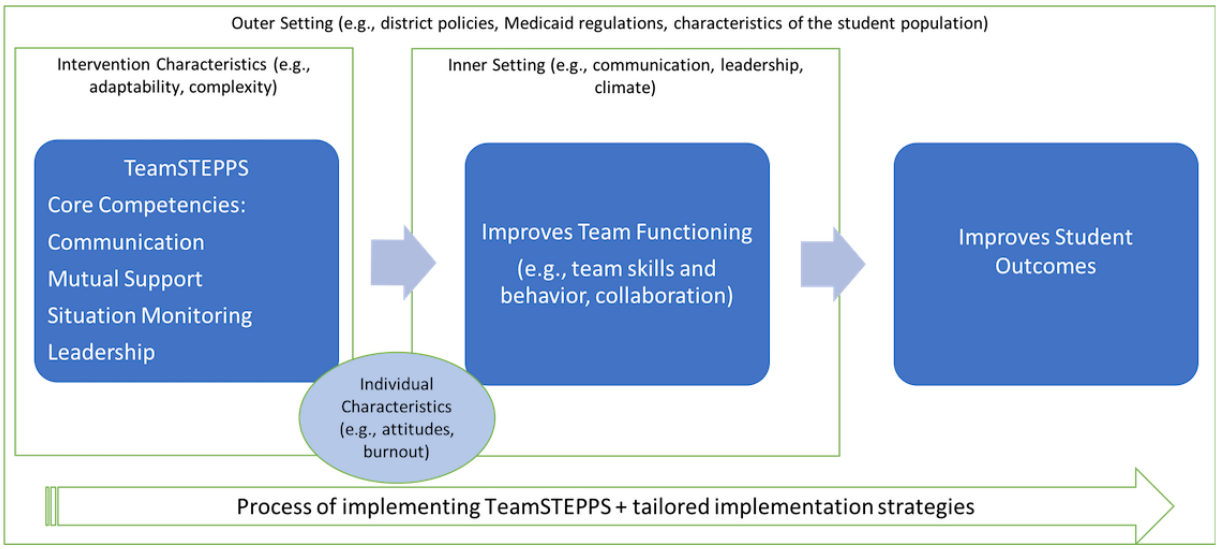
As TeamSTEPPS was developed for health care settings, it requires modifications for the school mental health context. Our team has previously adapted the intervention for mental health teams working in schools and has examined the feasibility and acceptability of the adaptation [33]. Relevant stakeholders from school mental health teams employed by community organizations advised the adaptation, and school staff did not

participate. Core TeamSTEPPS content remained largely unchanged in the adaptation because participants reported it was relevant as is; however, we adapted language throughout to be consistent with preferred nomenclature in schools (eg, "patients" was changed to "students" or "children") and revised case examples and vignettes with ones informed by community partners' experiences. Teams in six schools were randomized to receive the adapted TeamSTEPPS approach or usual supports. The results indicated that TeamSTEPPS was feasible and acceptable for implementation, and leadership emerged as an important facilitator. Barriers to implementation success included staff turnover, lack of resources, and challenges in the school-mental health team relationship [34]. Overall, this preliminary work suggested that TeamSTEPPS was promising for school mental health teams. Stakeholder feedback indicated that more robust supports, such as ongoing consultation and booster training, would enhance implementation efforts. Additionally, engaging school personnel directly in further adapting TeamSTEPPS was highlighted as an important next step. This study builds upon our previous findings by further adapting TeamSTEPPS in collaboration with school personnel, and defining and piloting implementation supports.

Current Study

This study will expand the adaptation of TeamSTEPPS using additional stakeholder feedback, develop a tailored implementation plan, and pilot the new adapted version. The Consolidated Framework for Implementation Research (CFIR) provides an overarching framework for the project to guide implementation (Figure 1). The CFIR, synthesized from the health services implementation literature, represents "an overarching typology - a list of constructs to promote theory development and verification about what works where and why across multiple contexts" [35]. The five major domains of the CFIR include intervention characteristics, outer setting, inner setting, characteristics of individuals involved, and implementation process. Complementary to the CFIR, the School Implementation Strategies, Translating Expert Recommendations for Implementing Change (ERIC) Resources (SISTER) [36] will be a guide for tailoring implementation strategies. The SISTER is a compilation of implementation strategies adapted from the ERIC taxonomy, specifically for schools.

Figure 1. Guiding conceptual model. TeamSTEPPS: Team Strategies and Tools to Enhance Performance and Patient Safety.



The specific aims of this project are to (1) characterize the use of school mental health services in urban districts within the United States, including challenges and successes, using multiple sources of information; (2) identify interorganizational challenges and required components of TeamSTEPPS to adapt (the product of aim 2 will be an adapted TeamSTEPPS for both school mental health and school-employed personnel, and specific tailored implementation strategies to improve services in schools in conjunction with TeamSTEPPS [TeamSTEPPS plus tailored implementation plan]); and (3) explore the feasibility, acceptability, and impact of TeamSTEPPS plus tailored implementation strategies on interprofessional collaboration, teamwork, and student outcomes. Primary implementation outcomes [37] of interest are the feasibility and acceptability of the adapted TeamSTEPPS. Secondary goals include exploring the impact of TeamSTEPPS plus tailored implementation strategies on interprofessional collaboration, teamwork, and student outcomes.

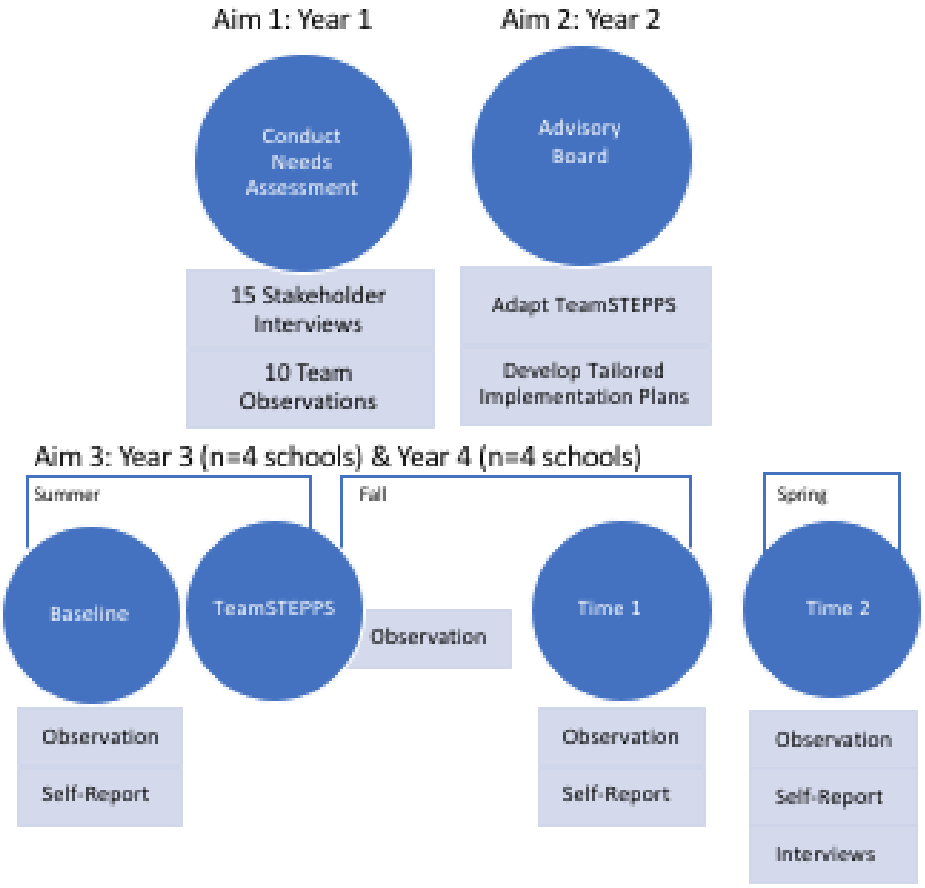
This study has a mixed methods effectiveness-implementation hybrid design. The effectiveness of TeamSTEPPS will be examined while knowledge of implementation barriers and facilitators are incorporated into an implementation plan [38].

Methods

Overview

Figure 2 presents an overall timeline for the study. The objective in year 1 is to better understand the needs of our district partners. The objective in year 2 is to adapt TeamSTEPPS and co-develop a tailored implementation plan with school and mental health team partners. During years 3 and 4, we will pilot test the adapted TeamSTEPPS plus tailored implementation plan. In year 5 (not depicted), data analyses will be performed.

Figure 2. Overall study timeline. TeamSTEPPS: Team Strategies and Tools to Enhance Performance and Patient Safety.



Aim 1

We aim to characterize the use of urban school mental health services, including challenges and successes, using multiple sources of information (needs assessment, observation, and administrative data).

Procedure

Recruitment

Participants will be recruited from public and charter schools and agencies implementing and overseeing school mental health services in the local metro area. Participants for needs assessment interviews will range from upper-level leadership to front line personnel. Schools are invited to participate via an introductory email sent to district and/or school leadership. Following approval from the district and/or charter entities, individual staff members will be invited to participate via an introductory staff meeting or email facilitated by our leadership partners.

Needs Assessment

First, we will conduct a needs assessment with 15 key informants who represent clinical leadership, clinical and paraprofessional providers from the mental health team, teachers, and school administrators. Key informants will be asked about (1) the history of mental health services in their school/district, (2) successes, and (3) challenges or unintended consequences of previous models. We will ask interviewees to recommend additional key informants, and we will include as many individuals as appropriate to better our understanding of the district's services. Key informant meetings will last approximately 1 hour.

Observations

We plan to observe school mental health teams providing services. Study staff will spend one full day per school observing team dynamics, service provision, and interactions with school personnel in 10 schools drawn from our partner districts. In light of COVID-19, if in-school observations are not permitted, we will utilize a "think aloud" exercise in lieu of observations.

Administrative Data

To understand the impact of previous and existing mental health service models in our partner districts, we will examine students' behavioral health and school outcomes using administrative data when available (eg, Medicaid claims or school records, which vary by district). These data may include (1) routine and acute behavioral health service use, (2) psychotropic medication use, (3) school absence, (4) grade promotion, (5) school suspension, (6) disciplinary referrals, (7) individualized education plan status, and (8) demographic data including sex and race/ethnicity. School-level data will include average annual school-level absence and suspension rates, average annual number of students with disciplinary school transfers, and annual number of students with an individualized education plan.

Measures

We will use an adapted version of the Oxford Non-Technical Skills (NOTECHS) scale [39] as the field observation tool along with detailed qualitative field notes. The NOTECHS is a validated tool to assess teamwork and cognitive skills in the airline cockpit and has been reliably and validly modified for medical teams [40,41]. It measures leadership and management; teamwork and cooperation; problem solving and decision making; and situational awareness. Observers code team behavior in each domain using three to five items rated from 1 (below standard) to 4 (excellent). Subteam specific modifiers further examine the unique contributions of various staff roles. Previously, our team adapted and piloted the NOTECHS for school mental health teams [42].

Analysis Plan

Quantitative Analysis

One-way analysis of variance (ANOVA) will examine the mean differences between schools on the NOTECHS total and for each domain. We will synthesize previous local evaluations that provide insights into the characteristics of an urban setting school, including student demographics and school climate such as suspension and absence rates, as well as children's behavioral health service use over time. The synthesis will inform key stakeholders about whether school mental health services have a positive effect on improving school outcomes and whether the school climate (school-level absence and suspension rates) moderates the effect of school mental health services on children's school outcomes. We will share the results with key stakeholders and obtain their views on the successes and challenges of school-mental health service delivery.

Qualitative Analysis

We will load all field notes into NVivo (QSR International) for data management and analysis. Analysis will be guided by an integrated approach [43] that includes identification of a priori attributes of interest (ie, constructs from the CFIR and key TeamSTEPPS domains), combined with the identification of emergent codes and themes. This integrated approach uses an inductive process of iterative coding to identify recurrent themes, categories, and relationships. After initial data exploration, a comprehensive coding scheme is developed and applied to all data in order to produce a fine-grained descriptive analysis. A portion of the transcripts will be double coded to assess the reliability of the coding scheme. Disagreements in coding will be resolved through team discussion. Coders will be expected to reach and maintain reliability of $\kappa \geq 0.85$.

Mixed Methods Analysis

We will integrate the NOTECHS observation data and field notes using the following taxonomy: the structure is Quan → Qual, the design is Convergent (we will use quantitative data [ie, NOTECHS] and qualitative data [ie, field notes] to explore similar questions to see if they reach the same conclusions), and the process is Connecting (to elaborate upon the quantitative findings to understand the process of implementation of school-based services as experienced by stakeholders) [44]. To integrate the quantitative and qualitative methods, we will follow the National Institutes of Health guidelines for best practices [45]. We will enter quantitative findings (ie, NOTECHS scores) into NVivo as attributes of each school. We will examine the distribution of NOTECHS scores and, if the distribution permits, will determine cut points to classify schools as high, medium, and low in team skills. Quantitative attributes will be used to categorize and compare important themes among subgroups and to triangulate to determine if quantitative and qualitative observational methods yield similar information.

Aim 2

We aim to adapt TeamSTEPPS in collaboration with an advisory board of diverse stakeholders and develop tailored implementation strategies to support the use of TeamSTEPPS.

Procedure

Building on aim 1, we will establish an advisory board guided by the recommendations of Southam-Gerow et al [46] for utilizing stakeholder involvement in the treatment adaptation process. CFIR will guide the adaptation process [47]. Best practice recommendations for advisory boards will be followed, including establishing formalized commitment from members and clarifying expectations in advance [48]. The primary focus of the advisory board meetings will be to understand challenges, including, but not limited to, the problem of limited coordination and collaboration between mental health providers and school personnel, and to identify possible solutions and further TeamSTEPPS adaptations.

The advisory board will meet regularly to consider issues as the adaptation proceeds module by module. Consensus on important points will be determined by a 70% majority, consistent with the literature [48]. Meetings are expected to occur in multiple short sessions over the course of the school year (eg, 90 to 180-minute sessions every other month). However, community partner preferences will be accommodated for meeting time, length, and location, with options for virtual attendance (an entirely virtual advisory board may be necessitated by COVID-19). Participants will be compensated for advisory-board participation.

The products of aim 2 will be (1) an adapted TeamSTEPPS, directed toward both school mental health and school-employed personnel, and (2) specific tailored implementation strategies to improve services in schools in conjunction with TeamSTEPPS. Based on previous experience, we expect the implementation plan will include established strategies [49] such as providing teams with training and ongoing consultation, designating implementation champions in each school, and suggesting leaders implement policy mandates that address core components of TeamSTEPPS. For example, designing an asynchronous online training for new hires may be needed as our preliminary work indicated that staff turnover represents a barrier. The tailored implementation plan will be defined in the context of SISTER [36] strategies in accordance with the CFIR [49].

Recruitment

The precise schools and participants to include will be determined during aim 1 in collaboration with our district leadership partners. We anticipate 10 to 15 participants, which

will likely include a variety of stakeholders, including school mental health providers, leadership from mental health organizations providing school-based services, teachers, school leaders/supervisors, and parents of youth receiving school-based mental health services. Participants will be formally invited by email or letter and asked to apply and agree in writing to participate to ensure they can commit for the duration of the research.

Aim 3

We aim to explore the feasibility, acceptability, and utility of TeamSTEPPS plus the implementation strategies generated in aim 2 in terms of interprofessional collaboration, teamwork, and student outcomes.

Procedure

We will pilot test the adapted TeamSTEPPS and implementation strategies in eight schools. Participating mental health team members and school personnel will complete self-report assessments measuring interprofessional collaboration, teamwork, feasibility, and acceptability at baseline (ie, before engagement in TeamSTEPPS) and the school year following participation at two time points (Figure 2). Participants will be compensated for completion of self-report measures. We will obtain written informed consent from all participants.

Recruitment

District leadership will provide guidance on the schools to invite for participation in the TeamSTEPPS pilot. We will recruit schools randomly without replacement from the pool of potential schools. We will compare the eight schools who agree to participate with those who decline in order to explore representativeness (eg, compare on the size of the school and number of mental health staff in the school). We plan to enroll the first cohort of four schools during year 3 and the last cohort during year 4 of the study (Figure 2). We anticipate 10 participants per school consisting of mental health team staff, teachers, nonteaching staff, and at least one administrator (eg, principal), but will collect data from additional relevant personnel when possible determined in conjunction with principals.

Training in TeamSTEPPS

We will work with schools to ensure that the initial TeamSTEPPS training is provided during regular professional development time to reduce burden for staff. We expect the initial training to be about 4 hours and to be delivered in person or online. The exact plans for ongoing support will be informed by the implementation plan developed in aim 2 with the advisory board.

Measures

Feasibility and acceptability of the adapted TeamSTEPPS will be assessed using a combination of qualitative and quantitative methods. Exploratory outcomes include teamwork, interprofessional collaboration, and behavioral and academic outcomes for students receiving school-based services, as well as potential contextual predictors of implementation. Interprofessional collaboration will be assessed via observation and self-report.

Dependent Measures

The Acceptability of Intervention Measure (AIM) and Feasibility of Intervention Measure (FIM) are each reliable and valid four-item tools to assess perceptions of the acceptability and feasibility of TeamSTEPPS [50].

Mental health and school staff will complete the Expanded School Mental Health Collaboration Instrument-Community Version (ESMHCI-CV) [51], a continuous measure of interprofessional collaboration in school mental health. Scores can be calculated individually or among groups working in the same school. For each subscale, an average score is calculated, with higher scores indicating strengths and lower scores indicating areas for improvement. The Cronbach α ranges from .81 to .94 for ESMHCI and .77 to .94 for ESMHCI-CV [51,52]

The TeamSTEPPS Teamwork Perceptions Questionnaire (T-TPQ) [53] is a 35-item self-report measure of individual perceptions of group-level team skills and behavior based on the five core components of teamwork that comprise TeamSTEPPS. Total scores are computed by summing all items, and higher scores indicate more favorable perceptions. The Cronbach α ranges from .88 to .95, and convergent validity is adequate [53].

The TeamSTEPPS Teamwork Attitudes Questionnaire (T-TAQ) [54] is a 30-item self-report measure of individual attitudes related to the core TeamSTEPPS components. A sum score is calculated across items, with higher scores indicating more positive attitudes. Constructs exhibit unique variance, and the Cronbach α ranges from .70 to .83 [54].

Exploratory Contextual Predictors

The Evidence-Based Practice Attitude Scale (EBPAS) [55] is a 15-item self-report measure of attitudes toward adoption of evidence-based practice (EBP). It consists of the following four subscales: appeal (is EBP intuitively appealing), requirements (would an EBP be used if required), openness (general openness to innovation), and divergence (perceived divergence between EBP and current practice). Higher scores indicate more positive attitudes, with the exception of divergence, which is reverse coded. The EBPAS has national norms, demonstrated validity, and good internal consistency (subscale α range from .67 to .91) [56,57].

The Maslach Burnout Inventory Human Services Survey (MBI) [58] is a 22-item self-report measure of burnout. Three subscales measure emotional exhaustion, depersonalization, and reduced personal accomplishment. Items are rated from 0 (never) to 6 (everyday), with higher scores on emotional exhaustion and depersonalization, and lower scores on personal accomplishment (reverse scored) indicating higher levels of burnout. Satisfactory internal consistency, and discriminant and factorial validity have been demonstrated [59-61].

Observations

Consistent with aim 1, a trained observer will spend one full day taking detailed field notes on team dynamics, service provision, and interactions among mental health providers, school personnel, and students along with using the adapted NOTECHS.

Interviews

We anticipate conducting 12 individual interviews of people randomly selected from all of the different stakeholder groups engaged in TeamSTEPPS, but will continue until saturation is achieved [62]. The semistructured interview protocol will ensure uniform inclusion and sequencing of topics and allow for valid comparison across interviews. The interview guide will have three parts, with the first and second querying about feasibility and acceptability, respectively. In the third section, we will present findings from the quantitative data assessing interprofessional collaboration and student outcomes and ask for respondent's reflections.

Administrative Data

In districts where required data are available, behavioral and educational outcomes of students will be analyzed using deidentified administrative data as described in aim 1.

Analysis Plan

Qualitative Analysis

We will use NVivo for analysis using the integrated approach as described in aim 1.

Quantitative Analysis

Feasibility will be determined by the proportion of schools that enroll/those that are invited and the proportion of participants who attend TeamSTEPPS training/those who are eligible to participate. We will also examine the distribution of AIM and FIM scores.

Collaboration and teamwork will be assessed observationally (ie, NOTECHS) and via self-report (eg, ESMHCI and T-TPQ). The mean total and domain scores in the NOTECHS will be computed for each school. Individual and school scores will be calculated for self-report measures. A series of one-way ANOVA assessments will examine differences between schools at each time point to assess the impact of TeamSTEPPS plus implementation strategies. Repeated measures ANOVA will examine scores on these measures within schools over time. Relevant individual and team factors, including EBPAS and MBI scores and team size, will be explored and included in the models as covariates where appropriate.

Behavioral and academic outcomes will be explored using administrative data as described in aim 1. These methods are described in detail elsewhere [63-67]. Using repeated measures ANOVA, we will compare student outcomes for students receiving mental health services the one full school year prior to the school's engagement in TeamSTEPPS in the subsequent school year. When data are available, we will explore whether school absence, suspension, and grade promotion differ 1 year before and after the implementation at the individual and school levels. Additionally, logistic regression analyses will examine if children's behavioral health service use differs before and after the school's engagement in TeamSTEPPS. All analyses conducted will accommodate nesting of participants (ie, teachers and mental health professionals) within clusters (ie, schools).

Mixed Methods Analysis

We will integrate the NOTECHS, self-report, and administrative data with the interviews and field notes following best practices [44]. The structure is Quan → Qual, the function is Complementarity, and the process is Connecting [43]. We will use findings from the quantitative data to identify patterns in the qualitative data. To do this, we will enter quantitative findings (eg NOTECHS ratings) into NVivo as attributes of each (1) school (for field notes) and (2) individual (for interviews).

Results

Recruitment for aim 1 of the study has begun. Goals for aim 1 are expected to be completed in Spring 2021. This project has been reviewed by the University of Pennsylvania (protocol 834488) and City of Philadelphia Institutional Review Board (study #2020-31).

Discussion

This study will examine the acceptability and feasibility of an adapted team training intervention, TeamSTEPPS, within school mental health. Our previous trial demonstrated both the preliminary acceptability and challenges of implementing TeamSTEPPS with school mental health service providers [33,34]. Results from the initial trial indicated the need to gather additional stakeholder feedback about TeamSTEPPS, the potential benefit of a co-developed tailored implementation plan, and the importance of leadership support.

This study has three main innovations. First, few implementation studies focus on improving interorganizational functioning [68]. Specific rigorous strategies to facilitate the alignment of two distinct yet related service settings, such as schools and contracted mental health teams, have not been sufficiently explored, contributing to the importance of this study. Second, we will use a community-partnered approach to engage stakeholders in understanding school mental health collaboration challenges and identifying solutions [46]. We will triangulate stakeholder perspectives, observations, and administrative data, moving the field beyond traditional trial and error implementation and improving rigor in implementation science. Third, few studies on school mental health services have given an equal voice to stakeholders from both schools and community mental health. TeamSTEPPS provides structured processes for improving collaboration across a range of stakeholders. While there are some limitations, including the lack of a randomized control group for aim 3, this project has the potential to improve school culture and climate, which in turn may improve student outcomes [32] and ready both mental health and school systems for EBP implementation. We anticipate that this project will lead to future studies testing the adapted TeamSTEPPS plus tailored implementation strategies in a randomized multisite implementation trial. The ultimate goal is to improve the quality of services underserved children receive in schools.

Acknowledgments

CBW is the principal investigator for the study protocol. CBW generated the idea and designed the study, and approved all changes. AK was the primary writer of the manuscript. All other authors are coinvestigators or collaborators on the grant and have provided input into the design of the study. All authors reviewed and provided feedback for this manuscript. The final version of this manuscript was vetted and approved by all authors. This work has been supported by the Agency for Healthcare Research and Quality (grant number 1 R18 HS026862-01A1).

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the Agency for Healthcare Research and Quality.
[PDF File (Adobe PDF File), 137 KB - resprot_v10i2e26567_app1.pdf]

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Abbreviations

AIM: Acceptability of Intervention Measure
ANOVA: analysis of variance
CFIR: Consolidated Framework for Implementation Research
EBP: evidence-based practice
EBPAS: Evidence-Based Practice Attitude Scale
ERIC: Expert Recommendations for Implementing Change
ESMHCI: Expanded School Mental Health Collaboration Instrument
FIM: Feasibility of Intervention Measure
MBI: Maslach Burnout Inventory Human Services Survey
NOTECHS: Oxford Non-Technical Skills
SISTER: School Implementation Strategies, Translating Expert Recommendations for Implementing Change Resources
TeamSTEPPS: Team Strategies and Tools to Enhance Performance and Patient Safety
T-TAQ: Teamwork Attitudes Questionnaire
T-TPQ: TeamSTEPPS Teamwork Perceptions Questionnaire

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Original Paper

Pediatric Respiratory and Enteric Virus Acquisition and Immunogenesis in US Mothers and Children Aged 0-2: PREVAIL Cohort Study

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Abstract

Background: Acute gastroenteritis (AGE) and acute respiratory infections (ARIs) cause significant pediatric morbidity and mortality. Developing childhood vaccines against major enteric and respiratory pathogens should be guided by the natural history of infection and acquired immunity. The United States currently lacks contemporary birth cohort data to guide vaccine development.

Objective: The PREVAIL (Pediatric Respiratory and Enteric Virus Acquisition and Immunogenesis Longitudinal) Cohort study was undertaken to define the natural history of infection and immune response to major pathogens causing AGE and ARI in US children.

Methods: Mothers in Cincinnati, Ohio, were enrolled in their third trimester of pregnancy, with intensive child follow-up to 2 years. Blood samples were obtained from children at birth (cord), 6 weeks, and 6, 12, 18, and 24 months. Whole stool specimens and midturbinate nasal swabs were collected weekly and tested by multipathogen molecular assays. Saliva, meconium, maternal blood, and milk samples were also collected. AGE (≥3 loose or watery stools or ≥1 vomiting episode within 24 hours) and ARI (cough or fever) cases were documented by weekly cell phone surveys to mothers via automated SMS text messaging and review of medical records. Immunization records were obtained from registries and providers. follow-up ended in October 2020. Pathogen-specific infections are defined by a PCR-positive sample or rise in serum antibody.

Results: Of the 245 enrolled mother–child pairs, 51.8% (n=127) were White, 43.3% (n=106) Black, 55.9% (n=137) publicly insured, and 86.5% (n=212) initiated breastfeeding. Blood collection was 100.0% for mothers (n=245) and 85.7% for umbilical cord (n=210). A total of 194/245 (79.2%) mother–child pairs were compliant based on participation in at least 70% (≥71/102

study weeks) of child-weeks and providing 70% or more of weekly samples during that time, or blood samples at 18 or 24 months. Compliant participants (n=194) had 71.0% median nasal swab collection (IQR 30.0%-90.5%), with 98.5% (191/194) providing either an 18- or 24-month blood sample; median response to weekly SMS text message surveys was 95.1% (IQR 76.5%-100%). Compliant mothers reported 2.0 AGE and 4.5 ARI cases per child-year, of which 25.5% (160/627) and 38.06% (486/1277) of cases, respectively, were medically attended; 0.5% of AGE (3/627) and 0.55% of ARI (7/1277) cases were hospitalized.

Conclusions: The PREVAIL Cohort demonstrates intensive follow-up to document the natural history of enteric and respiratory infections and immunity in children 0-2 years of age in the United States and will contribute unique data to guide vaccine recommendations. Testing for pathogens and antibodies is ongoing.

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KEYWORDS

birth cohort; RSV; influenza; rotavirus; norovirus; vaccines; vaccine effectiveness; immunology; pediatrics

Introduction

Acute gastroenteritis (AGE) and acute respiratory infection (ARI) remain major causes of morbidity and mortality in young children worldwide. AGE is estimated to cause more than 1.5 million deaths globally among children under 5 years of age each year [1-3]. Rotavirus remains a major cause of global pediatric disease burden, particularly among unvaccinated children [4,5], but in the United States norovirus has become the leading cause of AGE since the introduction of widespread childhood rotavirus vaccination [4]. Norovirus causes approximately 20% of all AGE cases among US children visiting emergency rooms and admitted to hospital [4,6-9], and an estimated population-wide annual burden of 19-21 million AGE cases, including 56,000-71,000 hospitalizations and 570-800 deaths [10,11]. ARI is estimated to cause 5 million deaths globally among children under 5 years each year [12-16]. Respiratory syncytial virus (RSV) is the most common cause of viral lower respiratory tract illness in young children, responsible for 58,000 hospitalizations and 2 million outpatient visits in children under 5 years of age in the United States [17]. In the United States and Australia, 2% of children are hospitalized with RSV infection before their first birthday [17-19].

Given the significant burden of disease that norovirus and RSV cause in young children, these pathogens are high priority targets for vaccine development. However, there are significant obstacles to this effort, and greater understanding of their natural history and immune responses is critical. For example, norovirus GII.4 strains undergo rapid evolution, resulting in emergent immune escape variants every 2-5 years which replace previous predominant strains. RSV infections do not result in sterilizing immunity and correlates of protection are not completely understood. Maternal vaccination is under investigation as a potential strategy to reduce the burden of RSV disease in young infants, but deeper understanding is needed of maternal–infant immune transfer and infant acquisition of immunity [20-25].

Rotavirus vaccines have been in use since 2006 in the United States (RotaTeq, Merck and Co.; and Rotarix, GlaxoSmithKline Biologicals). While efforts to better understand vaccine performance have been fruitful, factors that influence rotavirus vaccine effectiveness in the postvaccine era, as well as the persistence and transmission of rotavirus, now need to be considered for both mother and child. These factors were not possible to have been assessed in rotavirus vaccine prelicensure clinical trials, which occurred amidst the prevaccine global setting of persistent and population-wide rotavirus exposures causing regular immunologic challenges. Existing vaccines to prevent influenza (including live attenuated influenza vaccine and inactivated influenza vaccine) are not recommended for infants under 6 months of age, so understanding the impact of maternal–infant immunologic transfer in utero and via breastmilk is important to assess for infants too young to be protected by vaccination. Even for older infants and children, it is important to have a better understanding of the complementary and aggregate roles of antibody protection via breastmilk antibodies and naturally acquired immunity from a child's first and second annual influenza seasons; deeper knowledge of this dynamic could improve our knowledge of how the vaccines could be optimized.

Understanding of the early natural history of infection and immune response requires intensive birth cohort studies that identify both symptomatic and asymptomatic infections and the pattern of immunity that develops to natural infections within each child. A well-conducted birth cohort can determine the specificity of immune response to natural infections, including homologous or heterologous protection, and other information critical to vaccine development. This concept is exemplified by a classic birth cohort study conducted in Mexico that defined rotavirus natural history and immunity [26] and provided the epidemiological framework required to develop the currently licensed rotavirus vaccines. Because of high cost and logistical limitations, there has been a paucity of birth cohort studies of natural infection and immunity in the United States in recent decades. Most cohort studies have been conducted in low-resource countries where infectious disease rates are high and research staff can document the health status of children through frequent home visits. The studies from low-resource countries have been invaluable to public health worldwide. However, the lack of such studies in the United States continues an unfortunate knowledge gap regarding the population burden of disease and the potential effectiveness of childhood vaccines in the US context.

To address this gap in public health data, the Centers for Disease Control and Prevention (CDC) sponsored the PREVAIL

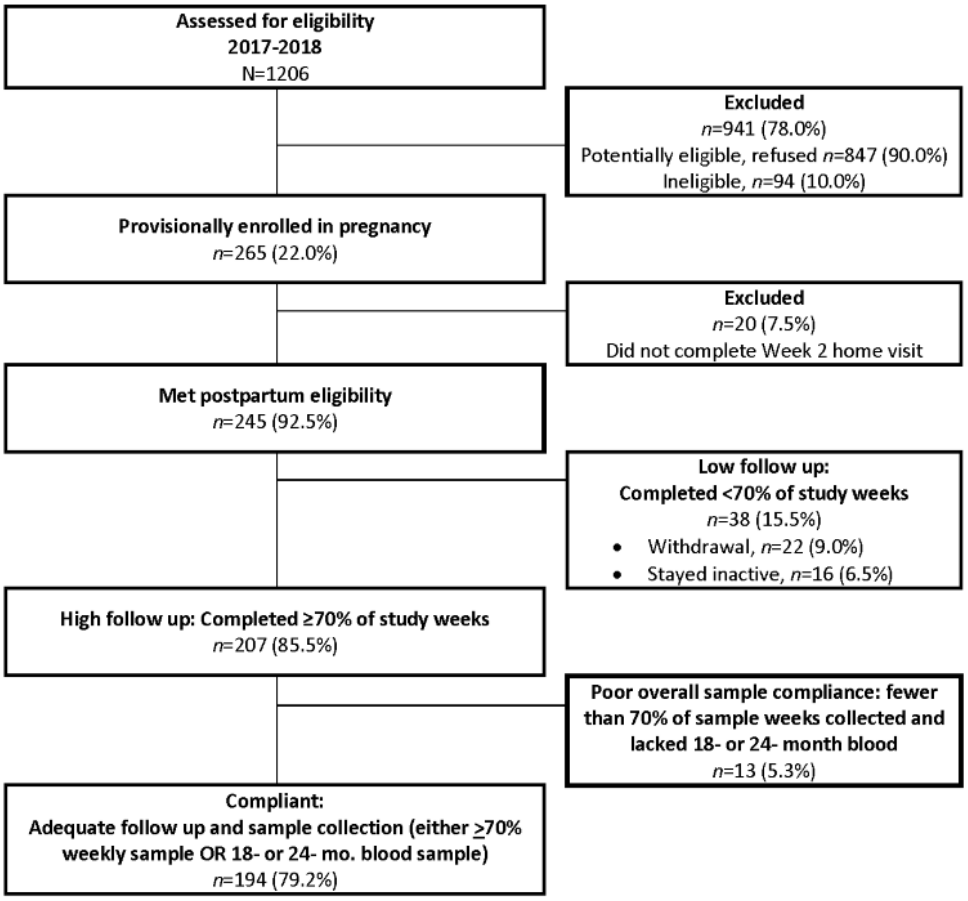
(Pediatric Respiratory and Enteric Virus Acquisition and Immunogenesis Longitudinal) Cohort [27]. The PREVAIL Cohort is a prospective, observational study of mother–child pairs residing in the Cincinnati, Ohio region. The study was designed to determine the natural history of endemic enteric and respiratory viral infections (norovirus, RSV, rotavirus, and influenza virus) and immune response to those infections in children. The aims of PREVAIL were to design and enact an intensive data and sample collection methodology for a birth cohort study of norovirus, rotavirus, RSV, and influenza virus infections and their immune responses in the United States. Novel elements of the design include collection of prospective samples enabled by electronic medical records alerts and trained hospital staff; weekly stool and nasal swab collections from study infants by their mothers, enabled by a courier service; as well as weekly data collection from mothers enabled by automated SMS text message surveys. In this paper we present the overall study design and describe our initial outcomes: maternal compliance with the study's intensive sample and data collection schedule and maternally reported AGE and ARI incidence in the cohort. Our experience demonstrates the feasibility of birth cohort studies in the United States enabled by available infrastructure and technologies.

Methods

Enrollment and Follow-Up

Launched in March 2017, the PREVAIL Cohort included generally healthy mother and child pairs followed actively from the third trimester of pregnancy until the child's second birthday. Recruitment was conducted in obstetrical clinics associated with the 2 study birth hospitals in Cincinnati, Ohio (Figure 1): University of Cincinnati Medical Center (UCMC) and The Christ Hospital (TCH). Target enrollment was set as 265 pregnant mothers in the last trimester of pregnancy and at least 240 eligible mother–infant pairs at postpartum week 2. Target sample size was based on 80% power, α=.05, and 2-sided tests of hypothesis to detect protection against repeat infections with norovirus or RSV. The target sample size was more than sufficient to provide robust estimation of AGE and ARI cases reported here. This study was reviewed and approved by institutional review boards at the CDC, Cincinnati Children's Hospital Medical Center (CCHMC), and the hospitals where maternal enrollment and delivery occurred.

Figure 1. Participant enrollment flow chart, PREVAIL Study, STROBE flow chart. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology [28].



Mothers were screened for potential eligibility using medical records and approached in the last trimester during an outpatient obstetric visit. Eligible pregnant women at or after 34 weeks of gestation were invited to participate. Those who elected to enroll completed a written, informed consent. Predelivery inclusion criteria for enrollment included singleton pregnancy, maternal age of 18 years or more, planned delivery at either study hospital, and a cell phone that could be used for SMS text

messaging. The cell phone criterion provided a means for close communication with study mothers. Predelivery exclusion criteria were living more than 20 mi from the birth hospital, illicit drug use, and HIV infection. Exclusion based on distance was due to the logistical requirements of weekly sample transport after the child's birth. Final inclusion in the postnatal follow-up portion of the study was contingent upon maternal delivery of a singleton, liveborn infant, lack of a major congenital anomaly, and active participation in the week 2 home visit. Enrollment was completed in July 2018.

Study mothers were trained in study procedures during the week 2 home visit by a research nurse, and reminders were provided during subsequent research visits. Maternal training emphasized techniques for sample collection, initiating courier pick-up, response to text questionnaires, and taking the child's temperature during illness. Mothers were provided with a notebook to provide specific guidance on study procedures, and information on how to call the research staff and the courier service. Each mother was provided with a thermometer and taught how to safely obtain a rectal temperature in infants up to 6 months, and an axillary measurement after 6 months.

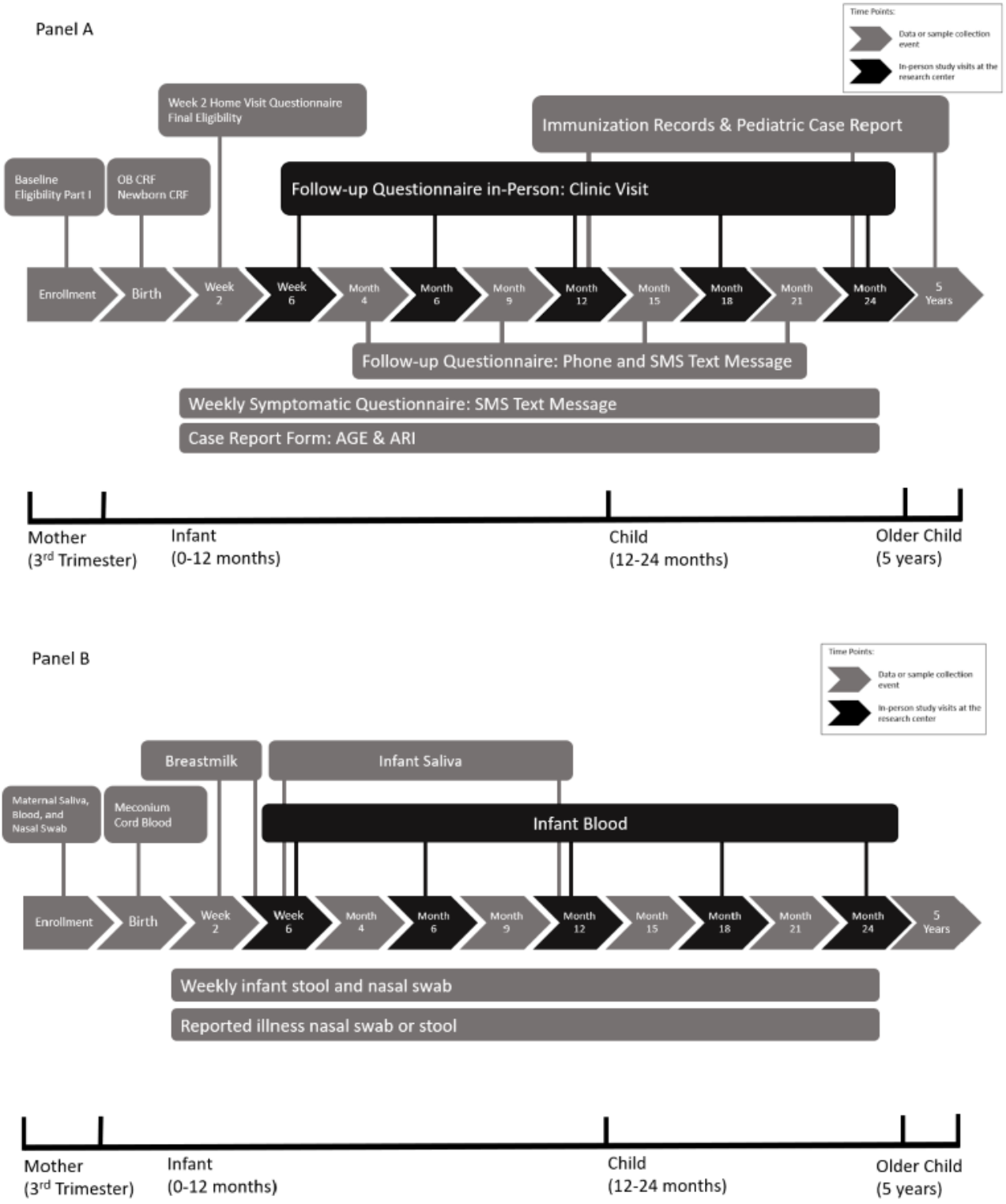
Participants under follow-up were monitored and classified as withdrawn, active, or inactive on an ongoing basis. Withdrawals were defined as participants who formally notified study staff that they no longer wished to continue participation. Inactive participants were defined as those who passively ceased meaningful participation, based on failing to attend a study clinic visit and cessation of all sample collection or SMS text message survey responses for at least eight consecutive weeks. Participation was closely monitored, and when several weeks of inactivity were observed, study staff reached out and made every effort to engage participants in the study.

To acknowledge the significant time and effort required of study mothers, we established a compensation schedule that included each study visit and each sample type. Compensation was provided using the ClinCard system [29], with funds loaded electronically onto mother's study card once a month. Mothers who completed all study procedures, from pregnancy through the infant's second birthday, were given a total compensation of up to US $1500. However, actual compensation varied, depending on adherence to the study procedures. To optimize weekly sample collection, we instituted a reward system of an additional monthly compensation if monthly sample compliance was 75% or more (ie, if at least three stool samples and three nasal swabs were received out of the four expected for each of the sample types). ClinCard payments were made on a rolling 4-week cycle for completion of weekly study requirements. Participants with sample compliance that fell below 75% were contacted by study staff to encourage participation, but there were no consequences for noncompliance other than loss of potential compensation.

Data and Sample Collection and Management

The study data system (Figure 2A) included comprehensive standardized questionnaires administered in-person during research visits, immunization and medical record abstraction, and automated SMS text message surveys administered weekly or periodically. The questionnaires applied throughout the study (Multimedia Appendices 1-6) captured infectious disease risk factors such as sociodemographic factors, immunization history, household composition, childcare and breastfeeding, as well as related child health factors such as nutrition and sleep practices.

Figure 2. PREVAIL study timelines. (A) Data collection; (B) sample collection. AGE: acute gastroenteritis; ARI: acute respiratory infection; CRF: case report form.



During the prenatal enrollment visit, a baseline questionnaire was administered to the mother regarding her household, health, and immunization history. Subsequent research visits were held at postnatal weeks 2 and 6 and months 6, 12, 18, and 24. Participants were required to complete the week 2 study visit within a 10-day window, and the week 6 to month 24 visits anytime during a 12-week window beginning with the due date. The week 2 visit was conducted in the mother's home. The remaining postnatal research visits were conducted in the clinic and included measurement of child weight and length. Between research clinic visits, a brief questionnaire was administered by phone (month 4) or through automated cell-phone SMS text messaging (months 9, 15, and 18) to determine any change in time-varying covariates such as breastfeeding or childcare.

Weekly reporting of symptoms in study children was conducted by automated cell phone SMS text messaging. The system used REDCap (Research Electronic Data Capture) [30,31], a secure, web-based software platform designed to support data capture and management for research studies. REDCap has a plugin to connect to the Twilio system [32], which supports fully automated delivery of the survey to enrolled mothers via their personal cell phone. Responses were automatically captured in the REDCap database without need for further data entry.

Affirmative maternal responses to weekly symptom surveys triggered a follow-up survey to ascertain type and severity of symptoms, illness start date, and whether the illness was ongoing. Once the child was reported as no longer symptomatic, an automated follow-up survey requested additional information on the episode, including the date ended, the location of any medically attended visits, and administration of any medications.

Electronic hospital records were systematically abstracted for pregnancy and perinatal histories of the mother and infant. The medical records at Cincinnati Children's Hospital, which includes its emergency room and affiliated clinics, were abstracted for all study children. Medical records are also currently being requested from all other pediatric providers. Record abstraction focused on AGE, ARI, and other medically relevant illnesses or conditions (eg, asthma, sickle cell anemia) and prescription of antibacterial or antiviral medications. Pediatric and maternal immunization records were obtained from Ohio and Kentucky immunization registries and identified health care providers. Maternal immunization records for influenza were also sought from employers.

Study data were entered directly into the REDCap database either by study staff at research visits via an internet-enabled tablet or by mothers responding to weekly SMS text message surveys. Maternal adherence to the protocol was routinely tracked for clinic visits and weekly sample and data collection. The REDCap database system included logic checks at the point of data capture. A data team comprising CCHMC and CDC staff systematically reviewed completed questionnaires to ensure completion of missing data and verify or correct improbable values.

Samples collected from study participants (Figure 2B) included midturbinate nasal swab, whole stool, blood, saliva, and milk. The pregnancy enrollment visit included collection of a maternal midturbinate nasal swab, saliva, and blood. Birth samples included cord blood collected at delivery and meconium stool samples collected during the delivery hospitalization. At the university birth hospital (UCMC), study mothers were identified in the hospital electronic medical records system as PREVAIL participants. Subsequently, when mothers were admitted for delivery, the UCMC electronic medical record system sent an automated phone SMS text message to on-call study staff notifying them of the hospital admission, and the research staff coordinated with the hospital delivery team to collect cord blood at birth. At the community birth hospital (TCH), there were no 24-hour research staff; instead, several labor-intensive procedures were instituted: TCH clinical staff were trained every few months on key study procedures, and reminded to collect cord bloods on study mothers, with posted signs prompting nurses to ask about the mother's study involvement; furthermore, mothers delivering at TCH were instructed to inform labor and delivery nurses that they were enrolled in the PREVAIL study. Regardless of study hospital, all study mothers were asked to collect their infant's meconium sample after delivery and ask their clinical nurses to keep the sample refrigerated until courier pick-up for delivery to the study laboratory.

At the week 2 home visit, mothers were trained in the remaining study procedures by the study nurse and provided with materials for sample collection and an organizer with instructions and materials. This training took about 45 minutes. Because of the importance and novelty of the instructions to the mother, key messages were repeated at the week 6 research visit, and close contact was maintained by text or phone to assist mothers who initially struggled with sample collection or weekly surveys.

Mothers were asked to collect a soiled diaper and a nasal swab from their child between Saturday and Wednesday of each week, with additional stool or nasal samples during illness. Stool collection involved having mothers wrap and place their child's soiled diaper into a resealable plastic bag, label it with the date of collection, and place the sealed bag into a disposable pouch designed for temperature control. Mothers were shown how to collect a midturbinate nasal swab using a flocked swab (Copan Diagnostics, Inc.) placed inside the child's nostril, not very far up, and gently rotate the swab in place. The swab was then placed into the vial containing BD Universal Viral Transport medium (Becton, Dickinson, and Co., Franklin Lakes, New Jersey), which was labeled with the collection date. The nasal swab vial was then placed into the pouch, sealed, and kept in the home refrigerator until time to contact the courier.

Stool and nasal swabs were sent to the study laboratory via courier within 1 to 2 days of collection. Mothers contacted the courier to initiate sample pick-up and placed samples into a small hard-sided cooler with an ice pack. The cooler was labeled for the courier and typically placed outside the door of the mother's residence. The courier service delivered samples from study homes to the study laboratory within a 4-hour window, trained its employees in study procedures, and contacted the study coordinator whenever sample collection issues arose. In the study laboratory, sample management and biobanking followed standardized procedures, including bar coding and entry of data into a professional software system for inventory management.

Study Outcomes

Study outcomes were maternal compliance with the study procedures and the incidence rates of AGE and ARI. Compliance was defined for this study as achieving at least 70% of intended follow-up duration (≥71/102 weeks) and at least one of the following: 70% of weekly sample collection during their period of activity in the study or a blood sample collected at 18 or 24 months. This level of compliance was considered adequate to identify infections in the first and second years of life. However, we also analyzed the impact of changing our standard for compliance to 80% of study weeks (≥81/102) and 80% of weekly sample collections or blood collection at 18 or 24 months; because we found that only 2 participants changed categories from compliant to noncompliant, the cut point was

maintained as 70% to be inclusive. All study samples were maintained for the periods for which mothers participated, including those who did not meet compliance goals. All participant data will remain available for analysis and will be selected or excluded based on individual study requirements.

An episode of AGE was defined as 3 or more loose or watery stools or 1 or more vomiting episodes within 24 hours at any time in the previous week. An episode of AGE was considered to have ended when 2 or more consecutive asymptomatic days occurred. Severity of AGE is scored using the modified Vesikari scale [33].

An episode of ARI is defined as the presence of cough or fever (temperature ≥38.0°C, rectal; ≥37.0°C, axillary) at any time in the previous week. When fever was reported, study staff asked the mother for the child's temperature, and the method for measuring temperature. Severity of ARI was based on the highest medical care sought for the child: hospital or emergency department use was considered moderate to severe.

Incidence rates of AGE and ARI were calculated as the number of cases reported divided by the number of weeks of SMS text message survey reporting by study mothers subtracting the weeks that the child was symptomatic for either AGE or ARI, multiplied by 52 to report cases per child-year and by 100 to report cases per 100 child-weeks.

Results

Enrollment and Follow-Up

Based on review of obstetrical records, a total of 1206 pregnant women were identified as potentially eligible and approached about the study (Figure 1). The 1206 screened patients were reported in medical records to be 44.78% White (n=540), 47.60% Black (n=574), and 7.63% other or unknown (n=92). On the day of initial screening contact, 8.21% (n=99) of mothers were identified as ineligible, 21.39% (n=258) refused participation, 15.42% (n=186) completed enrollment, and 54.81% (n=661) refused enrollment at that time but invited recontact about the study. Of the 192 mothers who provided a reason for nonparticipation, the primary reasons for refusal were lack of interest (n=126, 65.6%), not enough time (n=31, 16.1%), and the blood draws (n=14, 7.3%). Of the 661 women who refused immediate enrollment but allowed recontact, 79 (12.0%) were subsequently enrolled. Altogether, 265/1206 (22.0%) mothers who were screened consented to participate, which fully met our target enrollment goal. Enrollment in pregnancy was nearly evenly divided between the 2 birth hospitals.

Of the 265 mothers included in pregnancy, 245 (92.5%) met the postpartum criteria and completed enrollment (Figure 1), which modestly exceeded our planned enrollment goal. The 245 mother–child pairs who completed postpartum enrollment into the study are described in Table 1. Mothers ranged from 18 to 45 years of age. At the time of enrollment, 55.9% (n=137) were publicly insured, 43.3% (n=106) were privately insured, and 0.8% (n=2) were self-pay. Reported household income was less than US $25,000 for nearly one-third of study households (n=78), with the highest income category above US $100,000 for nearly one-quarter of study households (n=58). Nearly half of study mothers were married (n=118), with an additional 18.4% (n=45) of women unmarried but residing with their partner. As much as 4.5% (n=11) of infants were born late preterm, at 35 or 36 weeks of age. Most mothers reported their race as White (n=127, 51.8%) or Black (n=106, 43.3%); the remaining mothers identified themselves as biracial, Asian, or other. This racial distribution was like that identified at initial participant screening.

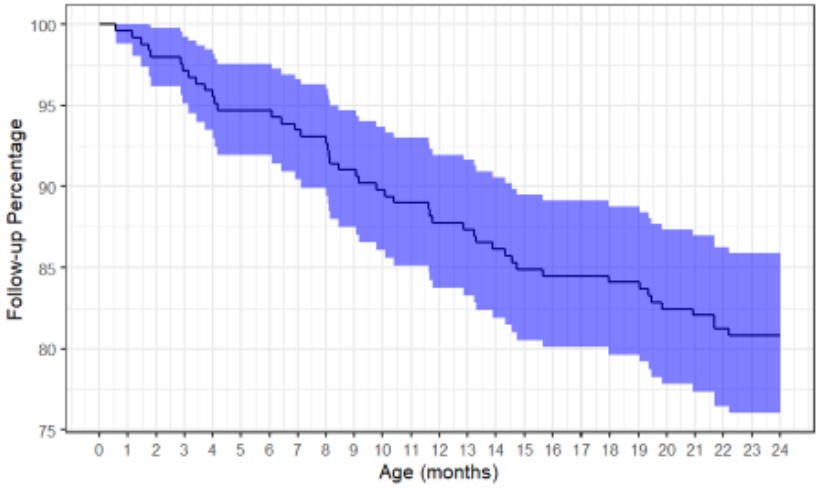
Table 1. Characteristics of the mother–child pairs in the PREVAIL Cohort.

Characteristics	All subjects (N=245), n (%)	Compliant (N=194), n (%)	Noncompliant (N=51), n (%)	*P* value
Maternal age				<.001
18-24 years	50 (20.4)	29 (14.9)	21 (41.2)	
25-34 years	155 (63.3)	132 (68.0)	23 (45.1)	
≥35 years	40 (16.3)	33 (17.0)	7 (13.7)	
Parity				.470
1	93 (38.0)	74 (38.1)	19 (37.3)	
2	67 (27.3)	56 (28.9)	11 (21.6)	
>3	85 (34.7)	64 (33.0)	21 (41.2)	
Maternal race				.630
Black	106 (43.3)	82 (42.3)	24 (47.1)	
White	127 (51.8)	103 (53.1)	24 (47.1)	
Biracial	5 (2.0)	4 (2.1)	1 (2.0)	
Asian and unknown	7 (2.9)	5 (2.6)	2 (3.9)	
Insurance				.008
Public	137 (55.9)	99 (51.0)	38 (74.5)	
Private	106 (43.3)	93 (47.9)	13 (25.5)	
Unknown	2 (0.8)	2 (1.0)	0 (0.0)	
Maternal education				.012
Less than high school	22 (9.0)	16 (8.2)	6 (11.8)	
High-school graduate	93 (38.0)	65 (33.5)	28 (54.9)	
Associate/trade	35 (14.3)	29 (14.9)	6 (11.8)	
College graduate	95 (38.8)	84 (43.3)	11 (21.6)	
Household income (annual)				.001
<US $25,000	78 (31.8)	57 (29.4)	21 (41.2)	
US $25,000-US $49,999	49 (20.0)	36 (18.6)	13 (25.5)	
US $50,000-US $99,999	48 (19.6)	45 (23.2)	3 (5.9)	
US $100,000 and above	58 (23.7)	50 (25.8)	8 (15.7)	
Unknown	12 (4.9)	6 (3.1)	6 (11.8)	
Marital status				.008
Married	118 (48.2)	103 (53.1)	15 (29.4)	
Lives with partner	45 (18.4)	31 (16.0)	14 (27.5)	
Divorced, separated, or single	82 (33.5)	60 (30.9)	22 (43.1)	
Delivery mode				.260
Vaginal	151 (61.6)	116 (59.8)	35 (68.6)	
Cesarean	94 (38.4)	78 (40.2)	16 (31.4)	
Infant gestational age at birth				.710
35-36 weeks	11 (4.5)	9 (4.6)	2 (3.9)	
37 weeks	44 (18.0)	37 (19.1)	7 (13.7)	
38-42 weeks	190 (77.6)	148 (76.3)	42 (82.4)	
Number of adults in household				>.99
2 or more adults	189 (77.1)	149 (76.8)	40 (78.4)	
1 adult	56 (22.9)	45 (23.2)	11 (21.6)	

Characteristics	All subjects (N=245), n (%)	Compliant (N=194), n (%)	Noncompliant (N=51), n (%)	*P* value
Total number of persons in household				.310
2 persons	14 (5.7)	11 (5.7)	3 (5.9)	
3 or 4 persons	146 (59.6)	121 (62.4)	25 (49.0)	
5 or 6 persons	61 (24.9)	44 (22.7)	17 (33.3)	
>6 persons	24 (9.8)	18 (9.3)	6 (11.8)	
Breastfeeding				.17
Initiated	212 (86.5)	171 (88.1)	41 (80.4)	
Did not initiate	33 (13.5)	23 (11.9)	10 (19.6)	

The 245 mother–child pairs enrolled in the study contributed 433.6 child-years of follow-up. Of these 245 mother–child pairs, a total of 47 (19.2%) were ever withdrawn or remained inactive in the study, of whom 38 were lost to follow-up prior to week 71 of the study; 9 became inactive between week 71 and the 2-year study visit. Loss to follow-up occurred fairly evenly from birth to 2 years of age (Figure 3).

Figure 3. Survival curve of 245 study participants and their participation over the 2-year follow-up period. The curve represents cumulative loss of 47 infants who withdrew or became and remained inactive prior to the final scheduled visit at 2 years.



Data and Sample Collection and Management

Overall, there was generally high adherence to completion of questionnaires, research visits, weekly data and sample collection, and completion of scheduled blood draws. A total of 1246 study visits were performed, 18,183 weekly SMS text message surveys were completed, and 13,809 weekly stool samples, 14,361 weekly nasal samples, and 1,176 infant blood samples were collected. Excluding only children who formally withdrew from the study by the time of each research visit, adherence to completion of study visits was 96.7% (233/241) at week 6 and 79.4% (177/223) at month 24. Lower adherence to coming into the research clinic for a blood draw for the 2-year study visit was a combination of time in the study or age, but also the COVID-19 pandemic occurred in Cincinnati when the last group of study participants were approaching the final study visit. For this last group, in-person study visits had to be postponed for a few months, at which point some indicated that they no longer wished to conduct the 2-year in-person study visit. We estimate a loss of as many as 15 participants from the 2-year blood draw due to interruption of human research by the pandemic.

Among all 245 enrolled participants, blood was obtained from all study mothers at the time of enrollment in pregnancy, and 88.6% (217/245) collection of umbilical cord blood samples was achieved from the birth hospitals. Blood sample collection was 80% or above throughout the first year of life but declined over time except in those identified as compliant (Table 2). During postnatal research visits, blood sample collection failed about 5%-10% of the time, resulting in rescheduling blood draws whenever possible.

Table 2. Follow-up, sample, and data collection.

Study parameter	All enrolled (N=245)	Compliant (N=194)
Follow-up time		
Total child-weeks	22,549	20,111
Total child-years	433.6	386.8
Withdrew or remained inactive, n (%)	47 (19.2)	4 (2.1)
Blood collection, n (%)		
Maternal blood, third trimester	245 (100.0)	194 (100.0)
Umbilical cord blood	210 (85.7)	164 (84.5)
Infant week 6	213 (86.9)	175 (90.2)
Infant month 6	205 (83.7)	178 (91.8)
Infant month 12	197 (80.4)	185 (95.4)
Infant month 18	186 (75.9)	184 (94.8)
Infant month 24	165 (67.3)	164 (84.5)
Weekly data and sample (percentage of study weeks), median (IQR)		
SMS text message survey response	91.8 (69.9-100.0)	95.1 (76.6-100.0)
Stool samples collected	62.1 (20.0-89.3)	71.8 (29.1-100.0)
Nasal swabs collected	61.0 (21.9-87.6)	71.0 (30.0-90.5)

Sample collection rates were also robust for other sample types. Saliva was collected from 234/245 (95.5%) study children for secretor status determination. In addition, of the 180 mothers who reported breastfeeding at the week 2 home visit, all provided at least one milk sample. Collection of cord blood was high but differed by hospital. The perinatal research system at UCMC produced a higher cord blood collection rate (114 of 125 expected samples, 91.2%) than the attentive but more ad hoc approach required for cord collection from TCH (96 of 120 expected, 80.0%, *P*=.017). By contrast, the collection of meconium, which depended upon study mothers, was obtained by 232 of 245 mothers (94.7%), and not influenced by birth hospital.

Study Outcomes

Of the 245 mother–child pairs enrolled in the study, 194 (79.2%) were defined as compliant, having achieved follow-up of 70% (≥71/102) or more of study weeks, and either collection of 70% or more of weekly samples during their period of activity or having a blood collection at 18 or 24 months of age. Compliant mother–child pairs contributed 386.8 of the 433.6 child-years (89.2% of the total follow-up time in the study; Table 2). Mothers who were compliant in the study were significantly (*P*<.05) more likely than noncompliant mothers to be older, privately insured, college educated, have higher income, and married (Table 1). Nevertheless, the characteristics of the 194 mothers defined as adequately compliant over the course of the study remained generally representative of our study population.

Among the 194 compliant mother–child pairs, blood sample collections ranged from 84.5% to 95.4% of children at each scheduled time (Table 2). Median weekly response to SMS text message surveys to report AGE or ARI in the study child was 95.1% (IQR 76.5%-100.0%) of active weeks (Table 2), though individual response to weekly SMS text message surveys was variable. Median weekly sample collection was 71% or more of study weeks for both stool (71.8%, IQR 29.1%-92.2%) and nasal samples (71.0%, IQR 30.0%-90.5%). None of the compliant mothers withdrew from study and only 4 became inactive, but this inactivity occurred after the child reached 71 weeks of participation.

AGE and ARI incidence rates did not differ between the 245 children enrolled and the 194 children who maintained adequate compliance with the study protocol (Table 3). The incidence of AGE was 2.0 cases per child-year, with a median duration of 3 days. The incidence of ARI was 4.5 cases per child-year, with a median duration of 4 days. The compliant mothers reported a total of 627 AGE episodes and 1277 ARI episodes in their children over the course of follow-up. Of these, 160 (25.5%) AGE episodes were medically attended, while 486 (38.06%) ARI episodes were medically attended (difference in proportion between AGE and ARI episodes, *P*<.001); 3 out of 627 (0.5%) AGE cases were hospitalized; similarly, 7 out of 1277 ARI episodes were hospitalized (0.55%).

Table 3. Maternal report of AGE and ARI in study children.

Measure	All (N=245)	Compliant (N=194)
AGE[a] cases reported		
Number of cases	671	627
Child-weeks at risk[b]	17,473	16,020
Child-weeks symptomatic[c], n/N (%)	710/18,183 (3.9)	657/16,677 (3.9)
Incidence: cases/100 child-weeks	3.8	3.9
Incidence: cases/child-year	2.0	2.0
Median days ill/case	3	3
Medically attended cases, n/N (%)	172/671 (25.6)	160/627 (25.5)
Hospitalized cases, n/N (%)	3/671 (0.4)	3/627 (0.5)
ARI[d] cases reported		
Number of cases	1349	1277
Child-weeks at risk[b]	16,244	14,836
Child-weeks symptomatic[c], n/N (%)	1939/18,183 (10.7)	1842/16,677 (11.0)
Incidence: cases/100 child-weeks	8.3	8.6
Incidence: cases/child-year	4.3	4.5
Median days ill/case	4	4
Medically attended cases, n/N (%)	521/1349 (38.6)	486/1277 (38.1)
Hospitalized cases, n/N (%)	8/1349 (0.6)	7/1277 (0.5)

[a]AGE: acute gastroenteritis.

[b]The number of child-weeks at risk is calculated as the number of weeks of follow-up minus the number of weeks symptomatic

[c]Child-weeks symptomatic is calculated as the number of weeks when mothers reported symptoms divided by the total number of weeks that the child was under follow-up.

[d]ARI: acute respiratory infection.

Discussion

The outcomes of the PREVAIL Cohort reported here are the generally high compliance rates that were obtained with our intensive study protocol, which was designed to ensure longitudinal characterization of repeated infections in the first 2 years of life. Of the 245 mother–child pairs enrolled, 194 (79.2%) were considered compliant with the sample collection and follow-up protocol. These mothers provided 384 child-years of follow-up, 13,048 stool samples, 13,546 weekly nasal samples, and 1050 scheduled blood samples from week 2 to year 2 of life. Median weekly completion of SMS text message surveys regarding the child's AGE or ARI symptoms was 95.1% (IQR 76.5%-100%), though individual response varied. While mothers who were noncompliant differed in some measures of socioeconomic status, compliant mothers remained generally representative of the study population. Furthermore, we found an incidence of 2.0 AGE cases per child-year, and 4.5 ARI cases per child-year among study children over the first 2 years of life, as reported by mothers. Of these, 1 of 4 AGE cases and nearly 2 of 5 ARI cases were medically attended. Furthermore, 0.5% of AGE (3/627) cases and 0.55% of ARI (7/1277) cases were hospitalized. These findings indicate that our cohort methodology works in the US context, and that AGE and ARI in early childhood represent a significant public health problem.

The PREVAIL Cohort design is based upon the concept that infectious disease outcomes are the consequences of a cascade of diverse immunologic attributes and exposures, formed while in utero and shaped throughout life. Furthermore, the cohort is founded upon the premise that fully understanding the development of symptomatic infections also requires information on periods of asymptomatic infection. If public health interventions are devoted to prolonging this healthy period, then both symptomatic and asymptomatic longitudinal observations are indispensable.

We designed this study to untangle the web of influences that create disease and immunity among an intensively followed cohort of US children from their third trimester in utero to their second birthday. A comprehensive portfolio of clinical, epidemiologic, behavioral, and immunologic factors was studied during periods of good health, predisease, symptomatic and asymptomatic infections, and convalescence. Birth cohort studies are irreplaceable in providing an estimated protective efficacy that could potentially be achieved from well-designed vaccines through observing the pattern of immunity that develops against natural infections. Such cohort studies can also guide vaccine policy toward important target or vulnerable

populations, optimal immunization ages, optimal vaccine dosage, and titer levels needed for long-lasting protection, and to better understand complementary interactions underpinning the creation of specific immunity at young ages.

Our study design was based upon the premise that understanding the true natural history of infection and immunity requires weekly sample and data collection, as exemplified by a Mexican birth cohort study that eminently provided the epidemiological framework required to develop both US-licensed rotavirus vaccines [34]. Through weekly data and stool samples and routine blood tested for rotavirus IgA and IgG from 200 Mexican children from birth to the 2nd birthday, that model cohort showed that first natural rotavirus infections are the most severe, but incremental and heterologous infections confer protection that typically leads to reduced severity—a concept now recognized as the operating principle for how the currently effective live-attenuated rotavirus vaccines work. In our cohort, we expect to describe antirotavirus immunologic responses by US mothers and infants during the postrotavirus vaccine era.

With the goals of enrollment and follow-up achieved, the PREVAIL Cohort successfully illustrates this proof of concept: It is possible to achieve an intensive infection and immunity birth cohort in the current-day US population, which involves keeping participants under weekly follow-up with high levels of compliance. Such efforts require significant infrastructure and technologic innovation to efficiently collect birth samples, weekly stool/nasal swab samples, weekly automated health status surveys, and systematically handle large-scale sample transport, management and analysis conducted by a collaborative network of public health disciplines.

This cohort anticipates applying these same methodological concepts to important norovirus vaccine development questions. Our observations of norovirus infections over time could improve the knowledge of how immunity against heterotypic strains is developed in young children. By comparing the symptoms associated with early norovirus infections with maternal antibody titers and markers of innate, genetic immunity (eg, polymorphism in *fucosyltransferase 2* [*FUT2*], which defines secretor status), this cohort could clarify antecedent contributions influencing infection risk and prolonging the asymptomatic period [6,35-37].

The PREVAIL Cohort aims to study pathogens contributing to serious ARI burden in the United States and worldwide, including RSV and influenza. Maternal and infant RSV vaccines are under investigation as potential preventive strategies, and a need exists to better understand vaccines designed to elicit antibodies to protect against infection in early life. Our data will characterize the infant immune response (neutralizing antibody titer and RSV-specific antibody profile) to primary and secondary RSV infections. We expect to better define the association of maternal RSV neutralizing antibodies (including the titer and RSV-specific antibody profile) with the risk of infant RSV infection, including correlations with transplacentally transferred RSV-specific maternal antibodies and breast milk immunomodulators. For influenza, we expect to longitudinally determine how initial and repeated natural influenza infections or influenza vaccinations (for both mother and offspring) shape immunity to future influenza exposures in the first 2 years of life. Ultimately, this information will be important to facilitate design of durable, broadly protective influenza vaccines.

Comparability of PREVAIL Cohort results to other published cohorts is not direct and should take into consideration wide variations in other cohort methodologies, low- and middle-income country settings, the ages of children studied, the degree of severity included in case definitions, and other factors. Sample collection and testing protocols also differ among cohorts, as described for norovirus cohorts by Cannon and others [38]. A limitation of many infection cohort studies worldwide has been that sample collection is undertaken on a monthly or less frequent basis, which could result in many missed asymptomatic infections. Weekly sample testing was the goal in the PREVAIL Cohort. While weekly sample collection was not perfect, it was achieved for the majority of child-weeks. We anticipate the combination of weekly sample testing and serology will optimize identification of infections, which we consider critical to deepen understanding of immune development.

There are other limitations in this study to consider. The AGE and ARI incidence rates reported here are based solely on maternal report. Medical records are currently being reviewed to obtain data on AGE and ARI events that resulted in health care system use that might not have been reported by the mother; these medical record data are not yet available for inclusion in this paper. Furthermore, laboratory analyses are underway to determine pathogen-specific outcomes and antibody response. The multiple outcomes measured in this cohort will be reported separately.

Lopman and Kang [27] argue that a cohort study of the natural history of infection is needed in the United States to guide maternal, infant, and childhood vaccine strategies, and this is applicable to all 4 of our focal pathogens (norovirus, rotavirus, RSV, and influenza). While incidence and severity may differ across regions and cohorts, many of the factors driving infectious disease burden at the youngest ages remain unknown, undermining our ability to estimate the impact of potential vaccines on disease burden. The National Academy of Science stated, “Without the comprehensive, longitudinal data provided by a [birth cohort study], it will be difficult to identify and make wise investments in policies that will promote health at the individual, community, and societal levels” [39]. The PREVAIL Cohort is expected to provide significant public health value by providing important information regarding the elicitation of immune protections against these childhood diseases, informing the development of new vaccines, improving upon vaccine strategies in this vulnerable infant population, and perhaps understanding the development of immunity for infectious diseases that are antigenically new to the human species.

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AM, MS, and DP designed and directed the study. MM, ED, ES, RB, AH, MB, SG, GL, NT, AC, JV, and UP provided subject matter expertise to study procedures. AC, SC, and AP coordinated the collection of data and samples, and design and oversight of the database. AM and SC conducted data analysis. AM and DP wrote the first draft. All authors reviewed and contributed to the realization of the study and its publication. We gratefully acknowledge the participation of PREVAIL birth cohort families. The authors also wish to thank our researchers at the University of Cincinnati, Cincinnati Children's Hospital, and The Christ Hospital - Cincinnati. We also gratefully acknowledge the hard work of the dedicated PREVAIL staff and Donna Wuest for her assistance with the manuscript. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PREVAIL AGE Survey.
[PDF File (Adobe PDF File), 69 KB - resprot_v10i2e22222_app1.pdf]

Multimedia Appendix 2
PREVAIL ARI Survey.
[PDF File (Adobe PDF File), 65 KB - resprot_v10i2e22222_app2.pdf]

Multimedia Appendix 3
PREVAIL Baseline Questionnaire.
[PDF File (Adobe PDF File), 110 KB - resprot_v10i2e22222_app3.pdf]

Multimedia Appendix 4
PREVAIL Week 2 Questionnaire.
[PDF File (Adobe PDF File), 272 KB - resprot_v10i2e22222_app4.pdf]

Multimedia Appendix 5
PREVAIL Month 24 Questionnaire.
[PDF File (Adobe PDF File), 171 KB - resprot_v10i2e22222_app5.pdf]

Multimedia Appendix 6
PREVAIL Weekly Survey.
[PDF File (Adobe PDF File), 41 KB - resprot_v10i2e22222_app6.pdf]

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Abbreviations

AGE: acute gastroenteritis
ARI: acute respiratory infection
CCHMC: Cincinnati Children's Hospital Medical Center
CDC: Centers for Disease Control and Prevention
CRF: case report form
FUT2: fucosyltransferase 2
PREVAIL Cohort: Study acronym: Pediatric Respiratory and Enteric Virus Acquisition and Immunogenesis Longitudinal Cohort
REDCap: Research Electronic Data Capture (data management system)
RSV: respiratory syncytial virus
TCH: The Christ Hospital
UCMC: University of Cincinnati Medical Center

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Protocol

A Value-Based Comparison of the Management of Ambulatory Respiratory Diseases in Walk-in Clinics, Primary Care Practices, and Emergency Departments: Protocol for a Multicenter Prospective Cohort Study

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Abstract

Background: In Canada, 30%-60% of patients presenting to emergency departments are ambulatory. This category has been labeled as a source of emergency department overuse. Acting on the presumption that primary care practices and walk-in clinics offer equivalent care at a lower cost, governments have invested massively in improving access to these alternative settings in the hope that patients would present there instead when possible, thereby reducing the load on emergency departments. Data in support of this approach remain scarce and equivocal.

Objective: The aim of this study is to compare the value of care received in emergency departments, walk-in clinics, and primary care practices by ambulatory patients with upper respiratory tract infection, sinusitis, otitis media, tonsillitis, pharyngitis, bronchitis, influenza-like illness, pneumonia, acute asthma, or acute exacerbation of chronic obstructive pulmonary disease.

Methods: A multicenter prospective cohort study will be performed in Ontario and Québec. In phase 1, a time-driven activity-based costing method will be applied at each of the 15 study sites. This method uses time as a cost driver to allocate direct costs (eg, medication), consumable expenditures (eg, needles), overhead costs (eg, building maintenance), and physician charges to patient care. Thus, the cost of a care episode will be proportional to the time spent receiving the care. At the end of this phase, a list of care process costs will be generated and used to calculate the cost of each consultation during phase 2, in which a prospective cohort of patients will be monitored to compare the care received in each setting. Patients aged 18 years and older, ambulatory throughout the care episode, and discharged to home with one of the aforementioned targeted diagnoses will be considered. The estimated sample size is 1485 patients. The 3 types of care settings will be compared on the basis of primary outcomes in terms of the proportion of return visits to any site 3 and 7 days after the initial visit and the mean cost of care. The secondary outcomes measured will include scores on patient-reported outcome and experience measures and mean costs borne wholly by patients. We will use multilevel generalized linear models to compare the care settings and an overlap weights approach to adjust for confounding factors related to age, sex, gender, ethnicity, comorbidities, registration with a family physician, socioeconomic status, and severity of illness.

Results: Phase 1 will begin in 2021 and phase 2, in 2023. The results will be available in 2025.

Conclusions: The end point of our program will be for deciders, patients, and care providers to be able to determine the most appropriate care setting for the management of ambulatory emergency respiratory conditions, based on the quality and cost of care associated with each alternative.

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KEYWORDS

emergency department; primary care; walk-in clinic; health economics; quality of care; patient preferences; patient-reported outcomes; outcome assessment, health care

Introduction

The Problem: Emergency Department Overuse and Misuse

Emergency departments (EDs) are specialized and costly resources designed to provide care for patients with urgent or life-threatening conditions [1]. In Canada, low-acuity ambulatory patients, who do not require a gurney or constant observation, represent 30%-60% of all ED visits [2-7]. This situation is increasingly considered as overuse and misuse of ED resources and a threat to the quality of care received by patients whose needs are more urgent [8]. Delays experienced in an overcrowded ED can lead to mortality, morbidity, and reduced quality of life [9-14]. ED overcrowding is widely regarded as a serious but largely avoidable public health risk exacerbated by ambulatory patients [15,16].

An Important Policy Issue

Many Canadian regional health authorities have developed policies so that low-acuity ambulatory emergency patients preferably present to walk-in clinics or primary care practices [17-19]. Over the past decade, numerous innovations have been implemented to improve timely access to primary care, such as extended walk-in clinic hours [17-19] and the advanced access model (timely access to a care provider) for registered patients [20-26]. In Ontario and Québec, governments have invested massively in new models of primary care to improve access to emergency care and thereby decrease ED visits by patients who are treatable in non-ED settings [18,27]. These health policy priorities rely on the assumption that walk-in clinics and primary care facilities offer less costly, more accessible, and more efficient alternatives to the local population [17,28,29] than overcrowded EDs [3,4,7,8,30-34]. As reasonable as this

assumption may appear, data supporting it are scarce and equivocal [35,36].

Determining the Best Care Setting for Ambulatory Emergency Patients: A Knowledge Gap

Few studies have tested the hypothesis that walk-in or primary care clinics offer better care than EDs to ambulatory patients with acute health concerns.

The Costs

A prospective study in Ontario in 2005 [28] concluded that for similar cases, ED costs were 3 to 4 times higher than the costs incurred in a family physician's office or a walk-in clinic. However, compared costs were not adjusted for comorbidities or severity of disease and did not include out-of-pocket expenses (eg, parking) and indirect costs to patients (eg, loss of income). Other studies, mainly from the United States, have reached similar conclusions [17,37-39] but using charges as proxies of health care costs, which has been shown to be an inaccurate costing method [40,41]. Some reports even suggest that walk-in clinics may in fact increase overall health care costs by duplicating care with frequent return visits after an initial visit [42-45].

The Quality of Care

Very few studies have considered quality of care and patient health outcomes in determining the best alternative setting for treating ambulatory emergency patients [8]. A 2017 review (Cochrane) of prospective studies comparing mortality, morbidity, and adherence to practice guidelines in walk-in clinics, primary care practices, and EDs found that none met this criterion [46]. However, three retrospective studies [47-49] and one study evaluating costs and return visits [28] suggested that (1) inappropriate use of antibiotics for self-resolving acute respiratory conditions occurs more frequently following visits to urgent care centers and family medicine offices than to EDs [47-50]; (2) the choice of antibiotics is more concordant with practice guidelines in walk-in clinics than in EDs and family medicine practices [48]; and (3) return visit likelihood within 72 hours is higher after an ED care episode than after any other outpatient clinic visit [28]. However, these fragmented and incomplete data come mostly from the United States. A comprehensive research program comparing acute care received in EDs, walk-in clinics, and primary care practices in Canada is long overdue.

The Patient Perspective

Deciders often prioritize certain care settings based on potential cost savings, *auctioning off* care paths to the lowest bidder from the government's perspective [51]. However, studies have shown that from a patient's perspective, the choice to seek care in either a primary care practice, a walk-in clinic, or an ED is determined not only by ease of primary care access but also by factors such as convenience and perceived severity of illness and previous health care experiences [35,52-56]. What patients value the most differs considerably from what other stakeholders tend to value [57]. The patient's perspective must be considered to determine the best ambulatory emergency care option. To our knowledge, no studies have compared these alternative settings from a patient's perspective.

Conceptual Framework: A Value-Based Approach

To compare the different care setting possibilities for ambulatory emergency patients, we propose value-based assessment, an approach first described by Michael Porter in 2006 [58,59] and widely adopted since by researchers and health quality organizations around the world [60-66]. Value is defined in terms of health outcomes achieved per dollar spent [58,67,68]. It promotes the best care at the lowest cost, without isolating clinical issues from economic issues. Two essential components are needed: (1) a feasible and reliable costing method and (2) valid, reliable, and readily available outcome indicators, consistent with the priorities of patients, deciders, and care providers. This comprehensive paradigm aligns patients, deciders, and clinicians behind shared goals, based on patient preferences and scientific evidence.

Previous Preliminary Work

Our team has conducted a pilot study in which an ED and a primary care clinic offering walk-in services for frequent ambulatory acute conditions were compared in terms of costs of care and compliance with practice guidelines [69,70]. We reviewed the medical records of 918 adults with one of 13 targeted ambulatory acute conditions during the 2015 and 2016 fiscal year and applied a time-driven activity-based costing method. Time-driven activity-based costing has been found to provide more precise accounting than methods based on diagnosis-related groups and is simpler than conventional activity-based costing [41,71-73]. It assumes that the cost of a care episode is proportional to the time that the patient spends receiving the care. Costs of care are determined by allocating all direct costs (eg, staff salaries) and overhead (eg, building maintenance) to activities related to patient care, including physician charges [74,75]. This costing method has been used successfully in many care settings [65,71,76,77], and we adapted it for use in EDs and primary care practices [41,69,78,79]. The adjusted mean costs in each clinical setting for upper respiratory tract infection (URTI), a condition for which antibiotics and x-rays are generally not recommended [80,81] were determined and the clinical settings were compared on the basis of the process of care applied (Table 1).

Table 1. Mean cost of care and percentage of use of nonrecommended care applied to upper respiratory tract infection in a primary care practice and an emergency department.

Variable	Primary care practice (n=102)	Emergency department (n=52)	*P* value
Cost of care[a] (US $), (mean 95% CI)	45.4 (38.4-53.4)	59.8 (49.4-72.3)	<.001
Process of care, % (95% CI)			
Chest x-ray	13.7 (7.7-22.0)	26.9 (15.6-41.0)	.05
Antibiotics	44.1 (34.3-54.3)	5.8 (1.2-16.0)	<.001

[a]Mean value adjusted for age, sex, vital signs, comorbidities, and number of regular medications for upper respiratory tract infection.

On the basis of this preliminary study, we conclude that (1) time-driven activity-based costing is feasible in ED and primary care settings without requiring advanced information technologies or rigorously coded electronic medical records, 2 major barriers to conducting research in outpatient clinics, and (2) significant variations in costs and quality of care may exist between EDs and clinics, suggesting that a multicenter cohort study is warranted. However, this retrospective study highlighted major issues that only a prospective design can resolve: comorbidities (crucial to risk adjustment), disposition plans (crucial to assessing quality of care), and discharge diagnosis are not readily extractable from databases in the outpatient setting and are often missing or incomplete in medical notes. By manually reviewing thousands of visits logged in electronic records, our research assistants identified eligible cases one chart at a time. These major hurdles apply to outpatient clinics in all Canadian provinces. A retrospective design for a multicenter cross-jurisdictional study would have major methodological flaws because of the unlikeliness of obtaining comparable information across settings. More importantly, a retrospective study on administrative databases would not allow us to assess patients' perspectives. Finally, a randomized controlled trial is not feasible for the population and settings under study because randomization would have to occur before any contact with the health system to assign patients to their treatment group. For these reasons, we believe that a prospective cohort study is the most appropriate design for identifying the best care setting for ambulatory emergency patients.

Objectives

Our goal is to compare the health outcomes and costs of care received in EDs, walk-in clinics, and primary care practices by ambulatory patients presenting with acute respiratory conditions, namely, URTI, sinusitis, otitis media, pharyngitis, tonsillitis, bronchitis, influenza-like illness, pneumonia, acute asthma, or acute exacerbation of chronic obstructive pulmonary disease (COPD). We selected these conditions because many performance metrics have been validated previously for assessing the quality of care provided [82,83]. Highly prevalent in ambulatory emergency care before the COVID-19 pandemic [16,50], acute respiratory conditions are now putting even greater strain on already overstretched health care systems. In addition, the pandemic has shifted primary care services significantly toward telemedicine (ie, remote consultation by phone or videoconferencing) [84]. Determining where these patients can get the most effective care is a crucial issue. Our 3 specific objectives are to (1) estimate the costs of care processes administered by care providers in EDs, walk-in clinics, and primary care practices for acute respiratory conditions from the public payer's perspective; (2) estimate and compare the cost of care episodes in EDs, walk-in clinics, and primary care practices for acute respiratory conditions from the public payer's and patient's perspectives; and (3) compare patient health outcomes and quality of care in these care settings when treating acute ambulatory respiratory conditions from the public payer's and patient's perspectives. To achieve these objectives, we propose a 4-year (from April 1, 2021, to March 31, 2025) research plan in 2 phases: a time-driven activity-based costing method study (objective 1) and a prospective cohort study (objectives 2 and 3).

Methods

Phase 1: A Time-Driven Activity-Based Costing Method Study

Setting

A time-driven activity-based costing study will first be performed for fiscal year April 1, 2021, to March 31, 2022. We shall estimate the cost of care processes administered by care providers (Objective 1) in 3 different models of ambulatory emergency care in Québec and Ontario: (1) discontinuous care in the ED (by physicians unfamiliar with the patients); (2) discontinuous care in a walk-in clinic (by physicians unfamiliar with the patients); and (3) continuous care in primary care clinic (patients attached to a primary care practice, seen by their family physician or a colleague on a same-day appointment for urgent needs).

We have confirmed the participation of 14 of the 15 planned patient recruitment sites (ED 5/5, walk-in 5/5, primary care 4/5; Multimedia Appendix 1). They have been selected in different types of urban areas, including small (Joliette), medium (Kingston), large (Québec City, Ottawa), and metropolitan (Montreal) cities. In each participating region, an ED will be paired with a nearby walk-in clinic and primary care practice. We are currently securing our final additional clinic in Ottawa with the help of BeACCoN (Better Access and Care for Complex Needs), a provincial primary care research network.

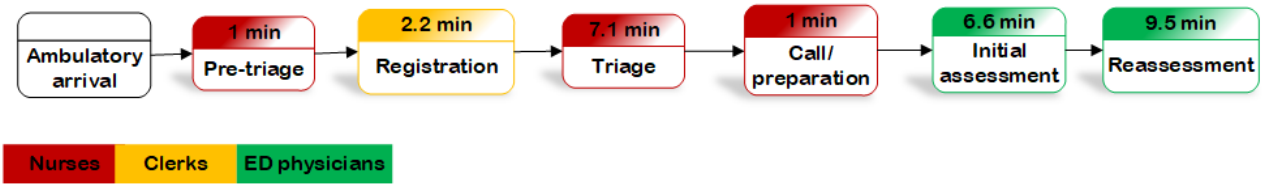
Design

The time-driven activity-based costing method [72,85] will enable us to derive for each setting the cost of care processes (eg, triage) and traceable supplies (eg, medication) potentially provided to patients with acute respiratory conditions, which includes telemedicine. This costing method requires only 2

parameters, namely, the unit cost of supplying capacity and the duration of processes, and comprises the following steps:

1. Process (eg, salbutamol in acute asthma) and resource (eg, respiratory therapist) mapping through discussion with local teams for each respiratory condition (Figure 1)
2. Validation of process maps and durations by on-field research assistants prospectively observing patients and measuring process duration using time-motion software (UMT Plus [Laubrass])
3. Calculation, with local administrative teams, of total annual overhead costs (eg, building maintenance) related to the care of ambulatory patients with acute conditions (Multimedia Appendix 2 for allocation rules)
4. Estimation of cost per time unit ($/minute) for the following cost elements obtained by dividing yearly expenses for a cost element by the total yearly number of minutes worked by professionals to care for patients in this facility (Multimedia Appendix 3): (1) human resources (eg, nurses, physicians) or equipment (eg, x-ray machine), (2) consumable supplies (eg, gloves, needles, paper), and (3) overhead costs
5. Estimation of the cost of traceable supplies (eg, laboratory testing)
6. Calculation of the average cost of each health care process (Multimedia Appendicies 3 and 4)

Figure 1. Process mapping for upper respiratory tract infections in the emergency department (truncated). Each box represents a process with its duration. Colors identify human resources (red=nurses; yellow=clerks; green=physicians). ED: emergency department.



The cost of a care process is proportional to the mean duration measured on field. For example, the cost of triage is estimated by adding up the expenses associated with the triage nurse, consumables, and overhead. These elements will be estimated by multiplying the mean triage duration by their unit costs as follows:

Cost of triage = mean triage duration × (unit cost of nurse + unit cost of consumables+ unit cost of overhead) = 7.1 min × (US $0.78/min + US $0.07/min + US $0.17/min) = US $7.24 (Can $1 [US $0.76])

The cost of telemedicine will be estimated following the same steps, from resource mapping and time measurement through allocation of overhead and consumables, all the way to average cost calculation.

Where applicable, the following adjustments will be made so that the estimated costs reflect the public payer's perspective: (1) expenses paid by physicians or owners of a participating clinic will be subtracted from the yearly expenses related to the appropriate cost element (eg, salaries, overhead); (2) similarly, government funding received by a clinic apart from physician remuneration will be added.

Financial Data Sources

The accounting department at each participating site will provide all financial data, except for physician charges. To calculate the unit cost for physicians, the total amount charged by all physicians per site per year will be obtained from local private billing agencies. This sum will be divided by the number of minutes spent delivering patient care, which will be obtained from physician schedules.

Intermediate Outputs of Phase 1

In addition to institution-specific costs, upon completing phase 1, we will create a list of standardized costs of care for each process and associated traceable supplies based on the average costs estimated in the 15 institutions (ED, walk-in, primary care, both provinces). Use of standardized costs will eliminate price effects because of differential costings between sites and provinces, thereby facilitating comparisons between the 3 clinical settings. In phase 2, the cost of a care episode will be calculated per individual by summing the standardized costs of care processes, supplies, and drugs received by each patient during their visit. Fixed and variable costs will be broken down to estimate and compare the care settings in terms of the marginal cost of each new patient assessed [86].

Phase 2: A Prospective Cohort for Comparing the 3 Health Care Settings

Design and Setting

A multicenter prospective cohort study will be conducted in the institutions included in phase 1 to compare the value of care in EDs, walk-in clinics, and primary care practices (Objectives 2 and 3).

Selection of Participants

We shall include patients (1) aged 18 years and older; (2) seen in person or via telemedicine in an ED, a walk-in clinic, or the primary care practice where they are registered; (3) ambulatory during the entire visit or consultation; and (4) discharged home with a diagnosis of URTI, sinusitis, otitis media, pharyngitis, tonsillitis, bronchitis, influenza-like illness, pneumonia, acute asthma, or acute exacerbation of COPD. We shall exclude patients (1) transported by ambulance, (2) not covered by the provincial health insurance plan, (3) having consulted for a similar problem in the previous 30 days as patients with refractory diseases representing a population with different care needs, (4) living in a long-term health care facility or incarcerated, or (5) receiving palliative care.

Recruitment Procedures on the Initial Visit

A research nurse in collaboration with local clerks at each site will screen eligible patients after on-site registration or

web-based scheduling, but before assessment by a physician, based on presenting complaints suggestive of acute respiratory conditions. After assessment and once a targeted diagnosis is confirmed, the same research nurse will prospectively (1) obtain consent from patients; (2) ensure that the discharge diagnosis, comorbidities, and disposition plans are fully documented; and (3) administer a questionnaire to assess patient experience of care and motivation for choosing one care setting over the other. Motivation will be classified into the 6 domains of the Conceptual Model of Emergency Department Use [35]. Participants will be asked to specify whether their choice of care setting was based on accessibility, convenience, their perception of the severity of illness, their beliefs and knowledge regarding these care settings, referral and advice from a care professional or an acquaintance, or costs. They will also be requested to rate their perception of illness severity. For on-site participants only, the research nurse will also (1) assess the severity using the Pandemic Medical Early Warning Score (PMEWS), a validated severity score allowing points for age, vital signs, comorbidity, social situation, and functional status [87], and (2) perform spirometry (measured parameter: forced expiratory volume in the first second [FEV_1]) on patients with acute asthma. A random sampling recruitment schedule will be planned to ensure a proportional representation of the hours of operation for each recruiting site. Participating EDs will recruit on a schedule similar to their paired participating clinics to include participants who could have consulted in an alternative setting and exclude night patients who differ significantly from patients seeking care during the day [88]. Recruitment will occur over a full year to encompass seasonal variability in the incidence of respiratory diseases.

Data Collection and Follow-Up Phone Calls

Research assistants at each site will complete data collection from local medical records. For on-site participants and, where appropriate, for those assessed by telemedicine, they will compile the following information: age, sex, gender, ethnicity, postal code, distance from facility to home, referral by the provincial telephone consultation service (811, Telehealth), enrollment with a family physician, presenting complaints, comorbidities, regular medications, date and time of arrival and discharge, vital signs upon arrival, investigations and interventions during care episode, discharge diagnosis, and prescriptions upon discharge. A follow-up phone call will be made to all participants 10 days after the initial visit to collect data initially unavailable in medical records and to evaluate primary and secondary outcome metrics. Patient-reported outcome and cost measures will be completed by the participants at this moment, either on the phone with the research assistant or independently using a secured online survey link, depending on the participant's preference. Text messaging and email reminders will be sent to improve participant retention [89]. We shall obtain information on health outcomes (eg, mortality) and physician charges via provincial databases. The charges billed by any physician 7 days after the initial visit will be used to estimate the costs of care for subsequent return visits and hospital admissions.

Outcome Measures

A value-based comparative assessment requires the simultaneous evaluation of health outcomes and costs. Our outcome measures were chosen from a guideline on the assessment of ED performance [90] and recent literature on patient experience assessment (Table 2) [91-95]. The initial visit, from arrival at a participating site to discharge, represents the unit of analysis for all outcome measures; however, the health system or patient costs incurred during the following week will be estimated and added to the cost of the initial visit. For participants assessed in person, the outcome will be scored per care setting and further stratified per discharge diagnosis and by province, using institution-specific costs for interprovincial cost comparisons. We will analyze the same outcome measures separately in the case of patients evaluated by telemedicine, as missing data (eg, vital signs) will prevent us from adjusting for the severity of their illness.

Table 2. Main study outcomes.

Outcome	Definition	Source
Primary		
Incidence of return visit (O[a])	Proportion of patients returning to any ED[b] or outpatient clinic at 72 hours and 7 days after the initial visit [83,96-99]. An adjudication committee will review records of return visits to classify them as planned or unplanned and avoidable or unavoidable.	Follow-up call at 10 days
Mean cost of care−the Ministry of Health perspective (C[c])	The cost per care episode calculated by summing the costs of all care processes delivered to a patient during the initial visit plus the costs of return visits and admissions at 72 hours and 7 days.	Electronic medical records and provincial billing databases
Secondary		
Median PROM-ED[d] patients scores (O)	Developed and validated by team member SV, the PROM-ED questionnaire provides a measurement of patient-reported outcome expressed as scores for symptom relief, understanding of health concern, reassurance, and having a plan for care [91,94].	Follow-up call at 10 days
Median scores on a PREM[e] (O)	We adapted and are validating a tool from patient experience surveys used in EDs and primary care clinics in Ontario [100-102]. This tool evaluates the patient's view of care delivery and measures various dimensions of patient experience relevant to all care alternatives, such as attitude of providers.	At the end of the initial visit
Mean CoPaQ[f] (C)	A questionnaire measuring patients' and caregivers' out-of-pocket expenses (eg, travel) and indirect costs (eg, loss of income) will be proposed to participants. This questionnaire was developed and validated by members of our team (ML, JG, SB) and further adapted for use in this study.	Follow-up call at 10 days
Incidence of admission, intensive care unit, or mortality (O)	Proportion of patients who were admitted to the hospital or the intensive care unit or died because of one of the targeted respiratory conditions within 30 days [83,103] after the initial visit.	Provincial databases: Med-Echo, ICES, death registries
Wait times	Median and mean length of stay and time spent waiting to see a physician.	Electronic medical records

[a]O: health outcome.

[b]ED: emergency department.

[c]C: health cost.

[d]PROM-ED: patient-reported outcome measure for ED.

[e]PREM: patient-reported experience measure.

[f]CoPaQ: cost-for-patient questionnaire.

To evaluate the quality of care in each group under study, compliance with practice guidelines (eg, corticosteroid prescription for asthma) for the treatment of respiratory diseases [104-109] will be compared (the full list of outcome measures is given in Multimedia Appendix 5 [83,91,94,96-103]). Return visits will be reported by the participants during the 10-day follow-up phone call. The Canadian Institutes of Health Research bridge grant obtained in April 2020 allowed our team to adapt questionnaires assessing patient perspective (Patient-Reported Experience Measure [PREM], patient-reported outcome measure for ED patients [PROM-ED], and cost-for-patient questionnaire [CoPaQ]) for use in any setting under evaluation. Their use for patients seen in person or by telemedicine in ambulatory patients with acute respiratory conditions will be validated further in the fall of 2020.

Sample Size

As our main analyses focus on patients assessed in person, our sample size calculation is based solely on their numbers. We estimate that the rate of return visit for ambulatory emergency conditions varies from 1% to 13% depending on the care setting [17,110,111]. To account for the potential similarity in outcomes among individuals in each of the 15 clusters, we assumed a realistic intracluster correlation of =0.02 based on previous studies and applied a correction to inflate our sample size calculation [112,113]. Using data from Campbell et al [28], at least 1485 patients (approximately 99 per cluster) will be needed to reveal a 5% difference in the proportion of return visits within 72 hours (eg, 5% vs 10%), assuming a 20% loss to follow-up and at least 30 participants per condition, based on multivariate logistic regression power analysis, type I error (α) at .05, and power at 80% ($1-\beta$). Assuming 240 recruitment days over a year at each site and the recruitment of at least 1 to 2 patients per day, our final cohort should include over 4000 patients and reach the minimal sample size in both participating provinces, which will allow for more robust comparisons and analyses.

Statistical Analysis

All main analyses will be conducted primarily on participants assessed in person in any of the care settings. Participants assessed by telemedicine will be analyzed and compared separately between sites where it is implemented. The value delivered at each participating site and on average in each care setting type will be illustrated with an operational effectiveness graphic [114]. Adjusted costs of care for acute ambulatory respiratory conditions will be plotted on the x-axis and adjusted return visits within 72 hours on the y-axis. Points closest to 0 on both axes represent the highest value of care (Multimedia

Appendix 6). Indeed, the lower the return visit proportion and cost of care, the higher the value of care. Similar graphics will be used for patient-centered outcome measures. To compare EDs, walk-in clinics, and primary care physician practices, multilevel generalized linear models will be used with probability distributions adapted to the outcome under evaluation. To adjust for confounding (differences in case mix between care settings), an overlap weights approach [115,116] will be used, wherein each individual receives a weight factor that is proportional to the inverse of the probability of choosing a particular setting. Subjects that differ fundamentally between settings are attributed a weight of 0 and are thus excluded. This approach is of the greatest interest when groups are initially very different [116]. Intuitively, overlap weights create a pseudopopulation for which treatment is independent of measured confounders, thus mimicking a randomized trial of those confounders. Overlap weights have been shown to be more robust than conventional inverse probability weighting and matching based on propensity scores [115]. The weights will be estimated using a multinomial logistic regression model in which the dependent variable is the chosen care setting and independent variables are potential confounders or risk factors [117] for the outcomes identified in the literature: age [118,119], sex and gender [118,120], ethnicity [118,121-123], registration with a family physician [20,124], comorbidities (the Charlson index; number of regular medications) [118,125,126], asthma, FEV_1 among patients with asthma, the Canadian deprivation index [127-129], patient perception of illness severity [130], and vital signs [131-135] as proxies for severity. The same independent variables will be used to adjust for differences in case mix between settings in the telemedicine cohort, excluding vital signs and FEV_1. Multiple imputation will be considered as a possible means to adjust for these variables in this cohort. Overlap weights will be calculated using the values predicted by this model. We shall verify that the care setting groups are comparable according to the measured confounders after weighting by computing standardized mean differences. Differences below 10% will be considered to indicate good balance [117]. If residual imbalances are present, the weighting model will be revised. Once an appropriate balance is achieved, separate models for each outcome will be fitted to the weighted data, for which the care setting will be the only independent variable. The robustness of results with respect to unmeasured confounding will be assessed using the E-value [136,137]. Clustering by setting (eg, province, practice unit) will be taken into account using multilevel modeling (random intercept on province and practice unit). Reported cost estimates will be calculated with item-specific standardized costs (eg, Québec and Ontario average nurse unit cost). Patients referred to the ED from a participating outpatient facility but discharged home after ED assessment will be analyzed in the care setting group where they first presented, and the ED referral will be considered as a return visit. The costs of any return visits and admissions up to 7 days after the initial visit will be estimated separately and attributed to the care setting where the initial visit took place. Results of the 3 questionnaires from the patient perspective will be reported as proportions (PREM), mean costs (CoPaQ), and median scores (PROM-ED) and adjusted using the overlap weights approach. As patients seek care for symptoms, subanalysis based on presenting complaints instead of discharge diagnosis will be conducted to provide meaningful patient-oriented results. Other subanalyses will evaluate which patient profile (eg, gender [120], motivation for choosing a facility), and institutional characteristics (eg, access to x-ray) predict high quality and low costs, keeping in mind that our value assessment might not yield similar results for all subgroups or even within a group of patients with the same diagnosis. Statistical differences will be assessed with a significance threshold set at .05.

Sensitivity Analyses

To assess potential uncontrolled confounding of the results, sensitivity analyses will be conducted by excluding separately and concurrently the participants most likely to influence the effects of the 3 types of care settings: (1) ≥65 years; (2) with ≥1 comorbidity; (3) with either asthma or COPD; (4) with ≥1 regular medication; (5) with any abnormal vital signs; (6) in the lowest and highest quartile of the deprivation index; and (7) smokers. The analyses will be repeated using PMEWS instead of vital signs as a marker of illness severity. To control for a potential Hawthorne effect, the analyses will be repeated, with the first 3 months of recruitment excluded to focus on the data collected after the providers have become used to being observed.

Results

Study Preparation

From our pilot studies reported earlier until now, our team has made significant progress to reach its goal of identifying the care pathways providing the highest value to ambulatory emergency patients. We have assembled a very strong research team composed of patients, clinicians, administrators, and researchers. Together, we have created this paper. Two patient partners met with us regularly and provided helpful comments to make our research plan more patient centered. We have secured 14 of 15 planned participating sites. We have adapted the 3 patient-centered tools (PREM, PROM-ED, and CoPaQ) and are currently validating their use on ambulatory emergency patients whether they receive care in an ED, a walk-in clinic, or a primary care practice.

Protocol Endorsement

Our protocol has been endorsed by the Network of Canadian Emergency Researchers (NCER). The broad support for our research initiative from leading Canadian organizations in emergency (NCER, Canadian Association of Emergency Physicians) and primary care (Réseau-1, Réseau de recherche axée sur les pratiques de première ligne, BeACCoN Ontario, Réseau sur les Innovations en soins de santé de première ligne et intégrés, Strategy for Patient-Oriented Research Unit), from the Ministries of Health of Ontario and Québec, and from organizations dedicated to improving health care throughout Canada (PULSAR, Canadian Institute for Health Information, Institut national d'excellence en santé et services sociaux, ICES) demonstrates the importance of the issue being addressed.

Study Timeline

Phase 1 will begin in 2021 and will allow us to compare the cost of care from the public payer perspective in 3 different settings and 2 Canadian provinces. We expect that the results from this phase will be available in 2023. Phase 2 will begin in 2023 and will evaluate the value of the care in each setting under study. The final results will be published in 2025 and 2026. Our 4-year program covering the period of April 1, 2021, to March 31, 2025, is presented in a Gantt diagram available in Multimedia Appendix 7.

Discussion

Overview

Our unique multidimensional approach to examining the quality and cost of care using both patient and system perspectives will provide knowledge that will be helpful in determining whether EDs, walk-in clinics, or primary care practices offer the best value to patients with acute ambulatory respiratory conditions. We expect our study to yield tangible benefits for all stakeholders.

1. For guiding policy and decisions: Despite weak evidence, Canadian provinces have invested massively in alternative care pathways to get ambulatory patients with urgent care needs to rely less on hospital EDs. Data generated by the proposed study will have an immediate impact by providing hard evidence in support of health care planning decisions intended to improve the service quality/cost ratio and hence outcomes in the largest patient category.
2. For patients: Current policies are designed for statistically average ambulatory emergency patients without considering patient perspectives and the widely variable severity of each diagnosed illness. As the needs and preferences of patients with pharyngitis likely differ from those with exacerbated COPD, our stratified results per condition will enable policy makers to structure urgent care systems to provide better-adapted higher value services to each specific category of patients. Our comprehensive research initiative will bring patient preferences and perspectives into policy making.
3. For clinicians: Our study will be a powerful driver for quality improvement in all care settings involved. Care quality can vary considerably, and we hope to generate unique opportunities for valid and meaningful comparisons and for quality improvement initiatives throughout the country.

Challenges and Mitigation Strategies

First, as patients choose their facility, those presenting at the 3 types of setting will likely represent different populations. However, we believe that the potential confounding bias due to self-selection of the care setting can be overcome using the overlap weights approach. Extensive testing of the robustness of our findings by sensitivity analyses should allow us to avoid reaching false conclusions under the influence of uncontrolled confounding. Second, the Québec and Ontario health systems might differ enough to yield results that will not be easy to generalize. When applicable, the sources of heterogeneity will be investigated. However, Canadian provincial health care systems have fundamental similarities that reduce the risk of poor generalizability. All are based on universal coverage; all suffer from a lack of integration between primary and urgent care resources [138,139]; institutions follow the recommendations of the same accreditation organizations; and care providers are trained according to the same standards and guidelines. Third, because of the pandemic, many outpatient clinics have ceased their activities or shifted to telemedicine. Our research plan already includes participants evaluated by telemedicine and will adapt easily to any increase in this practice. If the pandemic is still ongoing in November 2021 when phase 1 is launched, we will be able to collect financial data from participating institutions, which can be done remotely. Time measurement of care processes can be postponed until phase 2 in 2023, during which the recruitment of participants is planned. Finally, if the pandemic is still a factor in 2023, we will select clinics that continue to assess patients with acute respiratory disorders.

Conclusions

Ambulatory emergency patients account for 30% to 60% of all ED visits in Canada. This burden on emergency care is now exacerbated by the COVID-19 pandemic. This category of patients is thought to be amenable to using walk-in clinics or primary care practices and is the focus of redirection strategies meant to decrease ED overuse. However, current knowledge is inadequate for reaching any firm conclusions about which care settings are best suited for this purpose. The aim of this study is to compare the value of the care that these patients receive in EDs, walk-in clinics, and primary care practices, thereby providing arm administrators and care providers with new and robust knowledge that will enable them to determine the best care setting for the management of respiratory ambulatory emergency conditions. We all agree that the system can only benefit from patients receiving timely care in the proper setting from the most suitable provider.

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Authors' Contributions

SB is the grant holder and nominated principal investigator of the project. MB and JG are the coprincipal investigators. All authors contributed ideas and read and approved the final manuscript.

Conflicts of Interest

Dr. Patrick M. Archambault has completed research contracts with Thales Digital Solutions to develop medical decision support systems. Dr. Alexandre Messier is the inventor of a redirection solution via a web application and works as a medical consultant for Logibec, the company responsible for its marketing and distribution.

Multimedia Appendix 1
Participating sites per province and care setting.
[PDF File (Adobe PDF File), 289 KB - resprot_v10i2e25619_app1.pdf]

Multimedia Appendix 2
Summary of overhead expenses.
[PDF File (Adobe PDF File), 306 KB - resprot_v10i2e25619_app2.pdf]

Multimedia Appendix 3
Cost per time unit (Can $/min) of cost elements and estimated cost (Can $) of important care processes.
[PDF File (Adobe PDF File), 194 KB - resprot_v10i2e25619_app3.pdf]

Multimedia Appendix 4
Steps of the time-driven activity-based costing method.
[PDF File (Adobe PDF File), 342 KB - resprot_v10i2e25619_app4.pdf]

Multimedia Appendix 5
Complete list of study outcomes.
[PDF File (Adobe PDF File), 143 KB - resprot_v10i2e25619_app5.pdf]

Multimedia Appendix 6
Example of an operational effectiveness graphic with hypothetical numbers.
[PDF File (Adobe PDF File), 282 KB - resprot_v10i2e25619_app6.pdf]

Multimedia Appendix 7
Gantt diagram—value project.
[PDF File (Adobe PDF File), 211 KB - resprot_v10i2e25619_app7.pdf]

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Abbreviations

BeACCoN: Better Access and Care for Complex Needs
CoPaQ: cost-for-patient questionnaire
COPD: chronic obstructive pulmonary disease
ED: emergency department
FEV1: forced expiratory volume in the first second
NCER: Network of Canadian Emergency Researchers
PMEWS: Pandemic Medical Early Warning Score
PREM: patient-reported experience measures
PROM-ED: patient-reported outcome measure for emergency department patients
URTI: upper respiratory tract infection

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Protocol

Disparities in Care Outcomes in Atlanta Between Black and White Men Who Have Sex With Men Living With HIV: Protocol for a Prospective Cohort Study (Engage[men]t)

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Abstract

Background: The US HIV epidemic is driven by infections in men who have sex with men and characterized by profound disparities in HIV prevalence and outcomes for Black Americans. Black men who have sex with men living with HIV are reported to have worse care outcomes than other men who have sex with men, but the reasons for these health inequities are not clear. We planned a prospective observational cohort study to help understand the reasons for worse HIV care outcomes for Black versus White men who have sex with men in Atlanta.

Objective: The aim of this study is to identify individual, dyadic, network, neighborhood, and structural factors that explain disparities in HIV viral suppression between Black and White men who have sex with men living with HIV in Atlanta.

Methods: Black and White men who have sex with men living with HIV were enrolled in a prospective cohort study with in-person visits and viral suppression assessments at baseline, 12 months, and 24 months; additional surveys of care and risk behaviors at 3, 6, and 18 months; analysis of care received outside the study through public health reporting; and qualitative interviews for participants who experienced sentinel health events (eg, loss of viral suppression) during the study. The study is based on the Bronfenbrenner socioecological theoretical model.

Results: Men who have sex with men (n=400) were enrolled between June 2016 and June 2017 in Atlanta. Follow-up was completed in June 2019; final study retention was 80% at 24 months.

Conclusions: Health disparities for Black men who have sex with men are hypothesized to be driven by structural racism and barriers to care. Observational studies are important to document and quantify the specific factors within the socioecological framework that account for disparities in viral suppression. In the meantime, it is also critical to push for steps to improve access to care, including Medicaid expansion in Southern states, such as Georgia, which have not yet moved to expand Medicaid.

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KEYWORDS

HIV; men who have sex with men; health disparities; viral suppression

Introduction

For men who have sex with men in the United States, each step of the HIV care continuum [1] is marked by racial disparities—those between non-Hispanic Black men who have sex with men and non-Hispanic White men who have sex with men [2]. Disparities for Black men who have sex with men manifest from systemic and structural racism, among many other health and social disparities [3]. Black men who have sex with men living with HIV have the least favorable care and treatment outcomes of all men who have sex with men [4]. Recent national HIV care continuum estimates reflect that among all US men who have sex with men, Black men who have sex with men as a group have the worst clinical outcomes, measured in terms of linkage to care (both within 1 and 3 months of diagnosis), retention in care, and viral suppression [4].

Despite increases in the number of Black men who have sex with men taking antiretroviral therapy and developing viral suppression, they are still less likely than White men who have sex with men to be prescribed and adhere to antiretroviral therapy and sustain viral suppression [5-7]. The US Centers for Disease Control and Prevention estimates that 41% of Black men who have sex with men compared to 59% of White men who have sex with men sustained viral suppression in 2014 [8]. A 2015 study [7] of selected infectious disease practices documented lower levels of viral suppression in Black non-Hispanic men who have sex with men (72%) than in White non-Hispanic men who have sex with men (91%). Surveillance estimates after 2014 have not been published for Black men who have sex with men specifically, although 2018 estimates of viral suppression among people in care for HIV in the US were 56% among Black people and 69% among White non-Hispanic people [9]. Black men who have sex with men were also estimated to be more likely to experience longer periods with viral loads >1500 HIV RNA copies/mL, an indicator of increased risk of transmission [8].

The southern US census region has the highest concentration of people living with HIV among men who have sex with men in the country [10], and Georgia is the historically most impacted state in both absolute number and prevalence rate of men who have sex with men living with diagnosed HIV [11]. Racial disparities in HIV between Black men who have sex with men and White men who have sex with men in the southern US are comparable to those seen at the national level [12]. Data collected from Black and White men who have sex with men in Atlanta, Georgia, showed an HIV prevalence of 43% among Black men who have sex with men compared to 13% among White men who have sex with men [12]. There were also racial disparities in CD4 count and STI prevalence as well as in rates of poverty, unemployment, and median income [12].

The National HIV/AIDS Strategy goals for 2016 to 2020 prioritize reducing racial disparities in HIV care and treatment [13], and the Ending the HIV Epidemic Plan for America recognizes the critical role of viral suppression in reducing HIV morbidity and in preventing HIV transmission [14]. Gaining a better understanding of the factors underlying racial disparities in HIV care and prevention, and addressing them through interventions, is critical for actualizing improvements both locally and nationally. The Ending the HIV Epidemic plan does not explicitly address health inequities by race but identifies a number of focus areas in the southern United States, including Atlanta, as priority areas, and sets ambitious national goals for reducing new HIV infections in the United States by 2025 [14]. Achieving these goals will not be possible without reducing transmissions among men who have sex with men, who comprise approximately two-thirds of new annual HIV diagnoses [4,15]. The strategies correctly identify treating all people with HIV as early as possible as a key component to achieve reductions in HIV infections [14].

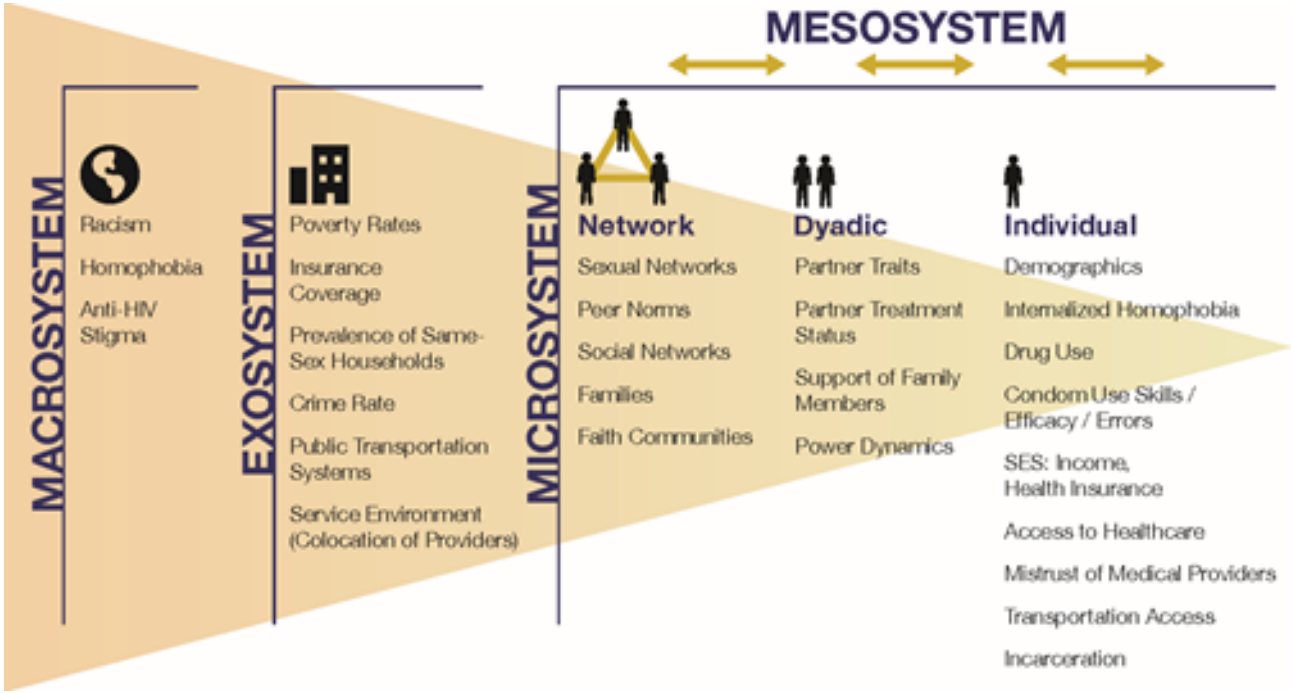
Furthering our understanding of disparities in HIV treatment, care, and prevention between Black and White individuals requires new types of data collection. Although data on the HIV care continuum by race are available through surveillance data sources and in some clinical settings, the traditional means of depicting care continuum data are limited in that they use cross-sectional data to describe a longitudinal process [1]. People living with HIV have to enter clinical care to be included in the research, and once someone is lost to clinic follow-up, they are typically absent from the data set. Lapses in care are not well described. Clinic-based cohorts do not capture people who may change clinics or relocate [16]. Research using cross-sectional data has produced overestimates of care continuum trends [17]. Data on viral suppression, for example, primarily focus on a single viral load measure per patient in care within a 12-month period [17-19]. Research suggests that this tends to overestimate the percentage of patients with HIV and with stable suppressed viral load by as much as 16% [17]. Cross-sectional estimates have also been shown to underestimate the extent of racial disparities along the care continuum.

The limited longitudinal data we have suggest a widening of the racial disparity in retention in care and viral suppression over time. Colasanti et al [18] found that the racial disparity in rates of retention in care among Black and non-Black patients living with HIV did not exist when measured 12 months after initial observation, but the disparity became apparent when measured at a 24-month timepoint and continued to widen over time. They found a similar trend in viral suppression over time [18]. In short, existing data sources do not capture the myriad reasons for retention (or lack of retention) in care. There is a clear need to follow individuals longitudinally as they navigate the care continuum from diagnosis to viral suppression, taking into account both individual and structural factors that affect care and treatment engagement and outcomes.

This protocol describes Engage[men]t, a prospective cohort study of 400 Black and White men who have sex with men living with HIV in Atlanta, Georgia. The study aims to longitudinally examine factors associated with disparities in key HIV care and prevention indicators between Black and

White populations. Key care indicators include lack of or delays in linkage to or retention in care, antiretroviral therapy nonadherence, and detectable viral load. Key prevention indicators include disclosure of HIV status to sex partners and condom use with susceptible sex partners. Advancing our understanding of the modifiable factors associated with these care and prevention indicators has the potential to inform the development of interventions that may improve care and prevention outcomes. We hypothesize a priori that there is no direct causal effect of race on care outcomes; rather, we postulate that the apparent associations between race and care outcomes are explained by indirect effects through intermediate individual- and community-level factors that may manifest because of systemic and structural racism. As such, our study is grounded in the Bronfenbrenner [20] ecological systems model, a framework situating the HIV care continuum disparities in individual, social, and cultural level influences and their relative impact on Black men who have sex with men and White men who have sex with men [21]. We chose to use the ecological systems model to frame this study because of data showing that disparities between HIV prevalence in Black and White populations are influenced by factors at multiple environmental levels, namely dyadic, network, and neighborhood levels (Figure 1) [2,12].

Figure 1. Socioecological model of factors potentially associated with worse HIV care outcomes for Black men who have sex with men living with HIV, adapted from Bronfenbrenner [20] and Baral [21].



Methods

Design

The study design is a prospective, observational cohort of 400 men who have sex with men living with HIV in Atlanta, Georgia with 2 groups: Black men who have sex with men and White men who have sex with men. Recruitment of the cohort took place from June 2016 to July 2017. Participants were followed for 2 years with study assessments at baseline, 3, 6, 12, 18, and 24 months. In our mixed methods design, we sought to use multiple types of data and modes of inquiry to address concepts of triangulation and expansion [22]; other data sources included HIV surveillance data reported to the Georgia Department of Public Health, medical records from participants' clinical encounters, and qualitative data collected through in-depth interviews with a subset of participants. Study inclusion and exclusion criteria are shown in Textbox 1. Black men who have sex with men with Hispanic ethnicity were excluded because we believed that the patterns of care outcomes and associated factors may be different for Black men who have sex with men who are Hispanic compared to Black men who have sex with men who are not Hispanic. The study was approved by the Emory Institutional Review Board (IRB00086663).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Self-report positive HIV status, confirmed by HIV antibody screening at baseline
- Assigned male sex at birth
- Currently identifies as male
- Age ≥16 years
- Self-report single race to be Black or White
- Able to complete survey instruments in English
- Lives in the Atlanta metropolitan statistical area
- Had at least one male sex partner in the 12 months before the baseline interview

Exclusion criteria

- Participant is determined to not be living with HIV per study testing at baseline
- Participant is currently enrolled in another HIV prevention or treatment clinical trial
- Self-report Hispanic ethnicity

Recruitment

Participant recruitment involved use of venue-based, web-based, or virtual and print recruitment methods. All 3 methods linked potential recruits to a web-based survey portal with a short description of the study and the opportunity to consent and complete a brief eligibility survey on a study tablet or personal electronic device. The eligibility surveys were hosted on a secure, Health Information Portability and Accountability Act–compliant server (administered by Survey Gizmo). Men were asked to leave their contact information at the end of the surveys so that study staff could follow up and schedule an enrollment (baseline) visit.

In-person recruitment occurred at gay bars and at community events with a large men who have sex with men or HIV focus such as gay pride. Events were selected for attendance based on venue-space time sampling [23], as previously implemented for other cohort studies of men who have sex with men in Atlanta [12]. At these events, potential recruits read a short description of the study and completed a brief eligibility survey on a tablet. Web-based recruitment used banner advertisements on social media sites, such as Facebook and Instagram, and on sex-seeking sites, such as Grindr and Bareback RT [24]. When possible, ad placement was targeted to male profiles with self-described Black or White race and an interest in other men, as these are among the study eligibility criteria. Potential recruits clicked on a banner advertisement that connected them to the study eligibility survey. Print recruitment included advertisements in gay magazines and on MARTA, Atlanta's public transportation system. Advertisements included a URL for the study eligibility survey and also had an option for men to text a phone number and receive a reply text with a link to an eligibility survey. Some men were recruited from a broader panel screener for multiple studies, administered to men in similar settings. Small numbers of men were recruited from other studies, from peers, and via the research group's website. All recruitment modalities had unique codes embedded in the eligibility survey URL to track recruitment sources.

Before completing the study's eligibility survey, men provided informed consent by clicking on a box affirming their decision to continue and consent to be screened for the study. At the conclusion of the survey, men were informed if they were preliminarily eligible for the study. Preliminarily eligible men were given the opportunity to leave their contact information for follow-up. Men who were not eligible were also provided an opportunity to leave their contact information for possible enrollment in other current and future studies within the research group.

Potential recruits were rescreened by study staff and eligible men were scheduled for an initial baseline visit at one of 4 sites where study enrollment occurred. These sites included an HIV-focused community-based organization, a public HIV medical clinic, an office location in Decatur, Georgia and Emory University's Rollins School of Public Health.

Data Collection

In-Person Study Visits at Baseline, 12 Months, and 24 Months

Eligible men attended a baseline visit that lasted approximately 3 hours and included the following activities: (1) meeting with a study counselor to confirm study eligibility; (2) completion of intake forms and assessment of HIV care experience in the preceding 12 months; (3) completion of the study questionnaire using computer-assisted self-interview software; (4) collection of biological specimens; and (5) discussion with the study counselor about HIV care and treatment and prevention strategies with sexual partners, and referrals to HIV linkage and care services and other social services. The types of data collected and their relationship to the conceptual framework are shown in Table 1.

Table 1. Assessment methods and outcomes for study indicators of effective HIV care and prevention.

Indicators of	Assessment methods	Baseline and cohort outcomes	Sentinel event qualitative data
Effective HIV care			
Linkage	• Survey responses • Medical record abstractions	First care visit within 3 months, if unlinked	Failure to have first visit in 3 months
Engagement and retention	• Survey responses • Medical record abstractions • Public health surveillance data	≥1 visit in 6-month window, if linked to care	Failure to have ≥1 visit in 6 months
Adherence	• Survey responses • Laboratory assessment of antiretroviral medication concentrations in blood • Medical record abstractions	No missed doses within previous week	Missed ≥1 doses within previous week
Suppression	• Survey responses • Medical record abstractions • Public health surveillance data	No detectable viral load in previous 6 months	Loss of suppression among previously suppressed
Effective HIV prevention			
Disclosure of HIV status to sexual partners	• Survey responses	Aim 1: Disclosure to all new partners in previous 6 months Aim 2: Disclosure to all current and new partners in previous 6 months	Previously diagnosed: Failing to disclose HIV status to a new partner before first anal intercourse Newly diagnosed: Not having disclosed HIV status to all ongoing anal intercourse partners within 3 months
Condom use with susceptible sexual partners	• Survey responses	Consistent and complete condom use with all HIV-negative or unknown anal intercourse partners in the previous 6 months, in light of preexposure prophylaxis use by partners and viral suppression status [25]	Unprotected anal intercourse with a susceptible (HIV-negative or HIV-unknown status) partner

The baseline questionnaire collected demographics as well as information about HIV care and treatment, hepatitis and other STIs, drug and alcohol use, HIV disclosure and condom use with anal sex partners, health care access and utilization (including use of Ryan White Care Act–supported services), mental health and other psychosocial influencers, housing, and transportation. Sexual health questionnaire elements built on a previously described questionnaire design to elicit partner-specific data [26]. Biological specimen collection involved testing for the following: HIV infection, viral load and CD4 count, antiretroviral medications, hepatitis C, urethral and rectal gonorrhea or chlamydia, syphilis, and heavy alcohol or nonprescription drug use.

The 12-month in-person visit was very similar to the baseline visit with the exception that participants had the option to complete the 12-month survey from home in advance of their visit, and there was a limited laboratory specimen collection. At the visit, if the participant had not completed the survey at home, they were asked to complete a short computer-assisted self-interview survey on their HIV care and treatment experiences since their baseline visit, they had a quick check in with the study counselor about any referrals they need for HIV and other supportive services, and they provided a urine specimen and had blood drawn to test for CD4 count, HIV viral load, heavy alcohol use (using a carbohydrate-deficient transferrin test) [27] and nonprescription drug use using iCup 10-Drug Panel Test Cup (BioScan Screening Systems Inc).

The 24-month in-person visit mirrored the 12-month in-person visit, with the exception that the laboratory specimen collection was expanded to include all tests from baseline except for testing for HIV infection status. Participants were compensated US $60 for their baseline and 12-month visits and US $75 for their 24-month visit.

Web-Based Surveys at Months 3, 6, and 18

At months 3, 6, and 18, we emailed participants with a URL to complete a web-based survey remotely. These surveys were similar to the ones completed at baseline, 12 months, and 24 months and collected updated demographics and longitudinal data on HIV care and treatment experiences, sexual behaviors, and drug or alcohol use. For each completed web-based survey, participants received a US $40 electronic gift card of their choice to either Amazon, Target, CVS, or Starbucks.

Individual In-depth Interviews

The prospective cohort study was supplemented by the collection of rich qualitative data on participants' HIV care and

treatment experiences, and the factors underlying racial disparities. We selected a subset of participants (n=21) to participate in a series of in-depth interviews at 6-month intervals over the course of the cohort study. Participant selection was based on a combination of survey data (from baseline and 3 months) and laboratory data. The survey and laboratory data were used to identify participants who had experienced sentinel events. Sentinel care events included incident lapse in care visits, antiretroviral therapy adherence problems, detectable viral load in a previously suppressed participant, lack of first care visit within 3 months of diagnosis, and lack of initial viral suppression within 6 months of diagnosis. Sentinel prevention events included a lack of discussion of seropositive status with a new or ongoing anal intercourse partner and lack of condom use with a susceptible partner. The goal was to sample participants for the individual in-depth interviews who had experienced a range of lapses in the continuum of care. Interviews utilized a timeline approach to capture clinical, social, and sexual life events over the course of a 6-month period before the interview [28,29]. The timeline created at the first in-depth interview covered the period 6 months prior to the date of the in-depth interview and was recreated at each successive interview for the past 6-month period. This participatory research method generated a visual tool that forms the foundation of questioning in the interview. For the first in-depth interview, the interviewer asked the participant to add the milestones of their engagement in HIV care to the timeline, serving to establish patterns of service use. Questions focused on barriers and facilitators to service use. At each interview, questions focused on recent engagement in HIV care, with participants marking these behaviors onto the timeline. Questioning sought to understand the context of engagement in HIV care, using the stem question “Tell me about what was happening in your life during (event in question)?” with specific probes for each of the distal and proximal factors. Respondents used stickers of various sizes and colors to represent domains of influence and perceived magnitude of influence. Respondents were also free to annotate the timeline with other issues.

Audio data from the in-depth interviews were recorded, transcribed, and deidentified. Timelines were scanned and turned into diagrams. Data were analyzed and coded in MAXQDA (version 18.2.5, Verbi GmbH). First, deductive codes were added to the transcripts to highlight key themes and guide comparisons, followed by inductive codes. Two staff members independently coded each transcript, with discrepancies in coding discussed and resolved at team meetings. Timeline diagrams were coded to develop phenotypes of patterns: analysis of phenotypes involved grouping timelines into similar sets or patterns, with a particular focus on identifying linkages across phenotypes. This allowed us to build concepts grounded in the data to explain phenomena observed and to identify phenotypes that may be specific to Black men who have sex with men or White men who have sex with men.

Medical Record Abstraction

We obtained permission for the release of medical records and abstracted the clinical records of a sample of our participants to augment the survey and laboratory data we collected and to gain a better understanding of the degree to which medical record data can be used to validate self-report survey data. Participants signed medical releases for all HIV clinicians they reported to us, and the releases were used by study staff to request copies of medical records. Clinical visits for the 1 year preceding and 2 years during study enrollment were abstracted.

HIV Surveillance Data

In an attempt to validate the quality of HIV care and treatment-related data from self-reported surveys and from medical record abstractions, and to obtain a fuller picture of HIV care outcomes, participants consented to the release of their reportable laboratory data to the study, and we requested individual-level HIV surveillance data from the Georgia Department of Public Health. By law, Georgia Department of Public Health receives all reports of HIV western blot tests, CD4 counts and viral load tests performed on patients in Georgia. On a biannual basis, we provided Georgia Department of Public Health with a list of names for all consenting participants, for whom we requested specific HIV surveillance data (eg, first HIV-positive test, CD4 count, or viral load in a date range). These data will allow us to assess the quality of our self-report, laboratory, and medical record data and provide a less biased data set for examining viral load outcomes.

Planned Analyses

Cross-sectional (Baseline) Analyses

Using the baseline visit interview and laboratory data from participants, we will initially identify factors associated with key care and prevention outcomes. Factors in the theoretical model will be considered as exposures; these factors are summarized by level of the socioecological model (eg, individual, microsystem, exosystem) in Table 2. Our approach assumes that there is no true direct causal effect of participant race on each outcome, and that the apparent associations between the 2 are explained via indirect effects through intermediate individual- and community-level factors. We will assess these factors by adapting traditional mediation analysis [30] to a change-in-estimate epidemiologic modeling strategy [31,32].

For each HIV care and prevention outcome *Y*, we will consider logistic regression models of the form:

where *R* represents participant race and each M_i represents 1 of *k* factors in Table 2 as potential mediators of the association between *Y* and *R*. Because binomial models can be unstable, we will use predictive-margins adjusted *PR* to compare the adjusted *PR* for participant race in models with subsets of potential mediators, in a stepwise fashion [12,33,34]. A criterion of 10% change in the *PR* will be used to identify factors that meaningfully reduce the *Y*-*R* associations. The *PR* in the fully specified model, which controls for all potential mediators, indicates how many of the *Y*-*R* associations are explainable by the measured factors and the extent of any residual disparity. For identified mediators, we will examine the race-specific prevalence and the strength of association of each with the outcome *Y* to inform the highest-priority targets of intervention

and research. Higher-order community and service environmental factors tend to be more distal to the *Y* of interest and operate through individual-, dyadic-, or network-level factors [35,36]. Therefore, these models will consider M_i at each explanatory level separately. This approach's strength is that it allows for the identification of the factors that account for the racial disparities in HIV care among men who have sex with men, the degree to which they account for those disparities, and their relative roles within each racial group.

Table 2. Proposed measures in the theoretical model.

Type	Measures
Individual	• Age, education, employment • Health insurance coverage • Incarceration history • Stable housing • Access to transportation • Health literacy • Health care perceptions and self-efficacy • HIV treatment self-efficacy and optimism • Depression, mental illness • Experienced, perceived, internalized HIV stigma • Experienced, perceived, internalized homophobia • Experienced, perceived, internalized racism • Drug use • Condom efficacy, skills, errors • Time since diagnosis • HIV disease stage • Social support
Microsystem	• Dyadic • Partner demographics, type, relationship strength • Substance use • Locations for meeting and sex • Power and dynamics • Network • Peer norms for HIV care
Exosystem	• Service environment • Distribution of providers by service type • Colocation of provider services • Transportation options • Community • Poverty, insurance coverage, crime rates, • Percentage same-sex households • Community HIV stigma, gay stigma, racism

Statistical Power

Study power was estimated for the key outcome of HIV viral suppression, at the final analytic step of assessing the relationship of mediators with the outcome, among racial groups. We assumed n=160 per racial group, α=.05, power 80%, and race-specific suppression levels constrained to national estimates for HIV-diagnosed men who have sex with men by race [6,37,38]. Given 21% overall suppression among Black men who have sex with men, we anticipate 80% power to detect a binary mediating factor that is associated with a ≥60% reduction in viral suppression among Black men who have sex with men (ie, 30% vs 12% suppressed between the 2 levels of the mediator). Given 41% overall suppression among White men who have sex with men, we anticipate 80% power to detect mediators associated with a ≥40% reduction in viral suppression in this racial group.

Among those who had a suppressed viral load at the baseline visit, we will use the viral load data from each follow-up survey and study visit to identify time of loss of viral load suppression. For participants who experience a loss of viral load suppression, time of loss of viral load suppression will be defined as the midpoint between the first study visit at which their viral load was >40 copies/mL and the most recent study visit at which their viral load was suppressed. We will fit Cox proportional hazards models of the form:

where $h(t|x)$ represents the hazard at time t conditional on a set of covariates x, h_0t represents the baseline hazard function, p signifies the number of parameters, and β values represent regression model parameters. We will estimate unadjusted hazard ratios for each of the variables considered. Time-varying measures will be used for variables that change over time (eg, substance use). Variables with statistically significant unadjusted hazard ratios will be included in a multivariable model to estimate the adjusted effect of each variable on time to viral load suppression.

Qualitative Data

Audio data from in-depth interviews will be recorded, transcribed and deidentified. Timelines will be scanned and turned into diagrams of sentinel events and their perceived influencers. Both the audio recordings and diagrams will be loaded into MAXQDA for coding and analysis. All interviewing and coding is team-based. We will implement a data handling and analysis plan based around principles of data reduction. We will use conduct grounded theory–based thematic analysis of the in-depth interview. Analysis of transcripts and diagrams began early in the data collection phase to identify emergent themes and we will continue iterative revision of the interview questions and probes. At weekly meetings, interviewers reviewed recent timelines and transcripts to identify codes and areas of questioning for future interviews. Through this process codebooks were developed that include a detailed description of each code, inclusion and exclusion criteria, and examples of the code in use. Deductive codes will be applied to the transcripts to highlight key themes and guide comparisons [39-41]. Principal deductive codes will be taken from the Bronfenbrenner model [20], and will include the codes *dyadic*, *network*, *community*, and *service environment*. Within each of these, subcodes will note the direction of influence as barrier or facilitator and the respondent's perception of the magnitude of the influence. Next, inductive codes that represent newly emerging themes will be added to the transcripts.

Using this codebook, 2 researchers will independently code each transcript, and transcripts will be assessed for intercoder reliability using Cohen α [42]. If the κ statistic is found to be <0.80, discrepancies in coding will be discussed and resolved at team meetings. After all transcripts are coded, we will generate code frequency reports and look for patterns of code co-occurrence by key demographic characteristics (eg, age and race). Throughout this process, we will apply the rule of saturation; development of new codes will cease when no new themes are seen in the transcripts. In addition to the coding process, the timeline diagrams will also be coded to develop phenotypes of patterns observed. For example, one phenotype may be those with repeated similar sentinel events (eg, repeated refusal of antiretroviral medication), while another may be respondents who experience sentinel events at each stage of the treatment cascade. This involves grouping the timelines into similar sets or patterns.

Data analysis will involve generating frequencies of the codes and comparing the frequency of code occurrence across age and race, across phenotypes of sentinel event experiences, and across new or prevalent HIV-positive status. A particular focus of the analysis will be on identifying linkages across codes (eg, the extent to which those with major network influences also report service environment influences) and comparisons in patterns of these linkages by age and race and new versus prevalent positive HIV status within age and race. We will also compare code frequency between interviews with providers and cohort participants to examine whether there are differences in the perceptions of domains of influence on HIV care. This will allow us to build concepts grounded in the data to explain phenomena observed. The result will be the generation of a unique data set that illustrates racial variations in dynamic and multilevel influences on successful HIV treatment and care.

Results

The study was approved in March 2016 and launched in June 2016. We enrolled 400 Black (n=206) and White (n=194) men in Atlanta, Georgia over the course of 1 year. Retention rates at 3, 6, 12, and 24 months were 95%, 95%, 87%, and 80%, respectively. A total of 53 qualitative interviews were conducted. The final study visit occurred in February 2019.

Discussion

Disparities are a stubbornly persistent feature of the US HIV epidemic, and we have an increased understanding of the confluence of factors that drive these disparities. Race is a marker for a myriad of barriers to effective care, and observational cohort data offer the opportunity to understand which factors related to race mediate the relationship between Black race and worse HIV-related outcomes. That understanding can suggest priorities to reduce disparities. In other words, we know that associations with race and poor clinical outcomes are not causal, and our study sought to identify the patterns of associations that explain observed racial inequities. For example, our previous cohort of Black and White men who have sex with men in Atlanta [12] documented large disparities in the incidence of HIV between Black and White men who have sex with men and identified factors that mediated that relationship: lack of health insurance and higher prevalence of unsuppressed HIV infection in sex partners effectively explained all of the disparity in incidence [43,44]. These data supported calls (albeit unsuccessful ones) for expansion of Medicaid in Georgia. We have used the same approach to understand the factors that might explain the reasons for lower levels of HIV viral suppression for Black men who have sex with men.

We acknowledge that our study is subject to limitations. First, we are susceptible to selection bias if we recruit men whose patterns of exposures and viral suppression are not reflective of the underlying community of men who have sex with men in Atlanta. We attempted to mitigate this risk by using systematic methods to select venues, by not recruiting men who have sex with men living with HIV from care settings, and by screening high risk populations to identify newly diagnosed men who have sex with men to include a heterogeneous group of participants. We also anticipated the risk of selection bias if we had differential loss of men to follow up by important baseline characteristics. By conducting active follow-up, having shorter check in visits between annual visits, and maintaining multiple modes of contact, we were able to maintain high retention in the cohort. We attempted to minimize the risk of information bias in several ways. To reduce misclassification, we validated key outcomes (eg, HIV infection status, viral suppression, recreational drug use, problematic alcohol use) with biological measurements. We also supplemented our self-reported and annual viral load measurements by including all viral load measurements during the study period through public health surveillance data. We recognize that the social determinants of health we are considering as possible mediating

factors in the association between Black race and lower levels of viral suppression are likely highly correlated with one another; in our analytic approach, we will assess mediation with a single factor at a time, and then use multivariable logistic regression to control for potential confounding.

Disparities in viral suppression for Black men who have sex with men are an inequitable health outcome that impacts the health of Black men who have sex with men living with HIV, and increases the risks of transmission for their partners. Identifying and addressing reasons for excess unsuppressed viral load in Black men who have sex with men is thus critical to improve the health and longevity of Black men who have sex with men living with HIV and to reduce levels of HIV incidence among men who have sex with men in the United States [10]. A further understanding of the factors associated with lack of viral suppression is critical to implementing programs to achieve national goals for effectively treating people living with HIV as part of the Ending the Epidemic: Plan for America [14]. We hope and anticipate that further elucidating the mechanisms for disparities in HIV care outcomes between Black and White individuals will help identify and advocate for targeted responses to improve viral suppression outcomes and reduce inequities. In the meantime, we already know from our work in Atlanta that Medicaid expansion is a critical step that can be taken now to benefit Atlanta men who have sex with men in terms of increasing preexposure prophylaxis uptake [45], reducing HIV incidence [43], and facilitating access to the HIV medications that can protect men living with HIV. We have sufficient data to call for an immediate expansion of access to health care for all Georgians, including Black men who have sex with men. According to our data, expanding access to health care would almost certainly reduce observed disparities in viral suppression.

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Conflicts of Interest

CK acknowledges research grants to their institution from the National Institutes of Health, the Centers for Disease Control and Prevention, Gilead, and ViiV. Other authors have no conflicts to declare.

Multimedia Appendix 1
National Institute of Health summary statement/peer reviews.
[PDF File (Adobe PDF File), 155 KB - resprot_v10i2e21985_app1.pdf]

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Abbreviations

AIDS: acquired immunodeficiency syndrome
HIV: human immunodeficiency virus
RNA: ribonucleic acid
STI: sexually transmitted infection

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Protocol

Development of a Breech-Specific Integrated Care Pathway for Pregnant Women: Protocol for a Mixed Methods Study

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Abstract

Background: The development of an integrated care pathway with multidisciplinary input to standardize and streamline care for pregnant women experiencing breech presentation at 36 or more weeks of gestation poses several challenges because of the divisive and contentious nature of the phenomenon. Although many clinicians are interested in obtaining the skills required to safely support women desiring a vaginal breech birth, the primary trend in most health care facilities is to recommend a cesarean section.

Objective: This paper aims to discuss the mixed methods approach used in a doctoral study conducted to generate new knowledge regarding women's experiences of breech birth in Western Australia and professional recommendations regarding the care of women experiencing breech presentation close to or at term. This study was designed to inform the development of an integrated care pathway for women experiencing a breech presentation. This mixed methods approach situated within the pragmatic paradigm was determined to be the optimal way for incorporating multidisciplinary recommendations with current clinical practice guidelines and consumer feedback.

Methods: A mixed methods study utilizing semistructured interviews, an electronic Delphi (e-Delphi) study, and clinical practice guideline appraisal was conducted to generate new data. The interviews were designed to provide insights and understanding of the experiences of women in Western Australia who are diagnosed with a breech presentation. The e-Delphi study explored childbirth professionals' knowledge, opinions, and recommendations for the care of women experiencing breech presentation close to or at term. The clinical practice guideline appraisal will examine the current national and professional breech management and care guidelines. This study has the potential to highlight areas in practice that may need improvement and enable clinicians to better support women through what can be a difficult time.

Results: Data collection for this study began in November 2018 and concluded in March 2020. Data analysis is currently taking place, and the results will be disseminated through publication when the analysis is complete.

Conclusions: The results of this study will guide the development of an integrated care pathway for women experiencing a breech presentation close to or at term, with the hope of moving toward standardized breech care for women in Western Australia. This study protocol has the potential to be used as a research framework for future studies of a similar nature.

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KEYWORDS

breech presentation; midwifery; methodology; Delphi technique

Introduction

Background

Birth of any kind, vaginal or cesarean section (CS), is not without risk [1]. The safest mode of birth for women experiencing breech presentation has created debate among academics and practicing clinicians for over 20 years [2]. Women who experience breech presentation late in the third trimester (between 35 and 42 weeks) are usually recommended to have a CS [2,3]. The *Term Breech Trial* [3] had a significant effect on breech birth practices, suggesting that CS was the safest mode of birth for women experiencing breech presentation despite concerns raised regarding the validity of the study [1,4,5]. A subsequent study by the same research team revealed no significant differences in the developmental outcomes of breech born children at 2 years of age, regardless of their birth mode [6]. However, this did not reverse the dramatic rise of the CS rate for breech presentation, which ranges from 69% to 100% [2]. The persistence of this trend has led to the deskilling of practitioners in relation to vaginal breech birth (VBB) [7] and a subsequent limitation of birth choices for women in most settings. The implications for women who have a CS include an increased risk of infection and deep vein thrombosis, greater postpartum blood loss, longer hospital stays, risk of complications such as placenta accreta, increta, and percreta (abnormal implantation of the placenta), and uterine rupture in subsequent pregnancies [8-11]. There is also evidence suggesting that the birth mode has the potential to affect the long-term health outcomes of children. Owing to a lack of exposure to their maternal microbiome, cesarean birth puts children at risk of metabolic diseases such as diabetes and respiratory issues such as asthma [11,12]. Despite leading guidelines supporting balanced, unbiased counseling and the option of a VBB for women meeting eligibility criteria [13], VBB is still not offered in many settings. However, VBB continues to occur and women still seek out clinicians who are supportive of their decision to attempt a vaginal birth [2]. Women have reported receiving limited information, the use of biased and coercive counseling techniques from clinicians to dissuade them from attempting a VBB, and a perceived lack of support from within their social support network (ie, family and friends) in their desire for a VBB, suggesting that negative views of VBB exist in the wider society [14,15]. Women in these studies valued balanced, evidence-based information and nonjudgmental counseling from clinicians who are experienced in and supportive of VBB [14,15].

Women come to decisions about birth mode through a complex interplay among their own preferences, social influences, clinicians' views and experiences, and health system support [16]. Diagnosis of a breech presentation in late pregnancy has been reported as a stressful event, as it was seen to change the trajectory of the pregnancy journey from one of relative normalcy to one of risk [15]. Previous Australian research exploring women's knowledge of breech presentation management and the mode of birth preferences regardless of presentation at birth indicated that 90.8% (158/174) of women favored a vaginal birth over a CS [17]. This has been supported by a research from the Netherlands that indicated that approximately 40% of women experiencing breech presentation at term wanted the opportunity for a vaginal birth, even if treatments such as an external cephalic version (ECV) failed [5].

Media representations of breech birth tend to emphasize the risks of a vaginal birth and focus on the relative safety of CS, which contributes to the societal perception of VBB as a dangerous option [18]. Women considering options that diverge from common practice (ie, ECV and CS) have reported the use of bullying and scare tactics when expressing their preference for a vaginal birth [15]. These women potentially face pressure from within the health care system and without. Australian-based breech studies have found that women with a breech fetus at term desiring a VBB often experience pressure from their families to have a CS [19].

However, with the growing international concern regarding the escalating rate of cesarean birth and its potential consequences for childbearing women and their current and possible future children [20], there has been a focus on health initiatives that aim at *normalizing* birth or reducing the rate of medical intervention [21]. Such initiatives include the implementation of specialized breech teams or clinics. Specialized breech teams or clinics and care pathways have been recommended as a way of providing balanced counseling and support for women during the decision-making process and, by extension, support their birth choices [22]. Specialized breech clinics also offer clinicians the opportunity to enhance and maintain their breech birth skill set, which is key to the safety of breech births [1,23,24]. Currently, although there are only 2 specialty breech clinics in Australia, both of which are in New South Wales (John Hunter Hospital and Women's and Newborn Health Westmead Hospital) [25], the midwives and obstetricians in such clinics work collaboratively to provide women with information concerning procedures to promote a head-down fetal position (ie, cephalic version) and birth mode options [23]. They have also been shown to decrease the rate of CS for breech by improving the uptake and success of ECV [26,27]. Furthermore, they have had success through the encouragement of women deemed suitable to opt for or continue to a VBB where ECV has failed, is contraindicated, or has been declined [27].

An integrated care pathway (ICP) is a formalized document which outlines the ideal pathway of care for people experiencing a particular health phenomenon and has been broadly used across aspects of health care [28-31]. ICPs have been shown to reduce hospital-related complications and the length of stay and to improve clinical documentation and patient satisfaction [29,32]. They also reportedly promote patient-focused care, facilitate patient education regarding their health phenomena, facilitate collaboration within the multidisciplinary health team, and introduce evidence-based care and treatments available to patients that can be adapted to suit local conditions while reducing costs and maximizing resources (ie, by minimizing unnecessary tests or procedures) [28]. A midwifery ICP was developed to promote vaginal births by Clarke et al, after an internal review showed that routine midwifery-led care sometimes resulted in unnecessary interventions. The vaginal birth ICP described by Clarke et al [30] was seen to legitimize the midwifery model of care in the Wales context, promoting

the midwifery role and redefining the midwifery territory, however it did not meet its original aim of reducing the CS rate [33,34]. Other ICPs used in perinatal care have been shown to improve communication between clinicians and consumers and increase consumer satisfaction [29]. In Australia, a range of clinical pathways for maternity care exist. These include a CS pathway, vaginal birth pathway, an assisted vaginal birth pathway, as well as various neonatal pathways and community care program pathways [31].

Database searches exposed reference to existing breech-specific ICPs; however, one could neither be found in the Australian context nor were the authors able to obtain a copy of an existing breech-specific ICP. An ICP for breech presentation has the potential to reduce unnecessary intervention and streamline care including timely referral and intervention and aid in promoting nonbiased counseling.

Objectives

Owing to the potential benefits of ICP, the results of this study will be used to guide the development of an ICP for women diagnosed with a breech presentation close to or at term (ie, approximately 35-40 weeks of gestation) to support the delivery of high-quality, evidence-based care. The development of a breech-specific ICP for women in Western Australia will be achieved through the amalgamation of expert opinion (ie, consensus reached in the electronic Delphi [e-Delphi] study), consumer feedback (ie, based on results from interviews exploring women's experiences of breech birth), and the incorporation of breech care guidelines [30].

Methods

Research Questions

The primary questions this research aimed to answer were the following:

- What barriers and facilitators do women experiencing breech presentation close to or at term experience in Western Australia?
- What optimal pathway of care is recommended for women with a breech presentation between 36 and 42 weeks?

Pragmatism

In the context of research, a *paradigm* refers to the philosophical assumptions that direct the researcher and describe their worldview [35]. Pragmatism as a research paradigm proposes that the researchers use methodological and philosophical approaches that will work best to answer the problem in focus [35,36]. Pragmatism began emerging in the United States during the 1870s through a discussion group in Massachusetts involving Charles Peirce, William James, Chauncey Wright, Oliver Wendell Holmes Jr, and Nicolas St Johns Green, with the main view that a full understanding of a particular phenomenon cannot be achieved from a single methodological or philosophical perspective (ie, positivist or interpretivist) [35,36]. The approach was further developed by several other academics and nonacademics, including John Dewey, George Herbert Mead, and Arthur F Bentley, and is commonly associated with mixed methods research [35,36].

Mixed Methods Research

Mixed methods research has been employed in health care research for decades [37]. Health care mixed methods research incorporates multiple methodologies, philosophies, or theoretical concepts as a means of exploring complex health-related phenomena [37].

Curran et al [28] outlined a process for developing an ICP, highlighting the importance of multidisciplinary collaboration with consumer and key stakeholder input and the integration of evidence (ie, local data and research) during the conception phase. This study was designed to incorporate these elements through the following methods to inform the development of a breech-specific ICP:

- Semistructured interviews with women who had experienced a live breech birth between 36 and 42 weeks of gestation within the past 5 years of their recruitment to the study
- An e-Delphi study with professionals having knowledge or experience of caring for women experiencing breech presentation
- A review of current clinical guidelines

Once the data have been analyzed and the ICP is formulated, the recommendations for the care for women with a breech presentation, as determined by the panel, will be compared with local [38] and international [13] breech clinical guidelines and presented in the ICP for review. All participants from the varying aspects of the study will be invited to provide feedback on the draft breech-specific ICP.

Semistructured Interviews With Women who Have Experienced a Breech Birth

The aim of this aspect of the study was to provide insights and understanding into what women in Western Australia who are diagnosed with a breech presentation experience in order to highlight the areas of care that may need improvement.

Women Participants

A preapproved graphic was circulated on social media sites such as Twitter and Facebook by the lead author in December 2018 as a means of generating awareness and interest in the study. The posts received 125 *shares*, which provided an effective and convenient method of *snowball* sampling. A minimum of 10 women, aged 18 years or above, who had experienced a live breech birth (ie, vaginal or by CS) between 36 and 42 weeks of gestation within the preceding 5 years were desired for this aspect of the project with the intent of continuing recruitment until data saturation was achieved (ie, no new themes emerged). Women were also required to be able to read and speak English.

Data Collection

Interviews were conducted and audiorecorded by the lead author. The interviews took place in a location according to the women's preferences—mainly in their homes or a neutral setting such as a local café. Women were also offered the option of a telephone or video call if it was difficult to schedule a date for a face-to-face meeting to take place.

Data Analysis

The audio files generated by the interviews were transcribed by the lead author. Conversation not pertinent to the aims of the study were briefly summarized and filler words such as "umm," "ahh," and "like" were removed and were otherwise transcribed verbatim. Transcript analysis was guided by Critical Theoretical concepts to identify and describe the potential barriers, constraints, and facilitators faced by women experiencing breech presentation at the end of their pregnancy.

Critical Theory

Critical Theory has its foundations in the Marxist tradition, which focuses on the emancipation of the working class from oppression by bourgeoisie society [39]. The tenets of this theory saw development through the early 20th century within the Frankfurt School [39,40]. Since then, the theory has seen applications mainly in the social sciences [40,41]. Critical Theories are used to examine the experiences of individuals in their social and political contexts to identify and understand power structures within their society with the intention of recommending and accomplishing change for the good of the group examined [41,42]. Michel Foucault examined the relationship between power and knowledge and how, when combined, these elements can be used in institutions such as hospitals and prisons, as a form of disciplinary control [43]. These concepts will guide the analysis of the resultant transcripts.

The Delphi Technique

The Delphi technique was originally developed as a way for military experts to forecast the effect of advancing technologies on warfare but has since been employed across many disciplines as a way of reaching consensus regarding matters of import [44]. In medicine and midwifery, it has been utilized to determine research priorities, analyze professional characteristics and competencies, educational program development, and the expansion of midwifery practice to include a specialist skill set [45,46]. It has also been utilized to explore aspects of breech presentation and care [46-48].

Consensus

Consensus is established through consecutive questionnaires, termed *rounds*, combined with controlled feedback. The initial round generally consists of open-ended questions, and the data obtained are used to generate statements that are distributed to the panel for evaluation in the subsequent rounds [49]. The process continues until the predetermined level of consensus is met by most statements. Levels of consensus have been reported to range from 50% to 100% in Delphi studies [49]. For this study, the predetermined level of consensus was set at ≥70% and has been used previously in breech-related Delphi studies [46,47]. An e-Delphi survey was utilized to explore and establish consensus among participants with the knowledge of or experience in caring for women diagnosed with breech presentation.

The Delphi Process and Analysis

Questions for the first round were guided by a previous study relating to breech presentation [22] and a review of the literature. Individualized, reusable links were generated in Qualtrics and circulated to potential participants via email. Those who consented to participate were given 4-6 weeks to complete the questions. A reminder email was sent 2 weeks before the expiration of the individualized link with the option of an extension of the allotted time for completion if requested by the participant. This process was employed in each round. Each round was divided into sections, with similar topics grouped together. Each page comprised 1-4 questions including matrix questions, depending on the amount of detail being sorted, and each round spanned several pages. For each question, there was the option to provide feedback through a free text box. Before submission, participants were able to review their responses by pressing the *back* button in each section. All feedback and comments were presented to the panel in a table format along with a graphical representation of the statements that reached consensus between the second and final rounds. The statements were amalgamated where possible, added or revised based on participant feedback. On the basis of participant feedback and the quantity of data generated in the first round, the second round was divided into 3 parts to facilitate the ease of completion for participants and the ease of analysis for the research team.

Participants

As breech care and birth are niche areas of interest compared with other health phenomena, a minimum of 10 professionals with in-depth knowledge of or experience in caring for women with breech presentation was desired for this study. The following inclusion criteria were set for the e-Delphi study: participants were required to be aged 18 years or above; have the ability to speak and read English; and have experience in supporting or caring for women during pregnancy, particularly those experiencing breech presentation. This study aims to capture a panel whose members had varying experiences of caring for women with breech presentation as experience is contextual; therefore, no predetermined years of experience was placed, a mix of convenience, purposive, and snowball sampling was used. Preapproved social media posts outlining the aim of the study and the contact details of the lead author were circulated on Twitter and Facebook groups such as the Coalition for Breech Birth and the Breech Birth Network for convenience sampling; and to the public to generate the interest of potential participants, encouraging them to make contact if they were interested in participating. All those who responded identified themselves as professionals who met the aforementioned selection criteria. This was verified throughout the processing of the data obtained from round 1. Recruitment took place between November 2018 and August 2019. The aforementioned posts were circulated numerous times. Participants were also encouraged to pass the study information to any of their colleagues who they believed might be interested in participating (ie, snowball recruitment). Recent breech literature was also reviewed as a means of identifying potential participants (ie, purposive sample). A minimum of 2 emails or direct messages through social media were sent to the participants identified through the literature.

Clinical Guideline Review

Current guidelines on breech management and care will be purposively selected from national and professional organizations in the United States, Canada, the United Kingdom, Europe, Australia, and New Zealand for review to aid in answering the second research question (ie, What optimal pathway of care is recommended for women with a breech presentation between 36 and 42 weeks?). The authors propose using the clinical practice guideline appraisal tool International Centre for Allied Health Evidence Guideline Quality Checklist to evaluate each guideline. This tool has been validated and was deemed best suited because of its ability to efficiently and effectively review the quality of clinical practice guidelines [50]. This review will also determine whether participants' opinions align with or diverge from the examined guidelines. Exclusions will include guidelines that have received no review within the past 5 years or have been superseded and are not available in the English language. It is proposed that the following search engines and databases will be utilized to obtain copies of the desired documents: Google, University WorldSearch, CINAHL Plus with full text, and PubMed. Reference lists of abstracted documents will be searched for any further relevant material.

Ethical Considerations

Permission to undertake this study was granted by the University Human Research Ethics Committee (project number 19566). All participants in this study were provided with an information sheet outlining the scope of the respective studies, the contact details of the research team, and the phone number for a helpline in the event that they experienced any emotional discomfort when recalling their experiences.

Women who met the inclusion criteria and were willing to participate in a semistructured interview were required to sign a consent form before participating. Women were advised that they would be able to withdraw from the study at any time before the completion of their interview. Confidentiality of the women was maintained through the deidentification of all transcripts by using codes based on the women's birth modes (ie, VBB1 or CS10) and the storage of sensitive documents and data in a secure location only accessible to the research team.

Participants of the e-Delphi study were required to indicate their consent to participate by answering a *yes* or *no* consent question before commencing each round. Before commencing each round, participants were advised that they would be able to withdraw from the study any time before the submission of their responses. If they withdrew or did not complete a round, they were advised that they would be excluded from future rounds.

All data were stored on the web in Qualtrics, which is password protected and only accessible to the research team, and all data were deidentified, if necessary, for consecutive rounds.

Results

Women's Results

In the interviews, women described their experiences of breech presentation from their diagnosis until after birth. The data generated from the interviews with women will be examined utilizing Critical Theoretical concepts to identify and describe the potential barriers, constraints, and facilitators faced by women experiencing breech presentation near term. This aspect of the study will provide insights into what women in Western Australia experience when diagnosed with a breech presentation near term, providing context and possibly the justification for the development of the breech-specific ICP. By applying the Critical Theoretical framework, the authors hope to explore and examine the unique issues faced by women who are diagnosed with breech presentation at the end of their pregnancy to make recommendations for change to bring about a more woman-centered approach to breech care in Western Australia.

Delphi Results

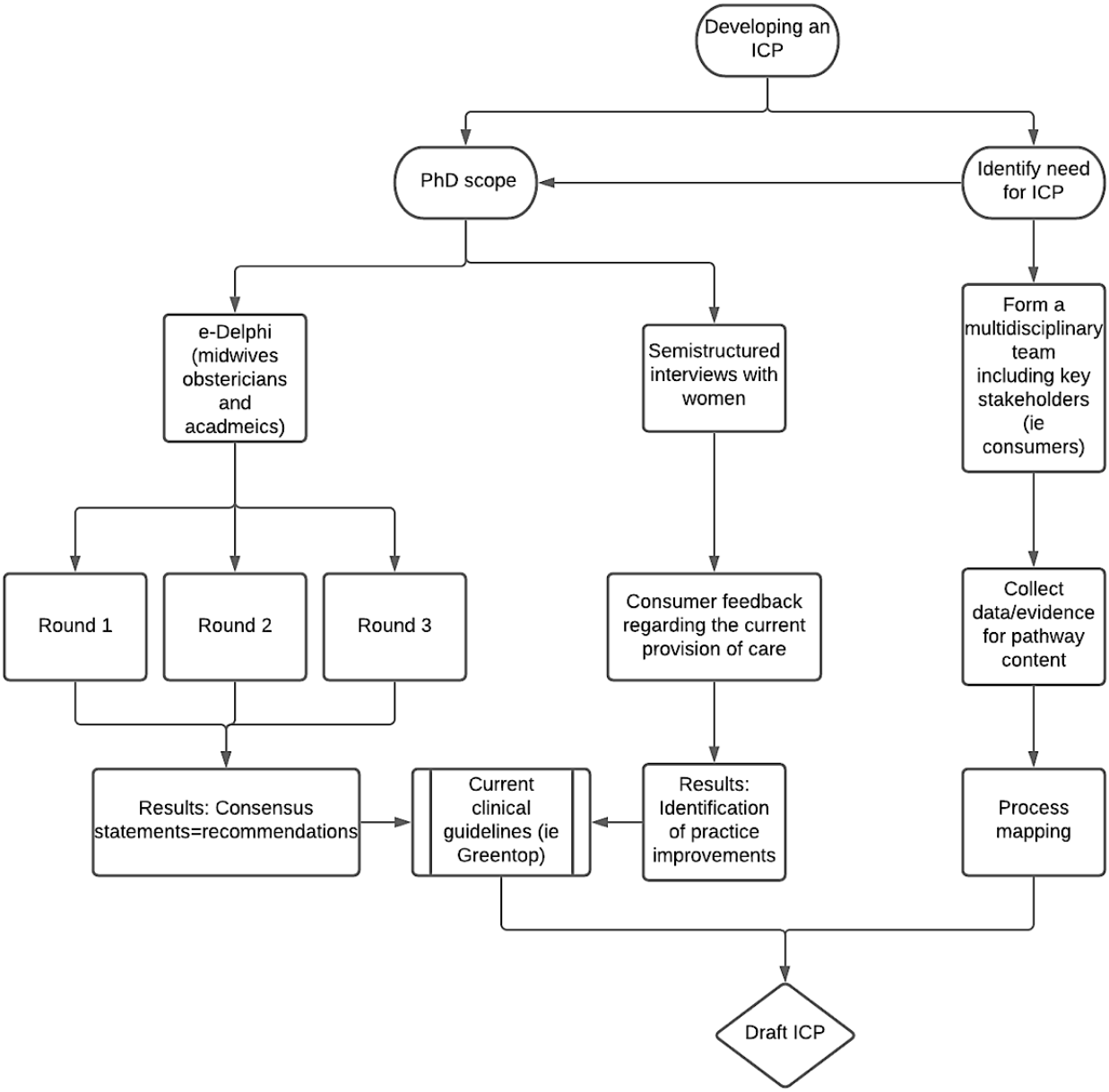
Round 1 comprised demographic and open-ended questions. The responses from this round were evaluated, coded, categorized, and amalgamated where possible to formulate statements for the following 2 rounds using the participants' own words by the lead author. These statements were then sent to the rest of the research team along with the raw data from round 1 for review. Feedback from the research team was incorporated, and the statements were refined and rechecked before distribution to the panelists. A similar process took place during each round based on the panelist comments made in each round and feedback from the research team members.

Statements were evaluated primarily using a 5-point Likert scale, in which responses ranged from strongly agree to strongly disagree. Owing to human error during the construction of round 2 in Qualtrics, a few statements were evaluated using a 7-point Likert scale. Regardless, if the predetermined level of consensus of 70% or more of the panelists agreeing (responses ranging from somewhat agree to strongly agree) or disagreeing (responses ranging from somewhat disagree to strongly disagree) with the presented statements was reached, consensus was deemed to be met in the third and final round.

Combining the Results

In-depth data analysis and review of consensus statements will be combined with an exploration of the women's experiences of breech birth in Western Australia analyzed using Critical Theoretical concepts and current clinical guidelines to aid the formulation of an ICP for breech presentation. A process adapted from the work of Curran et al [28] was adopted to plan the aspects of a PhD project with the aim of developing an ICP (Figure 1).

Figure 1. Integrated care pathway process. e-Delphi: electronic Delphi; ICP: integrated care pathway.



Reflexivity and Research Validity

Critical approaches emphasize the importance of researcher reflexivity [51], which acknowledges the role of the researcher as an active contributor to the construction of knowledge [52]. The lead investigator undertook an interview skill development workshop before conducting the abovementioned interviews to consolidate her previous experience. She also undertook self-reflection for the purpose of identifying preconceptions and possible biases regarding breech care and birth in order to minimize the potential effect these preconceptions and biases could have on the research.

Methods of ensuring the validity of the findings included transcript verification by participants and peer checking of the themes, concepts, and statements derived from the data from both research methods. Women who participated in the semistructured interviews were provided with a copy of their interview transcript and offered the opportunity to verify its contents based on their recollections of the interview. The resultant transcripts were also reviewed by and compared with the audio files by the coauthors to assess the accuracy of transcription. Corrections included typographical errors and 1 change in gestational age at diagnosis of breech presentation based on the woman's recall.

Peer checking of the themes, concepts, and statements derived from each data set by the lead author was accomplished through reflective discussion and review of field notes and e-Delphi responses by the coauthors. Adaptations were made if deemed necessary based on corroborative and constructive feedback.

Discussion

Preliminary Agenda

Using a pragmatic, mixed methods approach to answer the original research questions has allowed the collection of qualitative and quantitative data to provide a comprehensive examination of differing aspects of breech presentation in Western Australia and various continents around the world. The results will be used to guide the formulation of practice recommendations and a breech-specific ICP that will incorporate multidisciplinary collaboration with consumer and key stakeholder input and the integration of evidence on a local and international level.

The women's experiences explored in this study will provide insights and understanding into what some women in Western Australia have undergone throughout their breech pregnancy and birth experience and will aid in formulating recommendations to promote a more woman-focused approach to breech care and management. It is the author's hope that a breech-specific ICP for Western Australia will facilitate this process.

An ICP for breech presentation alongside a specialty breech service has the potential to promote a more women-focused approach to breech care in Western Australia, reduce the rate of CS for breech presentation, and aid data collection for practice review and quality improvement [28].

Benefits and Challenges

An advantage of mixed methods research includes a more comprehensive understanding of the phenomenon in focus instead of a singular point of view by incorporating qualitative and quantitative data and different theoretical perspectives [53]. This methodological approach provided flexibility in answering the complex health-related questions of this study and provided insight and depth into participants' experiences of breech presentation [54]. A challenge for all the chosen methods was that they were time consuming for both the research team and the participants at different stages of the study [44,54]. The sample sizes for both aspects of this study were relatively small; therefore, any findings will not be generalizable.

Interviews were chosen for their ability to explore and describe issues from the perspective of the participants [55]. The interviews allowed for trust and rapport to develop between the participant and the researcher, which resulted in deeper insights into participant experiences through conversation [54]. Semistructured interviews were utilized for this study as a means of guiding the *conversation*; clarification was able to be sought immediately and the researcher had the opportunity to probe further into the aspects of the topic that were of interest to elicit more in-depth understanding [54]. However, as with all qualitative research, there was the potential for the experiences and preconceived ideas of the researcher to influence the responses and findings of the study, despite efforts to minimize these influences [54].

The advantages of the Delphi method include achieving consensus without disregarding the minority, flexibility to adapt the protocol to suit the needs of the project, cost-effectiveness if done on the web, connectivity to geographically dispersed participants, and reduction of the influence of dominant personalities on others' responses [44,45]. However, its limitations must be acknowledged. This method is only quasi-anonymous, and there are no set guidelines regarding techniques, sample sizes, or determining consensus [44]. There is the possibility of biases occurring in Delphi studies, especially in a niche area of practice such as breech presentation, which is known to be divisive among many clinicians [2]. This may impede the achievement of a real consensus [56]. One must also acknowledge the risk of ambiguity within the questionnaire [44]. As panel members may interpret statements differently, there was also the risk of result polarization [56]. To mitigate the risk of ambiguity, a 5-point Likert scale was used; however, this is not a guarantee against the polarity of opinion [56]. Only quasi-anonymity could be offered to panel members; in a niche area such as breech, it was possible that the panel members might have known each other. However, participants were not privy to each other's responses, and any feedback provided in consecutive rounds was deidentified if necessary.

Conclusions

This paper describes the design of a mixed method study which will amalgamate expert opinion (consensus reached in the e-Delphi study), consumer feedback (based on the results from interviews exploring women's experiences of breech birth and the review of exisiting breech birth guidelines [30] to guide the development of an ICP for breech presentation. A breech specific ICP has potential benefits for women and clinicians alike. These include a reduction in unnecessary intervention, streamlining care (ie, including timely referral and intervention), aiding in promoting nonbiased counseling, and improving communication between women and clinicians. This is the first of its kind in Western Australia.

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Conflicts of Interest

None declared.

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Abbreviations

CS: cesarean section
ECV: external cephalic version
ICP: integrated care pathway
VBB: vaginal breech birth

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Protocol

Personal Accounts of Young-Onset Colorectal Cancer Organized as Patient-Reported Data: Protocol for a Mixed Methods Study

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Abstract

Background: Young-onset colorectal cancer is a contemporary issue in need of substantial research input. The incidence of colorectal cancer in adults younger than 50 years is rising in contrast to the decreasing incidence of this cancer in older adults. People with young-onset colorectal cancer may be at that stage of life in which they are establishing their careers, building relationships with long-term partners, raising children, and assembling a financial base for the future. A qualitative study designed to facilitate triangulation with extant quantitative patient-reported data would contribute the first comprehensive resource for understanding how this distinct patient population experiences health services and the outcomes of care throughout the patient pathway.

Objective: The aim of this study was to undertake a mixed-methods study of qualitative patient-reported data on young-onset colorectal cancer experiences and outcomes.

Methods: This is a study of web-based unsolicited patient stories recounting experiences of health services and clinical outcomes related to young-onset colorectal cancer. Personal Recollections Organized as Data (PROD) is a novel methodology for understanding patients' health experiences in order to improve care. PROD pivots qualitative data collection and analysis around the validated domains and dimensions measured in patient-reported outcome and patient-reported experience questionnaires. PROD involves 4 processes: (1) classifying attributes of the contributing patients, their disease states, their routes to diagnosis, and the clinical features of their treatment and posttreatment; (2) coding texts into the patient-reported experience and patient-reported outcome domains and dimensions, defined a priori, according to phases of the patient pathway; (3) thematic analysis of content within and across each domain; and (4) quantitative text analysis of the narrative content.

Results: Relevant patient stories have been identified, and permission has been obtained for use of the texts in primary research. The approval for this study was granted by the Macquarie University Human Research Ethics Committee in June 2020. The analytical framework was established in September 2020, and data collection commenced in October 2020. We will complete the analysis in March 2021 and we aim to publish the results in mid-2021.

Conclusions: The findings of this study will identify areas for improvement in the PROD methodology and inform the development of a large-scale study of young-onset colorectal cancer patient narratives. We believe that this will be the first qualitative study to identify and describe the patient pathway from symptom self-identification to help-seeking through to diagnosis, treatment, and to survivorship or palliation for people with young-onset colorectal cancer.

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KEYWORDS

colorectal cancer; PROMs; young-onset cancer; cancer; patient reported outcome

Introduction

Routine systematic collection of patient-reported outcome (PRO) and patient-reported experience (PRE) data is of considerable interest to health systems worldwide and is the subject of ongoing investment [1,2]. Validated instruments—most often in the form of standardized questionnaires—are regularly used to measure patients' perspectives on the quality of health services and personal outcomes of clinical management care. These data are considered foundational in understanding the effects of health care on patients' daily lives [3] and for making improvements in health care delivery [4,5]. Mixed-methods approaches [6] are increasingly becoming common in the collection of PRO and PRE data. Measurement instruments are sometimes supplemented with open-ended, free-text questions [7] to capture nuanced and idiosyncratic perspectives [5,8-10]. This descriptive material [7,11] has been shown to contextualize responses to closed questions [12] to provide more detail about the relational aspects of patients' experiences [11] and to be more specific about the aspects of care that can be improved to promote better outcomes [11-13].

Qualitative researchers investigating patients' experiences of care and perspectives on outcomes may have opportunities to facilitate mixed-methods approaches [6] for the collection of patient-reported data. In this paper, we present a methodology for producing qualitative data that effectively triangulates [6,14,15] with quantitative colorectal PRO and PRE data [16-19]. The methodology, which we call as Personal Recollections Organized as Data (PROD), pivots data collection and analysis around the validated domains and dimensions measured by PRO and PRE instruments [20-23]. The aim is to facilitate synthesis of patient-reported evidence across research projects. To our knowledge, this is a novel approach to qualitative patient experience data collection.

PROD draws on the "framework method" [24,25], in which free text or narrative data are organized into classifications that have been determined a priori and utilizes thematic/inductive techniques to facilitate the interpretation of emergent PRE and PRO topics [16-19], including quantitative text mining techniques, which are a resource-efficient means of identifying patterns and modelling relationships between topics [12,24,25].

The PROD method will be used to investigate the perspectives of people with young-onset colorectal cancer. The increasing incidence of colorectal cancer in people younger than 50 years has been described as an alarming phenomenon [26] within the wider population of patients with colorectal cancer [27-32]. The incidence of young-onset colorectal cancer has risen by up to 2% per year worldwide while that of colorectal cancer in older adults is declining by up to 3% per year [26,31,33,34]. Dietary and lifestyle changes framed by shifts in global food chains have been proposed as causes for the rise in young-onset colorectal cancer [35]. Additionally, colorectal cancer awareness campaigns and screening programs are directed at people aged 50 years and older [35]. Patients with colorectal cancer who are younger than 50 years are twice as likely as older patients to experience missed diagnostic opportunities by physicians [36], significantly more likely to be diagnosed at an advanced stage of the disease [30,32], have a greater likelihood of aggressive therapeutic management [32], and will commonly have poorer quality of life outcomes [13,37-39].

We have knowledge of this patient population from age-stratified data of the wider colorectal cancer population; however, there has been limited attention on patients with young-onset colorectal cancer as a specific patient community. Patients younger than 50 years are at that stage of life in which they are establishing careers, building relationships with long-term partners, raising children, and assembling a financial base for the future. Their perspectives on their experiences of health services and outcomes of care may be different from those of older patients with colorectal cancer.

Our study aims to address the gap in qualitative patient-reported data on young-onset colorectal cancer by investigating the personal accounts published online by these patients. Web-based autobiographical accounts of health care experiences and outcomes are emerging sources of qualitative patient-reported data on disease-specific and condition-specific patient experience [40-42]. The accounts we will access are extant texts [20,43] in contrast to interactive forms of web-based self-narration in blogs and social media, which have been investigated elsewhere [44,45]. These unsolicited narratives, not produced in response to a research inquiry [20], provide rich detail on the health care experiences and issues that matter to these patients [42].

Patient narratives commonly describe the entire health care journey—from initial help-seeking to current survivor or palliative care status [40]—from the patients' points of view [40]. They feature highly personal perspectives on the performance of health services and physical, emotional, and social outcomes of medical management across the trajectory of care [42]. As sources of patient-reported data, these narratives offer a counterpoint to data produced from cross-sectional surveys. They provide significantly more descriptive data than those that can be derived from supplementary free-text questions in PRE and PRO questionnaires. Given that qualitative research by participant interview can be a labor-intensive and time-intensive process, there is an advantage also in the accessibility of patients' unsolicited narratives with respect to ethical considerations [46]. The PROD methodology, with its clear thematization of coding around existing PRE/PRO dimensions, offers access to rich, longitudinally framed, patient-reported data.

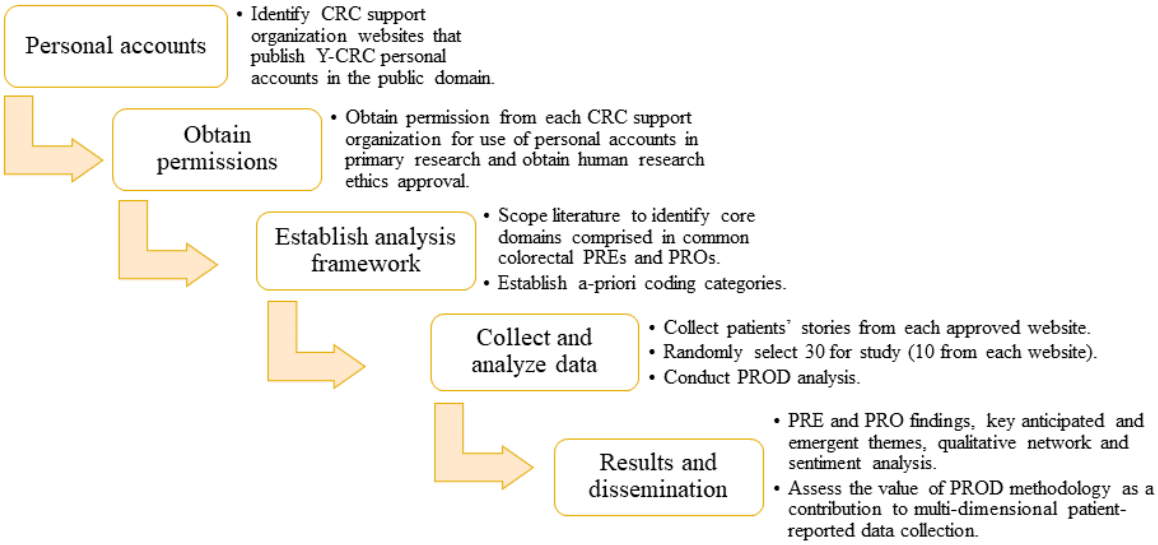
Methods

Design Methodology

A flowchart of the study design is depicted in Figure 1. This is a study of personal patient stories published on websites hosted by 3 established colorectal disease support organizations: Bowel

Cancer Australia, Bowel Cancer UK, and Bowel Cancer NZ. These countries were chosen as they are all English-speaking and have universal health care access. This project will access the public domain sections of these websites in which people post accounts of their experiences under banners such as "real life stories" or "your stories."

Figure 1. Flowchart of the study design. CRC: colorectal cancer; Y-CRC: young-onset colorectal cancer; PRE: patient-reported experience; PRO: patient-reported outcome; PROD: personal recollections organized as data.



Ethical Considerations

There is no established ethical stance relating specifically to research involving unsolicited web-based narratives. We have obtained permission from each of the organizations to analyze these personal accounts and to use deidentified excerpts and quotes in reports of findings from the study. The organizations that host the websites have agreements with individual patient contributors regarding the use of their information and narrative material. These contributors are not direct participants of our study. However, the study of unsolicited autobiographical narratives is a unique research space with particular ethical issues relating to recruitment [47]. To establish the ethical position of this study, we refer to the Australian National Statement on Ethical Conduct in Human Research (2007-Updated 2018) [48], which indicates that privacy concerns arise when the proposed access to, or use of, the data or information does not match the expectations of the individuals from whom this data or information was obtained or to whom it relates. Therefore, we were granted ethical and scientific approval for this project from the Macquarie University Human Research Ethics Committee (MQ HREC Reference No:52020666115757). In publishing their personal accounts on the selected colorectal support organization websites, these contributors agreed that their stories would be made available for public access and used to raise awareness of young-onset colorectal cancer. This study meets the expectations of the contributors. Moreover, this study does not place burdens of active research participation on these potentially vulnerable contributors [49,50]. Additionally, unsolicited accounts enact the values of patient-reported data.

Recruitment

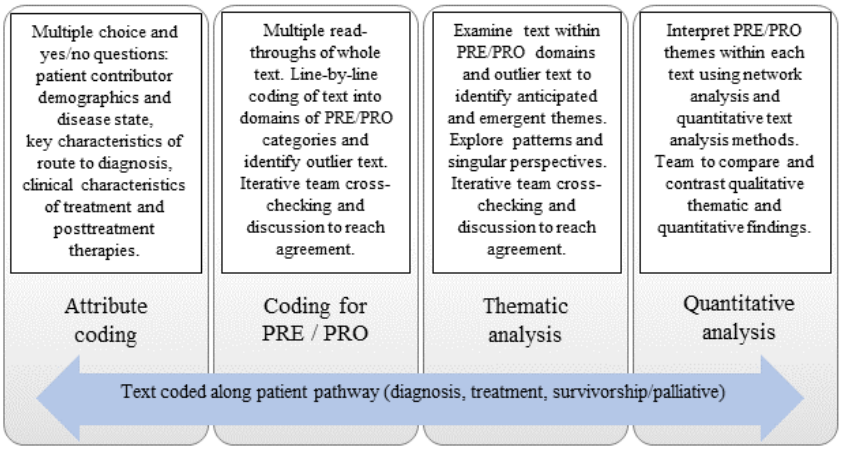
We defined inclusion and exclusion criteria to identify the types of personal accounts published on these sites that would be relevant to the study's aims. We will include personal accounts that are written by people diagnosed with colorectal cancer (self-reported disease state, including but not limited to cancer of the colon, cancer of the rectosigmoid junction, and cancer of the rectum) [13]; before their 50th birthday; published in the public domain spaces of websites hosted by the 3 prominent colorectal disease support organizations, under agreement for the public dissemination and republication of the material; written by people aged 18 years or older at the time of submitting their personal accounts for publication on the website; and autobiographical, first-person accounts of experiences and outcomes relating to care for colorectal cancer. We will exclude personal accounts from the study if they solely comprise feedback on, or criticism of, a named institution or clinician or substantially describe someone else's experiences and outcomes relating to care for young-onset colorectal cancer. We are not including serialized narrative material published as ongoing weblogs or blogs. We will take a random sample of 30 personal accounts from the eligible selection of personal stories using the Microsoft Excel (2011) random function, comprising 10 samples from the patient stories published on each of the 3 websites.

Data Extraction and Analysis

Narrative accounts will be downloaded from websites and collected and analyzed using the qualitative analysis software NVivo 12 Plus (QSR International) [51]. To avoid identification of individuals, each story will be deidentified and assigned a unique identifier code. Our framework method for qualitative analysis [24] identifies a priori what features to account for in our research reporting [16]. We detail our process for establishing the analytical framework in the following section on PRE and PRO domain coding. The PROD approach involves 4 key steps in creating a new structure for the data, as shown in Figure 2: (1) classifying attributes of the contributors, their

disease states, their routes to diagnosis, and the clinical features of their treatment and posttreatment; (2) coding each line of each narrative into PRE and PRO categories and domains according to phases of the patient pathway; (3) thematic analysis of content within each domain; and (4) quantitative analysis of the narrative content.

Figure 2. Overview of the framework for analysis. PRE: patient-reported experience; PRO: patient-reported outcome.



Manual coding and analysis will be undertaken by the process of line-by-line attention to the content in a series of iterative readings. Consistent with the principles of qualitative research, each step of the data extraction and analytical process will be undertaken by at least two researchers [18], as qualitative work with narrative data is interpretive, even when coding to a framework of categories and domains established a priori.

With research questions to guide their choices, 2 researchers working together and constantly comparing their findings can arrive at agreement on the significance of the narrative content and the conclusions that can be drawn from it [18]. The third researcher will validate the findings of the thematic analysis, the fourth researcher will undertake the quantitative analysis, and the team will collaborate to reach consensus on the significance of the findings in relation to triangulation with extant colorectal PRE and PRO data.

Attribute Coding

The first step of the PROD analysis is to identify and classify the key demographic characteristics of the patient contributors, their disease states, the features of their diagnostic pathways, and the clinical features of their treatment and posttreatment phases. We will organize these data in a framework of yes/no and multiple choice categories. The sets of selections are based on conventional research participant attributes and adapted to the level of detail obtainable from unsolicited narratives. In these accounts, attributes such as age, gender, relationship status, and current disease status information may be unknown from the basic information provided in a source website. These characteristics may only be identifiable with close attention to both content and language in a narrative [52], and even then, may only be inferred from implicit clues [40].

PRE and PRO Domain Coding

To develop a set of domains and subdomain items for the a priori analytical framework, we reviewed literature on core outcome sets for PRE and PRO measures [2,23,53] and mixed-methods approaches for analyzing PRE and PRO data [12,54-57]. Our conceptual approach to PRE and PRO domain coding is presented in Figure 3. The domains and subdomain items comprised in our analytical framework are presented in Table 1 and also described below.

Figure 3. Mixed-methods approach for capturing different dimensions in patient-reported data.

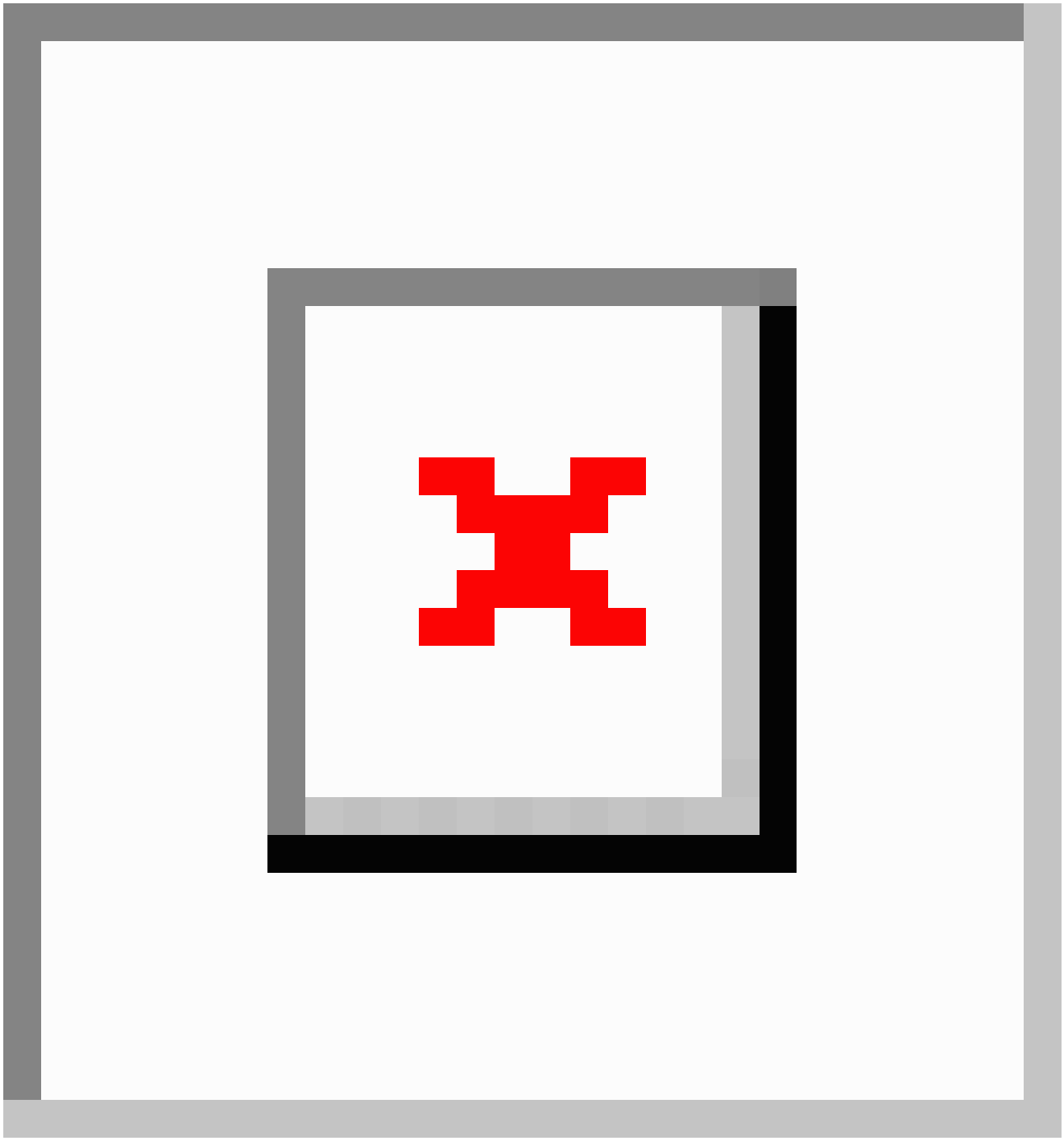


Table 1. Analysis of personal recollections organized as data using the a priori coding framework.

Domains, subdomains	Measures
Attribute coding	
Population characteristics	Gender, marital status, children, date of publication
Disease characteristics and management	Age at diagnosis, current status of disease/diagnosis, stage and type of bowel cancer at diagnosis, type of initial medical consultation for symptoms, family history of CRC[a], investigation for CRC, time from first consultation for illness symptoms to first diagnosis of CRC, discussion of immunotherapy/precision treatment, clinical trials, biomarker-based approach
Route to diagnosis	Symptoms prior to first diagnosis, diagnosis received prior to CRC diagnosis, treatments given for diagnosis prior to CRC, investigations undertaken to diagnose CRC, other conditions and genetic syndromes discussed
Treatment and posttreatment	Treatment received, posttreatment effects
Domain coding	
Patient-reported experience	
Functional	Financial impact or costs associated with care
	Physical context (access, cleanliness, and comfort)
	Process (continuity and co-ordination of care, scheduling, and waiting times)
	Quality and efficiency of clinical care
Relational	Collaborative nature of interactions (provider and admin)
	Informational or educational nature of interactions (clinical and practical information, scheduling and waiting times)
	Interpersonal nature of the interactions (provider and admin)
Patient-reported outcome	
Everyday living or usual activities	Caring for family or dependents
	Domestic chores
	Gastrointestinal function
	Getting around or mobility
	Holidays
	Independence
	Living conditions and environment
	Personal or self-care
	Recreation
Money matters	Finances or financial services
	Planning the future
	Work
Self and others	Anxiety or depression
	Body image
	Existential matters
	Isolation
	Pain or discomfort
	Sexual matters
	Starting a new family
	Support and communication
Additional issues	Others

[a]CRC: colorectal cancer.

PRO Domains

We reviewed general cancer and colorectal-specific PRO instruments [2,23,53,58,59], including the European Quality of Life Questionnaire-5 dimension (EQ-5D) [60], which assesses health outcomes of care across 5 quality of life domains—anxiety/depression, mobility, pain/discomfort, self-care, and usual activities [60]; the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-29-item colon and rectum cancer-site specific (EORTC-QLQ-CR29), the Medical Outcomes Study 12-Item Health Survey, the Functional Assessment of Cancer

Therapy-Colorectal (FACT-C), Edmonton Symptom Assessment System, and the Social Difficulties Inventory instrument-21 item (SDI-21), which assesses the impact of cancer on family life, social activities, personal matters, finances, and work. Of these, we selected the SDI-21 and the EQ-5D as being the most relevant to our research interests and for the collection of data from unsolicited free text narratives. We selected these instruments based on the volume of applications in the context of colorectal cancer [12,13,58,61], the applicability of these instruments in people with colorectal cancer across all disease stages and phases of treatment [59,61], and because the domains and items comprised in these instruments offer a balance of broad functional and psychosocial outcomes [13,61-63].

We used 3 core outcome sets from the SDI-21 as the thematic domains for PRO coding: "Everyday Living," "Money Matters," and "Self and Others." We also added a category for "Additional issues" to capture events and perspectives not comprised in these thematic domains. Where possible, we consolidated individual scaled items from SDI-21 outcome sets. For example, in the domain "Money Matters," we absorbed the items "Welfare benefits," "Finances," and "Finance services" into a single item called "Finances or financial services." Similarly, we synthesized 3 communication and support items into 1 item called "Support and communication." We also incorporated the SDI-21 single item set into 3 core thematic domains, bringing "Sexual Matters" and "Plans to have a family" into the "Self and others" domain and "Holidays" and "Where you live" into the "Everyday living" domain (Table 1).

While the EQ-5D questionnaire and SDI-21 feature common outcomes, the EQ-5D instrument also accounts for issues relating to pain and discomfort and the psychosocial aspects of everyday life, such as anxiety and depression. We included these items in the framework domain called "Self and others." To code for issues that are particular to people with colorectal cancer and to cover all items included in colorectal cancer-specific PRO questionnaires such as EORTC-QLQ-CR29 and FACT-C [53], we introduced the item, "Gastrointestinal function" into the "Everyday living" domain.

PRE Domains

PRE-questionnaires are commonly designed to examine patients' experiences of particular health organizations, such as the National Health Service National Cancer Patient Experience Survey, or the services offered in certain health settings [64]. The EORTC, for example, publishes PRE-questionnaires specific to inpatients and inpatient experiences, communication with professionals, and information provision. Given that our data set was drawn from websites in 3 countries and that contributors chose the aspects of their experiences that they wished to describe, we required a broad-ranging generic set of PRE domains and subdomain items for our analytical framework [64].

Rather than selecting domains from a particular PRE instrument, we reviewed the literature to identify the core concepts underpinning PRE-questionnaires. We identified that patient experience outcomes are measured broadly for either relational or functional aspects of experience [64-66]. We used these as the 2 PRE domains in our analytical framework. Relational outcomes account for the interpersonal nature of patient-provider communications, patient-provider collaboration, and information provision to patients [65,67]. Functional outcomes account for the organizational and practical aspects of care, environments of care delivery, and the financial impact of care [65,67] (Table 1).

Patient Pathway Coding

From patients' perspectives, experiences of health services and outcomes of care occur as a continuum of patient journey within and across the phases of the patient pathway [40]. We will undertake a patient pathway analysis of the PRE and PRO data by coding for 3 key phases of the patient pathway: diagnosis, treatment, and survivorship/palliative care (Figure 2) [36,68,69].

Thematic Analysis

There are 4 steps in our thematic analysis: coding for concepts, categorizing codes into groups, detecting patterns across categories, and interpreting themes within and across these patterns [70]. This process transforms the text into a narrative dataset, moving from highly descriptive findings to highly interpretative findings [16,20].

Quantitative Analysis

We will investigate opportunities to interpret the data quantitatively by means of network analysis [71] and quantitative text-based analysis, which uses automated natural language processing to analyze topics across different documents [12] and can measure sentiments within texts. This method may draw out aspects that contextualize other findings [12,13]. Quantitative approaches to analyzing unstructured text are emerging; however, as yet, there is little consensus on optimal strategies [12,46].

Methodological Limitations

Our methods will have limitations, including that we will be dealing with text not written for research purposes, not all text will map to our framework, and the data are subjective and will require interpretation. Additionally, data reported in different health systems will need to be seen in the light of those structural and contextual differences. Further, regardless of validity, there are limitations to standardized instruments and these limitations will be reflected in the a priori domains and dimensions that are the foundation of our analytical framework.

Results

After searching the 3 colorectal cancer patient support and advocacy websites selected for this study, we found that each featured story meets all the inclusion criteria. All texts were downloaded from the internet into the NVivo analysis software, and analysis commenced in September 2020 on the 30 texts randomly selected for this study. We will complete the analysis in March 2021 and we aim to publish the results in mid-2021.

Discussion

The PROD method for systematically extracting relevant patient-reported data from free-text patient stories aims to maximize the benefits of rich detailed patient-perspective data

that can be drawn from patient narratives while framing findings to facilitate data triangulation with patient-reported results from PROs and PREs. Young-onset colorectal cancer is a contemporary issue in need of substantial research input [32,69]. We believe that this will be the first qualitative study to identify and describe the patient pathway from self-symptom identification to help-seeking through diagnosis, treatment, and into survivorship or palliation for people with young-onset colorectal cancer. Unsolicited autobiographical narratives offer a unique opportunity to collect patient-reported data that expose this real-world perspective [40], which is particularly valuable in this age of SARS-COV-2.

The findings from this study have the potential to provide information in a form that can modify habitual thinking and influence clinicians' cognitive biases [72,73] about age-related criteria for colorectal cancer risk assessment and diagnostic practice. Knowledge of the diagnostic and therapeutic experiences of patients with young-onset colorectal cancer may facilitate greater awareness of colorectal cancer symptoms in people younger than 50 years [74], promote patient proactivity in seeking help, and highlight the importance of identifying hereditary conditions that predispose young people to colorectal cancer [28,75,76]. There is significant potential for the patient-reported data from this study to make a real-world difference to people with young-onset colorectal cancer.

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Authors' Contributions

KL devised the study. KL, DFP, and YT undertook the detailed design of the study, in consultation with all authors. KL and DFP prepared the study materials. KL wrote the first draft of the manuscript. All authors contributed to and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

EORTC-QLQ-CR29: European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-29-item colon and rectum cancer-site specific
EQ-5D: European Quality of Life Questionnaire-5 dimension
FACT-C: Functional Assessment of Cancer Therapy-Colorectal
PRE: patient-reported experience
PRO: patient-reported outcome
PROD: personal recollections organized as data
SDI-21: Social Difficulties Inventory instrument-21 item

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Protocol

Feasibility of a Web-Based Platform (Trial My App) to Efficiently Conduct Randomized Controlled Trials of mHealth Apps For Patients With Cardiovascular Risk Factors: Protocol For Evaluating an mHealth App for Hypertension

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Abstract

Background: Mobile health (mHealth) interventions can improve health by improving cardiovascular risk factors, but their adoption in care by physicians and patients is untapped. Few mHealth apps have been evaluated in clinical trials, and due to the fast pace of technological development, those previously evaluated are often outdated by the time trial results are available. Given the rapid pace of change in this field, it is not feasible to rigorously evaluate mHealth apps with current methodologies.

Objective: The overall aim of this pilot study was to test the feasibility of using a web research platform called Trial My App to conduct efficient and rigorous web-based randomized controlled trials (RCTs) of mHealth apps relevant to patients with cardiovascular risk factors by evaluating an app that targets hypertension.

Methods: For this study, 200 participants with suboptimally controlled hypertension will be recruited through advertisements in newsletters, media, and the internet, as well as through referrals from their health care providers. Screening, consent, randomization, and collection of patient-important health confidence and self-management ability outcomes will be conducted online through the Trial My App research platform. Participants will be randomized into 2 groups: 100 that will use an mHealth app for tracking hypertension and 100 that will be considered as an educational control. All participants will complete questionnaires at 0, 1, 3 and 6 months after enrolment. A substudy to validate the method of blood pressure readings and the consistency of data entered through Trial My App will be conducted with 40 participants.

Results: The development of the Trial My App web platform has been completed. The creation of survey instruments has been completed in collaboration with our patient partners and advisory board. Recruitment is expected to begin in the first quarter of 2021; data collection and analysis are expected to be completed approximately 1 year after study commencement. Results will

be disseminated through conferences and publications. The primary outcomes of this study include the feasibility of conducting an RCT using the Trial My App platform by reporting recruitment, retention, and completion statistics. We will validate app-entered data with a standard 7-day home blood pressure measurement method. Lastly, the pilot, nonblinded RCT will assess the effectiveness of the mHealth app in improving the control of hypertension compared with the control of hypertension in the educational control group.

Conclusions: This study will determine if it is feasible to use the Trial My App web-based platform to evaluate the effectiveness of mHealth apps for patients with cardiovascular risk factors. As more mHealth apps are evaluated in RCTs, patients will be able to select apps that meet their needs and physicians will be able to make evidence-based recommendations to their patients for apps aimed at improving cardiovascular health.

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KEYWORDS

mHealth; mobile health; hypertension; app; patient-oriented; feasibility; cardiovascular disease; internet-administered; randomized controlled trial

Introduction

Smartphones provide continuous connection to the internet and can run sophisticated software apps. Globally, over 3.5 billion individuals own a smartphone [1]. The delivery of health care interventions via mobile phones is known as mobile health (mHealth). In 2017, 86% of the Canadians surveyed owned a smartphone or tablet and 78% downloaded mHealth and other types of apps to these devices [2]. Of the 66% of Canadians who indicated that they self-track at least one aspect of their health, 40% used electronic devices to do so and 32% reported using at least one mHealth app to monitor their health [2,3]. Other authors have reported that up to 58% of the smartphone users have downloaded an mHealth app [4] and 3.6 billion health apps were projected to be downloaded in 2017 [5]. Since smartphones are used to track health and are often continuously carried by users, mHealth apps allow for frequent data collection and feedback for behaviors that affect health, and interventions can be deployed to many users at a relatively low cost [6].

Health behaviors, including smoking, inactivity, and poor diet, are the major contributors to cardiovascular disease [7]. The American Heart Association has endorsed provider and patient self-management of cardiovascular disease risk factors as an effective form of secondary prevention [8]. Though the field of mHealth is in its infancy, early studies have shown that apps can improve health-related behaviors and reduce cardiovascular risk factors, largely through knowledge translation, by improving adherence to or by uptake of medications and behaviors that are known to be effective [9]. Randomized controlled trials (RCTs) report that apps can help patients lose weight [10-14], quit smoking [15], and increase physical activity [16]. An RCT of lifestyle-focused text messages reduced low-density lipoprotein cholesterol levels, systolic blood pressure, and BMI in patients with coronary heart disease [17], and a systematic review of RCTs of home blood pressure telemonitoring showed reduced systolic and diastolic blood pressure [18,19]. Thus, current data suggest that mHealth interventions can improve health by improving such cardiovascular risk factors, but their adoption in health care by physicians and patients is minimal. The 2014 National Physician Survey of licensed Canadian physicians reported that 83% did not recommend mobile apps to their patients, although 72% of the general practitioners and 53% of the specialists referred patients to websites and 50% used mobile apps such as e-textbooks or calculators in their practices [20]. We recently conducted a needs assessment survey of 113 physicians, which showed that over half of the physicians recommended apps to their patients despite their lack of clinical evidence. Many physicians in the survey indicated that they rely on personal opinions and patient recommendations to support their recommendations of apps despite wanting to choose apps that have a higher level of evidence such as RCTs or expert panel reviews. Our needs assessment also indicated that physicians do not recommend apps because they are not aware of them or do not have time to review their clinical efficacy. Without proper testing and evaluation, gaps in app development, including lack of expert involvement, poor user input validation, lack of evidence base, and poor quality of information, may pose clinical risks and safety harms to consumers [21]. With the growing interest in mHealth to monitor patient health, it is imperative that physicians stay informed and minimize their medical-legal risks by recommending apps with proven efficacy.

Despite this desire for better evidence, only a minority of the mHealth apps available in web-based app stores and commonly downloaded by patients have been evaluated in clinical trials, and due to the fast pace of technological development, those that have been evaluated are often outdated by the time trial results are available. Of the top 100 grossing health and fitness apps, researchers found that none had been formally evaluated in clinical studies [22]. Multiple reviews have highlighted the lack of quality research evidence on the efficacy of apps [9,23-25]. mHealth research has several unique challenges contributing to this problem. Chiefly, technology is rapidly progressing and equally rapid techniques for evaluating such technology are needed. Testing must be cost-efficient, given the limited funding for evaluating mHealth interventions compared with pharmacological interventions or medical devices [9]. These constraints limit the evidence base and the incorporation of apps in patient care.

The rapid proliferation of smartphone technology provides untapped potential to improve the efficient conduct of such research. Using internet-enabled devices to perform research can potentially (1) accelerate large-scale enrolment by contacting and screening potential participants who do not frequently interact with the health system through clinics or hospitals and (2) reduce costs and improve participation by allowing frequent and inexpensive data collection directly from participants. With the rapid development of internet-connected and smartphone-connected consumer devices that can collect biometric data, smartphones also have the potential to collect objective, real-time data directly from patients [26].

Methods

Overview

We have developed an innovative research approach using a web-based platform called Trial My App, which is designed to perform efficient trials of apps relevant to patients with cardiovascular risk factors. In our initial phase, we engaged an advisory board of patients to codevelop criteria for app and trial outcome selection, which will be used to support further deployment of Trial My App. The patients used apps for goal setting, decision-making, information sharing, and empowerment in managing their health. From these themes, we derived a series of survey questions to determine if an app was meeting these outcomes, and we included this survey in the pilot trial. Content analysis by the advisory board also indicated that patients considered a number of favorable technical factors when selecting their mobile apps: (1) relevant feedback on progress, (2) security, (3) low cost, (4) customizability, (5) usability, (6) information credibility, (7) multifunctional app integration, and (8) interdevice compatibility. The undesired features were as follows: (1) unreliable technology, (2) distraction, (3) collection of personal information, and (4) learning curve. These criteria were applied to shortlist apps for hypertension, and through discussion with the research team and patient partners, we identified Sphygmo BP as the intervention app for this pilot trial (Multimedia Appendix 1). Sphygmo BP was created in partnership with the University of Alberta to help patients with hypertension to self-manage their blood pressure. The app tracks and averages blood pressure, glucose levels, weight, temperature, respiratory rate, and oxygen saturation. It also includes educational components to facilitate better patient awareness of management strategies for blood pressure and is designed to facilitate patient-physician communication through telemonitoring.

Objectives

The primary objective of the study is to test the feasibility of conducting an RCT of an mHealth hypertension-tracking app using the Trial My App platform. The secondary objective is to test if the use of the Sphygmo BP app reduces blood pressure in patients with suboptimally controlled hypertension when compared with the use of a website with information on hypertension. It would be valuable for patients and physicians to know whether the use of the app is likely to result in reductions in blood pressure that have been shown to reduce clinical outcomes.

Study Design

This is a pilot, nonblinded parallel-group RCT, comparing the use of a hypertension app versus an education control in participants with suboptimally controlled hypertension. Outcomes include feasibility, clinical, and patient-important endpoints.

Eligibility Criteria

The inclusion criteria are as follows: (1) age over 18 years, (2) diagnosis of hypertension, (3) interested in using an app for hypertension management, (4) access to a smartphone with internet connection, and (5) access to a blood pressure monitoring device (in home or community setting, eg, pharmacy). The exclusion criteria are as follows: (1) participant-reported blood pressure within target (target range for patients with diabetes is systolic blood pressure <130 mm Hg and diastolic blood pressure <80 mm Hg; for those without diabetes, target range is systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg according to Hypertension Canada guidelines [27]) within the 2 weeks prior to enrolment, (2) emergent hypertensive concerns (potential participants with systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥120 mm Hg will be advised to seek medical attention and will be excluded), (3) current use of a mobile app for hypertension management, (4) living outside of Canada, (5) pregnancy, and (6) unwillingness or inability to give informed consent.

Recruitment

The primary study site will be the Health Information Research Unit at McMaster University in Hamilton, Ontario. A combination of passive and active recruitment strategies will be used. A variety of recruitment materials will be distributed by a research assistant throughout the community and outpatient or specialty clinic waiting rooms. These materials include videos, papers, and web-based posters/postcards, emails, as well as posts advertising on social media. Social media recruitment on Facebook, Twitter, and Google Network will consist of general posts and targeted ads using Facebook Ads Manager. Partner newsletters and websites include Hamilton Academy of Medicine, McMaster Institute for Research on Aging, McMaster Okanagan Charter, and RSearch. We will also engage clinicians and their administrative staff within the McMaster Department of Medicine, Hamilton Health Sciences outpatient clinics, Queen Square Family Health, and other community, primary, and specialty clinics in Ontario to identify potential participants and invite them to register with Trial My App to determine if they want to participate in the trial. Snowball sampling through participants and personal networks may also be used. Interested candidates will be provided a link or a quick response code to access the website within the marketing materials. They could also contact our research assistant through a dedicated Trial My App email account if they prefer the initial contact by email or phone.

All trial stages, including screening, consent, randomization, and collection of clinical and patient-important outcomes data, will be performed virtually using the Trial My App platform. This phase includes a substudy to validate the web-based

collection of patient data. Ethics approval of the substudy will be sought separately. Participants will be asked to register on the Trial My App site with an email and a password. The informed consent form is in Multimedia Appendix 2. Once they have electronically consented to using the web app, they will complete a user profile questionnaire and be screened for participation in the pilot trial in a subsequent survey. Multimedia Appendix 3 contains all user baseline, screening, and follow-up questionnaires. If participants meet inclusion criteria, they will be asked to electronically consent to take part in the pilot trial and provide data at 0, 1, 3, and 6 months. The participant flow is shown in Figure 1. The diagram of the app flow is shown in Figure 2.

Figure 1. Participant flow diagram. RCT: Randomized controlled trial; mHealth: mobile health.

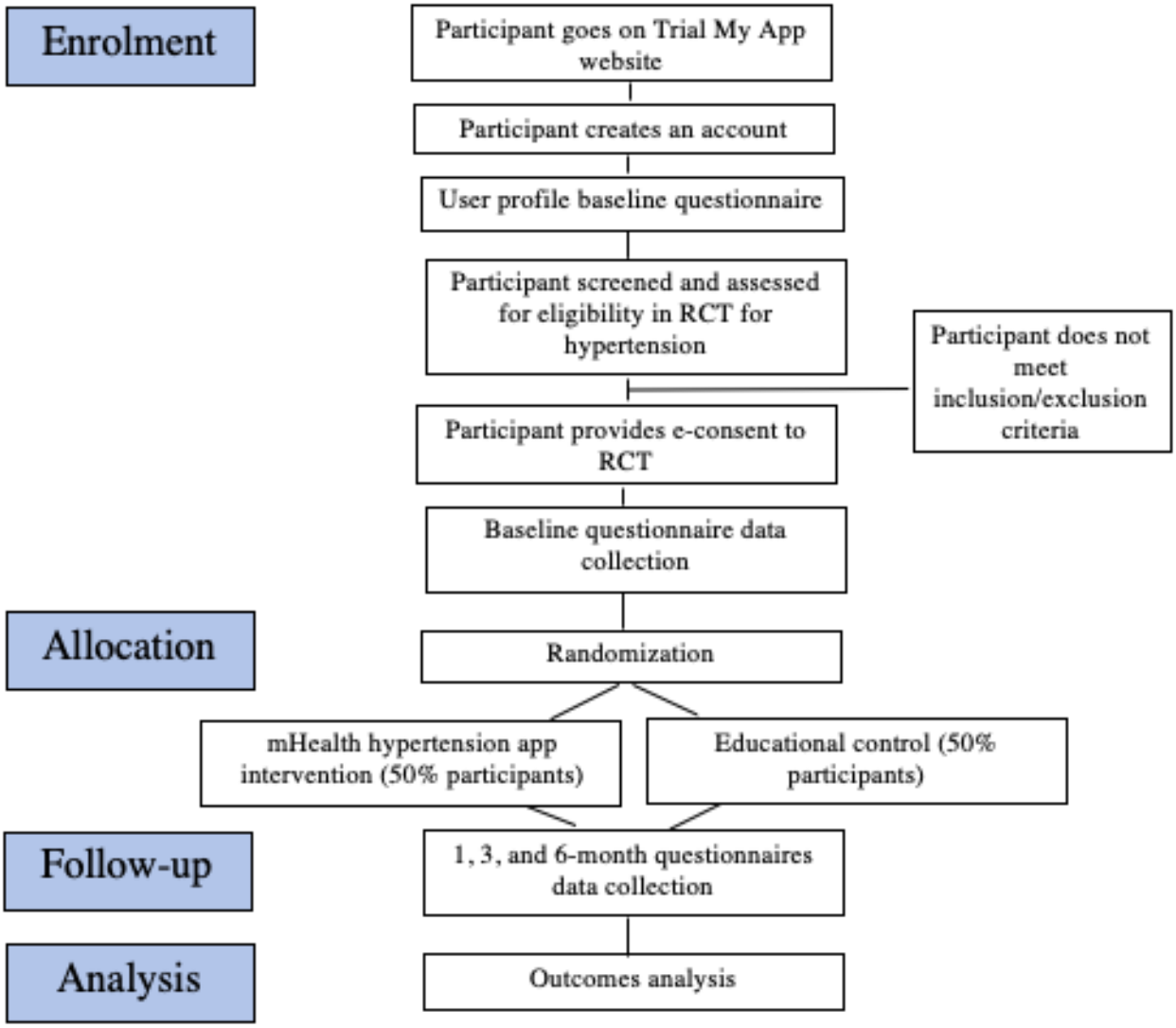
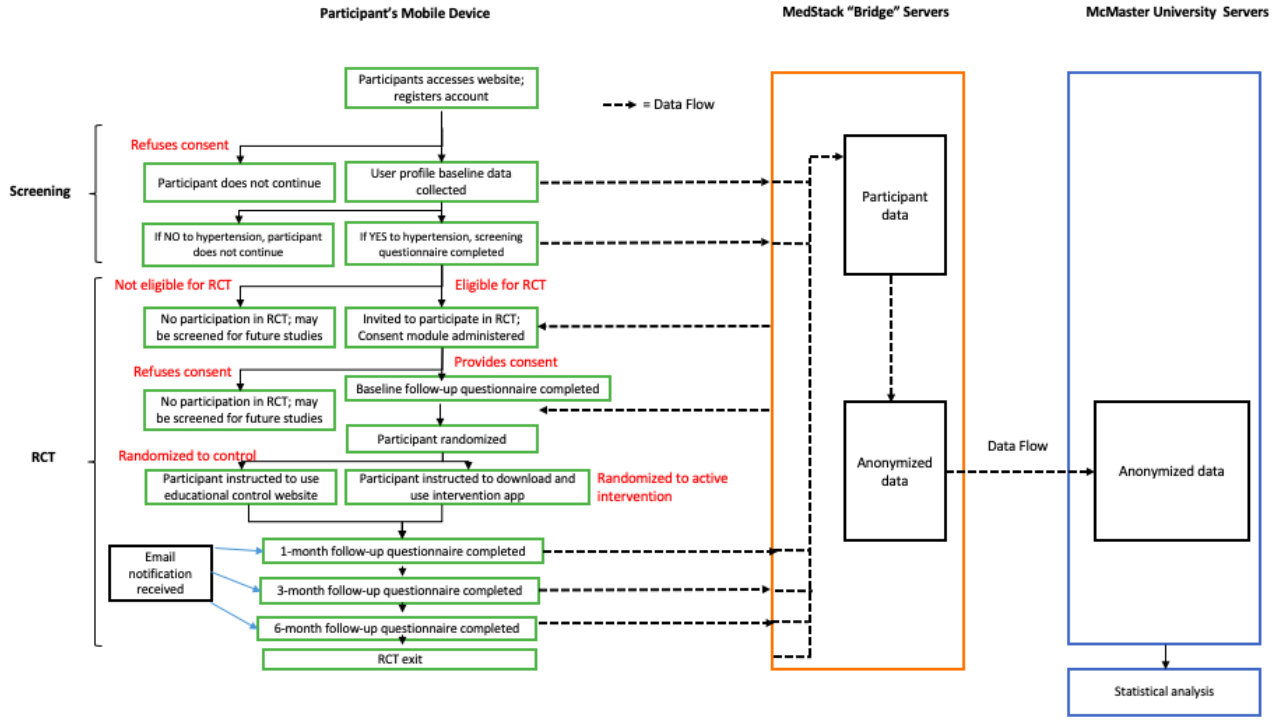


Figure 2. Trial My App web flow diagram. RCT: randomized controlled trial.



Sample Size

In the feasibility study, at least 80% of the participants in each group who successfully complete the final questionnaire within 1 year of trial start will be considered as the primary feasibility outcome. To estimate a completion rate of 80% in each group within a margin of error of 8% and with a confidence interval of 95%, we estimated a sample size of at least 100 participants in each group, and 200 participants in total is required. With a sample size of 200 participants in total (ie, 100 per group), we will have 80% power to detect a reduction in blood pressure of 8 mm Hg, which is considered a minimally clinically important difference. Assuming an 18 mm Hg standard deviation in systolic blood pressure, to detect an 8 mm Hg difference between groups with a power of 80% and a type I error of 5%, we would ideally require 81 participants in each arm [28]. Accounting for a 20% dropout rate, we aim to enroll 100 participants in each arm. We recognize that the selected app may not result in such a large difference in the systolic blood pressure, but the calculation is to guide our recruitment targets. If a difference in the blood pressure is found, we will be able to inform patients and physicians that this app may have a major impact on clinical outcomes such as heart attack, stroke, and congestive heart failure.

Intervention

After screening and baseline questionnaires, participants will be randomized using a web-based blocked randomization list of 4, 6, or 8 block sizes and a 1:1 allocation ratio. The intervention group will be instructed to download the Sphygmo BP app via a link provided within the Trial My App. The control group will receive a link to the Heart and Stroke foundation website, which includes information on hypertension management and measuring blood pressure [29]. All participants are expected to continue to receive usual care by their physician, including any anti-hypertensive medication and lifestyle changes.

Data Collection

At 1, 3, and 6 months after enrollment into the RCT, Trial My App will send email reminders with a link to follow-up questionnaires to all participants to assess self-reported blood pressure and several patient-reported outcomes. Completing follow-up will be defined as answering the questionnaire within 7 days of receipt of the questionnaire notification via email. To encourage participation and reduce attrition, participants will receive a Can $10 (US $1=Can $1.27) electronic gift card for each completed assessment and an additional Can $10 gift card if they complete all 4 follow-up assessments.

Outcomes

Feasibility Outcomes

Our primary goal at this stage is to determine whether the Trial My App platform can be used to conduct RCTs evaluating mHealth apps by the ability to complete an adequately powered RCT of least 80 participants in each group that successfully complete the study and the 6-month questionnaire within an arbitrarily defined reasonable time frame of 12 months. The remaining feasibility outcomes and associated indicators are shown in Table 1.

Table 1. Feasibility outcomes and indicators.

Outcome	Definition	Indicator	Minimum required sample size
Participation completion	Number of participants who successfully complete the final questionnaire within 1 year of trial start	80% out of total randomized participants in each group	100 participants per group is needed to achieve a margin of error of 8% with a 95% confidence level
Eligibility	Proportion of participants who sign up that meet eligibility criteria	At least 50% of responses to baseline and screening questionnaires are eligible	200 participants in total to achieve a margin of error of 7% with a 95% CI
Recruitment	Number of eligible participants recruited and consented	At least 50% of target sample size of 200 randomized within 6 months	200 participants in total to achieve a margin of error of 7% with a 95% CI
Retention	Proportion of withdrawal and dropouts after recruitment	Less than 20% of the participants lost to 6-month follow-up	200 participants in total to achieve a margin of error of 5.5% with a 95% CI
Outcome acceptability	Follow-up questionnaire completion rates	70% of the questionnaires that are submitted within 7 days of notification reminder	200 participants in total to achieve a margin of error of 6.3% with a 95% CI
Intervention acceptability	Frequency of app usage in the intervention group	Answers to frequency of use and features used questions in follow-up questionnaires	N/A[a]
Appropriateness of data collection processes	Completeness of data	50% of the questionnaires completed and less than 20% of the missing response rates in each questionnaire	N/A

[a]N/A: not applicable.

Pilot Efficacy Outcomes

The secondary objective of the RCT is to conduct a trial comparing the intervention hypertension app with a control group. The main outcome is clinical changes in blood pressure based on self-reported answers in the questionnaires. The remaining patient-reported outcomes and their associated indicators from baseline to 6 months are shown in Table 2. Adherence to hypertension self-care behaviors will be scored using the validated H-SCALE (Hypertension Self-Care Activity Level Effects) [30] and health care self-efficacy will be scored using the validated Health Confidence Score [31]. Similar outcome measures (eg, medication adherence, diet, physical activity) have been used in other studies of hypertension apps and measure hypertension-specific self-efficacy scores [32].

Table 2. Efficacy outcomes and indicators.

Outcome, definitions	Indicator
Clinical assessment	
Difference in mean change in blood pressure from baseline to 6 months between groups	Statistically significant difference in mean change in systolic blood pressure measurements (defined as $P<.05$ using a Pearson test)
Proportion of patients at their recommended blood pressure	Blood pressure measurements compared to standard ranges
Self-management ability	
Difference in mean change of self-managing behaviors	H-SCALE[a] score and statistically significant correlations with blood pressure at 95% CI
Difference in mean change in feelings of self-efficacy	Frequency distribution and mean of Health Confidence Score at 95% CI
Patient-reported outcomes	
Descriptive analysis of patient-oriented experiences between groups at baseline and 6 months	Agreeability with goal setting, decision making, sharing data, and empowerment statements in questionnaires developed from the advisory board themes (at 95% CI)

[a]H-SCALE: Hypertension Self-Care Activity Level Effects.

Statistical Analysis

Descriptive statistical analysis will be performed on the data set using appropriate statistical methods to measure feasibility. Efficacy outcomes will be compared between the intervention and control groups by using logistic regression.

Ethics Approval

This study has received approval from the Hamilton Integrated Research Ethics Board, #8039. This is a minimal risk study and the subject matter is not likely to be distressing to participants. Participation in this study may be inconvenient, taking about 10-20 minutes to complete at each timepoint (baseline, 1, 3, and 6 months). In the event of possible emotional distress,

participants will be able to discontinue the use of the web app. Participant identifiers will be replaced with a code number; therefore, the data that researchers will access are not identifiable. As the intervention app is designed to track blood pressure to facilitate management and communication and participants will continue to receive usual care, no other harms are foreseen. Participants will be asked to complete an electronic consent form. The research team will have access to the final trial data set and ensure that all privacy policies are strictly maintained. Data will be securely stored on a MedStack server built into the Trial My App platform. MedStack is a health data privacy compliance automation platform that builds, measures, and actively manages compliance and provides secure, flexible, and single-tenant cloud infrastructure tailored to Trial My App. Medstack complies with Ontario's Personal Health Information Privacy Act legislation. The information collected will be anonymized and encrypted before transferring to a secure server and firewall-protected network on a password-protected computer located at the Health Information Research Unit at McMaster University.

Results

Trial Progress

The development of the Trial My App web platform has been completed with a software developer and has undergone functionality and remote usability testing to uncover technical bugs and improve the design. The creation of survey instruments has been completed in collaboration with our patient partners and advisory board. Recruitment is expected to begin in the first quarter of 2021; data collection and analysis are expected to be completed approximately 1 year after study commencement. Dissemination of results will occur through conferences and publications.

Patient Engagement Strategy

Two patients with lived experience of cardiovascular diseases are collaborating as partners on the research team and additional patients serve on an advisory board overseeing the development of Trial My App. They have identified criteria for selecting apps to evaluate in future RCTs and aided in developing outcomes that are relevant to patients managing their cardiovascular risk factors with apps. Key contributions of our patient partners include joining bimonthly meetings with the research team to discuss project planning, developing questions for and taking part in the advisory group, testing the usability of Trial My App, reviewing and contributing to publications and other knowledge translation outputs, and contributing to production and circulation of recruitment materials. Any required training on these skills is provided by the research team.

Discussion

To our knowledge, this study is the first of its kind to create a web-based platform to conduct RCTs of mHealth apps for cardiovascular risk. A limitation of this methodology is the collection of self-report data as it is subject to several response biases, including social desirability, recall, or measurement error biases. The research team will include an additional substudy to measure the concordance of self-reported blood pressure measurements submitted via the Trial My App web app and the reference standard of 7-day average home blood pressure measurements [33]. A subgroup of participants will measure their blood pressure by using identical automatic home blood pressure monitoring devices 4 times daily for 1 week. The research team anticipates that participants will use the apps to varying degrees to help them manage their health, as they would normally; assessing these elements are beyond the scope of the study. The investigators expect that the pilot findings will demonstrate the feasibility of gathering valid patient-reported outcomes via web-based questionnaires that can be applied more broadly to other clinical studies. The findings of this trial may inform the evaluation of other mHealth apps for other conditions at a relatively low cost and more quickly than using traditional RCT methods. These results will also provide useful information for app developers who are interested in testing their apps for clinical effectiveness as well as patients and clinicians who are interested in incorporating effective mHealth apps into their care.

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Authors' Contributions

CL, VB, and IG conceived the original study idea. CL is the principal investigator and drafted the manuscript. CL is the grant holder. VB, IG, JV, JDS, MG, and EV provided clinical and feasibility testing expertise. JM provided statistical expertise. MB and our advisory board provided help with the development of questionnaires and patient-relevant outcomes. ZM (ZLTechnovation) provided expertise in the development of the web platform. All authors contributed to the review of the study protocol and approved the final manuscript.

Conflicts of Interest

VB reports honoraria and an educational grant from Pfizer, honoraria from Bayer, and loan of devices from Apple for research purposes.

Multimedia Appendix 1
Description of the blood pressure management app used for the study.
[DOCX File , 508 KB - resprot_v10i2e26155_app1.docx]

Multimedia Appendix 2
Information and consent form.
[DOCX File , 64 KB - resprot_v10i2e26155_app2.docx]

Multimedia Appendix 3
Study instruments.
[PDF File (Adobe PDF File), 170 KB - resprot_v10i2e26155_app3.pdf]

Multimedia Appendix 4
Peer review report.
[PDF File (Adobe PDF File), 446 KB - resprot_v10i2e26155_app4.pdf]

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Abbreviations

mHealth: mobile health
RCT: randomized controlled trial

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Corrigenda and Addenda

Correction: The Effect of Question Order on Outcomes in the Core Outcome Set for Brief Alcohol Interventions Among Online Help-Seekers: Protocol for a Factorial Randomized Trial

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Correction of: https://www.researchprotocols.org/2020/11/e24175

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In "The Effect of Question Order on Outcomes in the Core Outcome Set for Brief Alcohol Interventions Among Online Help-Seekers: Protocol for a Factorial Randomized Trial" (JMIR Res Protoc 2020;9(11):e24175) the authors noted one error.

The protocol included an appendix which contains questionnaires which have been proposed to measure a core outcome set for brief alcohol interventions. However, rather than including their own appendix, the authors acknowledge that they should have referenced the Open Science Framework project which contains materials for the core outcome set.

The file labelled as Multimedia Appendix 1 in the originally published article has been removed from the corrected version. In-text references to this appendix have been replaced by a citation to Reference 18, which contains a link to the Open Science Framework project. Accordingly, the file labelled as Multimedia Appendix 2 in the originally published article has renamed Multimedia Appendix 1 in the corrected version. In-text references to Multimedia Appendix 2 have been changed to Multimedia Appendix 1. These changes affect the text in the following places:

In the Methods section, under "Trial Design and Interventions", the sentence:

> *The 10 COS outcomes will be divided into 4 clusters (for details, please see Multimedia Appendix 1)*

has been replaced by:

> *The 10 COS outcomes will be divided into 4 clusters [18]"*

Under "Setting and Participants", the sentence:

> *An example of an advert is shown in Figure 1, and study information presented to individuals who click on the advert can be found in Multimedia Appendix 2.*

has been changed to:

> *An example of an advert is shown in Figure 1, and study information presented to individuals who click on the advert can be found in Multimedia Appendix 1.*

Likewise, the sentence:

> *Individuals will be asked to read the study information presented when the advert is clicked on and confirm that they are at least 18 years old and consent to take part in the trial (see Multimedia Appendix 2).*

has been changed to:

> *Individuals will be asked to read the study information presented when the advert is clicked on and confirm that they are at least 18 years old and consent to take part in the trial (see Multimedia Appendix 1).*

Under "Outcomes", the sentence:

The primary outcomes are the 10 outcomes of the COS measured using the recommended questionnaires (Multimedia Appendix 1)

has been changed to:

The primary outcomes are the 10 outcomes of the COS measured using the recommended questionnaires [18]

The correction will appear in the online version of the paper on the JMIR Publications website on February 1, 2021, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: mHealth-Supported Delivery of an Evidence-Based Family Home-Visiting Intervention in Sierra Leone: Protocol for a Pilot Randomized Controlled Trial

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Related Article:

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In "mHealth-Supported Delivery of an Evidence-Based Family Home-Visiting Intervention in Sierra Leone: Protocol for a Pilot Randomized Controlled Trial" (JMIR Res Protoc 2021;10(2):e25443) the authors noted one error.

The name of the last author in the originally published paper was listed as *"Theresa Betancourt"*. This has been corrected to *"Theresa S Betancourt"*.

The correction will appear in the online version of the paper on the JMIR Publications website on February 4, 2021, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Self-Administered Behavioral Skills-Based At-Home Virtual Reality Therapy for Chronic Low Back Pain: Protocol for a Randomized Controlled Trial

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In "Self-Administered Behavioral Skills–Based At-Home Virtual Reality Therapy for Chronic Low Back Pain: Protocol for a Randomized Controlled Trial" (JMIR Res Protoc 2021;10(1):e25291), the authors noted five author names missing middle initials.

In the originally published paper, the list of authors appeared as follows:

> *Laura Garcia, Beth Darnall, Parthasarathy Krishnamurthy, Ian Mackey, Josh Sackman, Robert Louis, Todd Maddox, Brandon Birckhead*

The list has been corrected as follows:

> *Laura M Garcia, Beth D Darnall, Parthasarathy Krishnamurthy, Ian G Mackey, Josh Sackman, Robert G Louis, Todd Maddox, Brandon J Birckhead*

The correction will appear in the online version of the paper on the JMIR Publications website on February 12, 2021, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Protocol

Initiatives, Concepts, and Implementation Practices of FAIR (Findable, Accessible, Interoperable, and Reusable) Data Principles in Health Data Stewardship Practice: Protocol for a Scoping Review

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Abstract

Background: Data stewardship is an essential driver of research and clinical practice. Data collection, storage, access, sharing, and analytics are dependent on the proper and consistent use of data management principles among the investigators. Since 2016, the FAIR (findable, accessible, interoperable, and reusable) guiding principles for research data management have been resonating in scientific communities. Enabling data to be findable, accessible, interoperable, and reusable is currently believed to strengthen data sharing, reduce duplicated efforts, and move toward harmonization of data from heterogeneous unconnected data silos. FAIR initiatives and implementation trends are rising in different facets of scientific domains. It is important to understand the concepts and implementation practices of the FAIR data principles as applied to human health data by studying the flourishing initiatives and implementation lessons relevant to improved health research, particularly for data sharing during the coronavirus pandemic.

Objective: This paper aims to conduct a scoping review to identify concepts, approaches, implementation experiences, and lessons learned in FAIR initiatives in the health data domain.

Methods: The Arksey and O'Malley stage-based methodological framework for scoping reviews will be used for this review. PubMed, Web of Science, and Google Scholar will be searched to access relevant primary and grey publications. Articles written in English and published from 2014 onwards with FAIR principle concepts or practices in the health domain will be included. Duplication among the 3 data sources will be removed using a reference management software. The articles will then be exported to a systematic review management software. At least two independent authors will review the eligibility of each article based on defined inclusion and exclusion criteria. A pretested charting tool will be used to extract relevant information from the full-text papers. Qualitative thematic synthesis analysis methods will be employed by coding and developing themes. Themes will be derived from the research questions and contents in the included papers.

Results: The results will be reported using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews) reporting guidelines. We anticipate finalizing the manuscript for this work in 2021.

Conclusions: We believe comprehensive information about the FAIR data principles, initiatives, implementation practices, and lessons learned in the FAIRification process in the health domain is paramount to supporting both evidence-based clinical practice and research transparency in the era of big data and open research publishing.

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KEYWORDS

data stewardship; FAIR data principles; health research; PRISMA; scoping review

Introduction

Advancement in information communication technology is impacting the health ecosystem's technological and analytical capabilities to store, curate, share, and analyze data from standard and nonstandard sources [1]. In the human health domain, big data may be obtained multidimensionally from records in health care facilities, biomedical research institutions, population surveys, surveillance, and patients [2]. Together, professional data management and big data analytics offer high-potential knowledge to transform health care delivery and life sciences research. The availability of data from numerous sources and advanced analytics promise to improve the prevention, diagnosis, and treatment of diseases and the well-being of individuals and societies [3]. However, health data are often stored in independent noncommunicating silos, where open data sharing remains a challenge [4].

Digitalization brings opportunities and concerns in health care data processing. Despite many potential benefits, it also poses potential threats, such as breaches of privacy, disinformation and misinformation, and cyberattacks [5]. There is a need to balance an individual's rights to the protection of personal data from potential threats with the institutions' needs to process these data. The EU General Data Protection Regulation (GDPR) informs this context. The recent reform in the GDPR focuses on the rights and freedoms of people and the establishment of rules for the processing of personal data [6]. The concerns about privacy and personal data protection resulted in reforms of the existing legislation in the European Union. The GDPR aims to reform the existing measures on the topic of personal data protection of EU citizens with a strong input on the rights and freedoms of people and the establishment of rules for the processing of personal data [7]. OpenEHR is a standard that embodies many principles of interoperable and secure software for electronic health records [8].

The European GDPR is the most recent data regulatory framework as of September 2020 and has implications on the ethical sharing of research data [9]. As the EU population continues to be more conscientious about the data protection regulations for citizens' sensitive personal data (eg, EU GDPR), patients and the general public are becoming more aware of the use of their personal data [10]. The principle of data minimization implies that personal data shall be adequate, relevant, and limited to only what is necessary in relation to the purposes for which they are processed [7].

Boeckhout et al [11] highlighted that the GDPR also ensures that the terms of data use, data subjects, and rights in further processing are clearly defined. It has been suggested that FAIR (findable, accessible, interoperable, and reusable) data and metadata standards could help facilitate compliance with the principle of data minimization by allowing for an assessment of which data to reuse based on an analysis of metadata [11].

Beyan et al [12] have shown that an enormous amount of usable health data is currently imprisoned inside the organizational territories of hospitals, clinics, and within patients' devices due to ethical concerns and data protection rules. However, data reuse, even if secondary to data collection and first analysis, may drive more extensive and valuable new research directions than intended for the primary purpose [13]. In Germany, for example, the Medical Informatics Initiative aims to use clinical data to improve health research and facilitate the digitalization of medicine on a national scale [14]. France has also launched the Health Data Hub with similar aims [15]. Currently, researchers and stakeholders are working on infrastructure to support distributed and federated solutions to make the data, software, or digital objects smart in their original silos [12]. Europe would benefit from an integrated infrastructure in which data and computing services for big data can be easily shared and reused, and plans are underway to establish the Europe Research Area for this purpose [16]. Finally, funding agencies and open science advocates are insisting on adherence to open science policies and strategies to manage publicly funded research processes and outcomes [17]. The Health Research Board (HRB) of Ireland, for example, has put in place the HRB Policy on Management and Sharing of Research Data, which requires research to be open. This policy is applicable to data gathered and generated in whole or in part from HRB-funded research, starting from January 1, 2020.

The need for good data stewardship among different stakeholders in scientific research is the basis on which the FAIR data principles (findability, accessibility, interoperability, and reusability) were coined in 2014 by the FORCE11 (The Future of Research Communication and e-Scholarship) community [18,19]. These principles were formed to serve as guidance to achieve better research data stewardship practices in the life sciences [20]. They also serve as a set of widely applicable "permissive guidelines," offering a basis for developing flexible community standards for the health data community [21]. Since research papers and data products are now being recognized as key outcomes of the scientific enterprise, various stakeholders in scientific and governmental institutions are increasing their efforts toward establishing more comprehensive plans for data management and stewardship [16,22]. Adherence to the FAIR principles has been shown to lead to a more transparent approach to data stewardship, which in turn contributes to the maximal use and reuse of data in the scientific community [23]. Consequently, adherence to the FAIR data principles is more frequently expected by researchers, publishers, funding agencies, and policy makers [24]. Achieving data FAIRness also enhances the discovery of, access to, integration of, and analysis of scholarly and scientific data [25].

In 2020, Vesteghem et al [26] outlined data sharing challenges that make data aggregation costlier and more labor intensive in precision oncology. Obstacles include legal issues that hinder data sharing between research groups, privacy issues, ethical issues, data storage issues, and system incompatibility issues [26]. Various initiatives have been launched to tackle these challenges by standardizing and facilitating the implementation of data pipelines [27,28]. Although the application of the FAIR

data principles in data stewardship is a fairly new approach in health research, it has been shown to be instrumental in addressing these challenges in the field of precision oncology [14]. It has also been suggested that FAIR data may be useful in addressing the need to generate and share high-quality data to facilitate the World Health Organization elimination goals for neglected tropical diseases [29]. Much work has been conducted to implement the FAIR principles in other domains, such as computational workflows [30], food and nutrition [31], materials science [32], and oceanography [33].

The aims for conducting this work are to (1) provide an overview of applications of the FAIR data principles that are focused on health data research and (2) map out the existing evidence accordingly.

Methods

Study Framework

This scoping review will adopt the framework outlined by Arksey and O'Malley [34]. The authors will employ this method to quickly map key concepts underpinning the research area of interest and the main sources and types of evidence available. Our work is focused on an area that we have not seen being reviewed comprehensively. The framework includes the following steps: (1) identifying the research question; (2) identifying relevant studies; (3) selecting the studies; (4) charting the collected data; and (5) collating, summarizing, and reporting the results.

Stage 1: Identifying the Research Questions

We have already conducted a pilot overview of the existing literature as an informal desk review and literature exploration. This overview included published works in PubMed, Google Scholar, and Web of Science. The medical and public health research librarian used the FAIR data principles' keywords to match medical subject headings (MeSH) used to tag PubMed peer-reviewed literature, along with combinations of terms used in clinical research, public health, health care, pharmacology, and patient data. Multimedia Appendix 1 enumerates the results of these advanced searches.

As part of the ongoing evidence synthesis from medical and human health research journal articles that used FAIR data markup, the bibliographies of key papers were scrutinized for other complementary publications, and those articles were added to the PubMed collections shared with the authors. Further, as the key FAIR data and health articles inspired new citations, often authored by similar consortia of writers or networks of researchers, the newer citing articles were added to the stage 1 collection to demonstrate possible progress in the field of shared or open medical data. Recurrent alerts were set up to capture newly published literature on PubMed, Google Scholar, and Web of Science (Multimedia Appendix 1). White papers, conference publications, guidelines, and other grey literature from the Google and Web of Science alerts were scrutinized and added to a Dropbox of publications for the principal researchers to review. Close examination of key references in bibliographies and citing articles to gauge the impact of FAIR shared data on ensuing research and health practice will be followed as part of the secondary analysis. Publications from 2020 focusing on open sharing of COVID-19 data will be of particular importance in gauging the impact of the FAIR principles on human health data in pandemics.

Our informal desk review has shown that many approaches used in the implementation of the FAIR data principles are applied to the life sciences domain [18]. We have also seen in the literature that there is indeed a growing interest in following the phases of the research life cycle when conducting research [35,36]. These findings resonate with the authors' motivation to better understand the approaches used in the implementation of the FAIR data principles and the impact that these implementations may have on the way research in health will be conducted. These findings are also the basis on which the research questions were formulated. As we formulated the research questions, we decided that the review should only include works that show either an actual approach to implementing the FAIR data principles in the health domain or the recorded results of the implementation of the FAIR data principles. The review will exclude works that introduce or give an overview of the FAIR principles. Works that show the implementation of the principles in a domain other than health will also be excluded.

As we intend to conduct this exploratory review in an iterative manner, further refinement of the research questions may become necessary. Close examination of key references in bibliographies and citing articles to gauge the impact of shared data on ensuing research and health practice will be followed as part of the secondary analysis. All proposed refinements of the research questions and search methods will be scrutinized by the authors prior to approval. We will also provide comprehensive provenance information on changes in the protocol to be fully transparent.

Objectives and Research Questions

The general objective of this protocol is to conduct a scoping review to identify concepts, approaches, implementation experience, and lessons learned from the FAIR data principle initiatives in the health domain. The following research questions (RQs) have been formulated to meet the objective of the scoping review:

- RQ 1: What approaches are being used or piloted in the implementation of the FAIR data principles in the health data domain since the conception of these principles in 2014?
- RQ 2: What are the challenges and risks regarding the approaches used in the practical implementation of the FAIR data principles in the health data domain?
- RQ 3: What are the suggested concepts and approaches to mitigating the concerns of the implementation of the FAIR data principles in the health data domain?
- RQ 4: Which are the active public and private research and service networks involved in the implementation of the FAIR data principles in the health data domain?
- RQ 5: What are the reported outcomes for data sharing, data reuse, and research publication after the implementation of the FAIR data principles in the health data domain?

Stage 2: Identifying Relevant Studies

With the aid of an experienced research librarian, at least two researchers will identify relevant studies from 3 primary electronic databases: PubMed, Web of Science, and Google Scholar. In addition to those, relevant grey literature from existing networks, relevant organizations, and conferences as well as the reference lists from potential papers will be searched. The keywords for the scoping review search strategies have been categorized tentatively to terms related to the FAIR data principles, data sharing, and health. Although refinement of the selected MeSH terms are possible, open terms have been proposed for the construction of the search strategy of this protocol. The Boolean operators "AND" and "OR" will be used to guide the search strategy. The following descriptors and keywords and their combinations were used to construct the strategies: "open science," "data collection," "data provenance," "open access publishing," "data*," "repositor*," "registr*," "pharma*," "health*," "research," "biomedical research," "data management," "FAIR data principles," "FAIR principles," "FAIR guiding principles," "Data steward*," "Data management systems," "findable," "findability," "access," "accessibility," "interoperable," "interoperability," "reusable," "reusability" (Multimedia Appendix 1).

The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews) reporting guidelines will be used for reporting the findings [37]. The operational definition of "health" for this scoping review is based on the European Union's 2018 General Data Protection Regulation and the health ecosystems components framed by the World Health Organization [2,6]. Accordingly, health data in this protocol are defined in the context of data from service and research practice in health services (clinical records, electronic health records and electronic medical records, prescribing, diagnostics, laboratory, insurance, disease surveillance, immunization records, public health reporting, vital statistics, registries, clinical trials, clinical research, and public health research).

As an inclusion criterion, we will consider literature published between January 1, 2014, and December 31, 2020. The start date in 2014 is chosen due to the fact that FAIR concept initiatives and official publications became first available in that year. Moreover, to be included as a potential paper, the literature needs to be published in English and include the scope of FAIR principle applications in the health domain (defined by the operational definition). Literature published before 2014, in a language other than English, and in domain areas other than health or the operational definition of health will be excluded. All search results from online databases and grey literature sources will be exported to a reference management software to eliminate duplications. Unique search results will be exported to a screening tool to facilitate an independent screening process for the potential papers.

Stage 3: Study Selection

Rayyan software (Qatar Computing Research Institute) has been chosen as the primary screening and data extraction tool to expedite the initial screening of abstracts and titles using a semiautomated process while incorporating a high level of usability. This software supports research teams in the easier exploration of literature searches within a shorter time as well as in sharing and comparing individual researchers' decisions to include or exclude studies [38]. According to the inclusion and exclusion criteria, nonrelevant studies will be excluded from the study at this point. If the relevancy of the publication is unclear from the title or abstract, the reviewer will read the full publication to determine the eligibility of the publication. Any further changes to the search criteria to improve the search findings will be made at this stage as necessary. In the next step, the eligible publications screened in the first stage will be independently read in full by 2 researchers to further determine the relevance of the publication content to the research questions. When agreement cannot be reached during the initial screening and full-text screening stages, an independent researcher will be consulted. A PRISMA flow diagram will be generated to provide visual data for the selection process [37].

Stage 4: Data Charting

A data-charting form will be used by the reviewers to determine which variables to extract. The form is flexible for continuous updating in an iterative manner during the data-charting process, but any changes will be tracked. The descriptive analytical approach, as described by Arksey and O'Malley [34], will be employed in the data collection process. In this process, the researchers will critically examine the identified articles and documents that meet all of the eligibility criteria and extract the relevant data from each publication using the pretested charting form. The data will be organized into a chart with 2 main sections to describe the overview or summarized basic information of the publication (metadata) and the research questions based on our objectives (Table 1). Initially, 2 authors will independently extract data from the first 5 included studies using the data-charting form and meet to determine whether their approach to data extraction is consistent with the research question and purpose.

Table 1. Data-charting form.

Section	Description
Section 1: Overview	Summary of the basic information of the publication
Publication type	Peer reviewed or grey literature
Country	Name of the country or countries where the study took place or focused on
Objective	Aim or objective of the publication
Methodology	The specific procedures or techniques used to identify, select, process, and analyze information
Study design and data management	Includes whether the researchers used quantitative, qualitative, or mixed-method approaches
Setting of the study	The site in which the researcher conducted the study
Summarized results	A short summary of the findings
Section 2: Research questions	Includes the research questions and the date that the literature was published
Suggested health care domain–specific FAIRification[a] concepts and approaches	A description of FAIRification concepts and approaches in the health care domains
FAIR implementation challenges, risks, and lessons learned	Encountered challenges or anticipated changes and lessons learned at different stages of FAIR data principle concept introduction, infrastructure implementation, and FAIRness evaluation
Active networks involved in the implementation of the FAIR data principles in the health domain	Dedicated networks of scientific communities, research institutions, repositories or data archives, consortia, funding agencies, and citizens who are actively engaged in advocating FAIR principle data stewardship in the health care domains
FAIRification reported outcomes	FAIR implementation outcomes in terms of data sharing, data reuse, and research publication after imposing FAIR data principles in health domain

[a]FAIR: findable, accessible, interoperable, reusable.

Stage 5: Collating, Summarizing, and Reporting the Results

This scoping review focuses on the range of data curated and the health data research content identified. Quantitative assessment is limited to a count of the number of sources reporting a particular FAIR thematic issue or recommendation. After charting the relevant data from the studies in spreadsheets, the results will be collated and described using summary statistics, charts, figures, and common tools for analytical reinterpretation of the literature [34]. Mapping the themes derived from the research questions (FAIR implementation approaches, available FAIR networks, FAIR infrastructural and security challenges, etc) and other emerging themes during charting and analysis will be done. Moreover, the impact of the findings in relation to the overall study purpose, implications for future research, practice, and policy will be discussed accordingly [34]. The results will be reported using the PRISMA scoping review reporting guidelines [37].

Results

Overview

Our PubMed preliminary search has yielded 360 results (Multimedia Appendix 1). The search strategy we used to identify these results will be iteratively revised as we search for the results that best fit the inclusion criteria. We are also working on translating this MeSH search strategy into terms for alerts on the Google Scholar and Web of Science databases. The identification of relevant studies began in April 2020. Data extraction will be carried out in the last quarter of 2020. After completion of steps 1 to 3, we will use the title and abstract and a full-text review to determine the number of studies that meet the inclusion criteria. Full-text data extraction will also be used to confirm the number of studies included. Step 5 will involve summarizing and synthesizing the results. We anticipate finalizing the manuscript for this work by March 2021.

Anticipated Outcomes

This scoping review will provide insight on the initiatives, concepts, and implementation practices of FAIR data principles in health data stewardship. More specifically, it will allow for the exploration of (1) approaches being used or piloted for the implementation of the FAIR data principles in the health domain since the conception of these principles in 2014; (2) challenges, risks, lessons learned, and the suggested concepts and approaches to mitigate the concerns of implementation of the FAIR data principles in the health domain; (3) active research and service networks involved in the implementation of the FAIR data principles in the health domain; and (4) the reported

outcomes for data sharing, data reuse, and research publication after the implementation of the FAIR data principles in the health domain. We anticipate increases in data repositories demanding FAIR data markup suitable for artificial intelligence extraction of statistics. We also anticipate a greater demand for the implementation of the FAIR principles in light of the ongoing COVID-19 pandemic as well as more open research activities by public and private research and service networks involved in the implementation of the FAIR data principles in the health domain. An example of such an initiative is the Research Data Alliance [39].

The results will be used to generate recommendations on how to integrate the FAIR principles in health research, and we will generate different knowledge dissemination materials to share project results with various stakeholders, partners, associations, and networks who may benefit from this work.

Discussion

Future Work

The findings of this proposed work may be used to help identify the types of available evidence that support the incorporation of FAIR data principles in health. The results will also help to clarify key concepts in the scientific literature and serve as an introduction to how research on FAIR practices is conducted. This methodological framework will help us identify the overall state of research activities that explore initiatives, concepts, and implementation practices of FAIR data principles in health data stewardship. The outcome of this review can be used to further determine areas of research based on current gaps in the literature. Conducting this scoping review will also help determine the practicality and relevance of a full systematic review on the same issues by assessing the availability of literature. Similarly, gaps that still exist in the uptake and implementation of the FAIR principles in health research will also be identified as areas of further research. This work will be of interest to various stakeholders, including health and academic institutions, publishers, researchers, and funding agencies. In the wake of the COVID-19 pandemic, it is extremely critical that health data stewardship is practiced in a FAIR manner to facilitate the globally coordinated response [40]. As this work intends to include works that have been published up until December 31, 2020, we expect that we will gather a lot of information about what has been done worldwide regarding the FAIR data principles in health during this critical time. For purposes of the dissemination of the results of this work, the authors will consider submitting abstracts for presentation to various scientific forums and submit a manuscript for publication in a peer-reviewed journal.

Ethics

Once complete, this work will be published in a peer-reviewed journal, and the results will also be presented at appropriate forums or conferences. Ethical approval is not required, as only secondary data from published sources will be included in the scoping review and the public is not invited to participate in this work.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary Material.
[DOCX File , 20 KB - resprot_v10i2e22505_app1.docx]

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Abbreviations

FAIR: findable, accessible, interoperable, and reusable
FORCE11: The Future of Research Communication and e-Scholarship
GPDR: General Data Protection Regulation
HRB: Health Research Board
MeSH: medical subject heading
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews
RQ: research question

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