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Protocol

Comparing Telemedicine and Face-to-Face Consultation Based on the Standard Smoking Cessation Program for Nicotine Dependence: Protocol for a Randomized Controlled Trial

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Abstract

Background: Smoking is a major public health concern. In Japan, a 12-week standard smoking cessation support program is available, however, its required face-to-face visits are a key obstacle in completing the program. Telemedicine is a useful way to provide medical treatment at a distance. Although telemedicine for smoking cessation using an internet-based video system has the potential for ensuring better clinical outcomes for patients with nicotine dependence, its efficacy is unclear.

Objective: The aim of this study is to determine the efficacy and feasibility of a smoking cessation support program using an internet-based video system compared with a face-to-face program among patients with nicotine dependence.

Methods: This study will be a randomized, controlled, open-label, multicenter trial. Participants randomized to the intervention arm will undergo an internet-based smoking cessation program, whereas control participants will undergo a standard face-to-face program. We will use the *CureApp Smoking Cessation* (CASC) for both arms, which consists of the CASC smartphone app for patients and a Web-based patient information management system for clinicians with a mobile carbon monoxide checking device. The primary endpoint will be the continuous abstinence rate (CAR) from weeks 9 to 12. Secondary endpoints will be: (1) the smoking cessation success rate at 4, 8, 12, and 24 weeks; (2) CAR from weeks 9 to 24; (3) changes in scores on the mood and physical symptoms scale and 12-Item French Version Of The Tobacco Craving Questionnaire; (4) Kano Test for Social Nicotine Dependence scores at 8, 12, and 24 weeks; (5) time to first lapse after the first visit; (6) nicotine dependence and cognition scale scores at 12 and 24 weeks; (7) usage rate of the CASC; (8) qualitative questionnaire about the usability and acceptability of telemedicine; and (9) presence of product problems or adverse events.

Results: We will recruit 114 participants who are nicotine-dependent but otherwise healthy adults from March to July 2018 and follow up with them until January 2019 (24 weeks). We expect all study results to be available by the end of March 2019.

Conclusions: This will be the first randomized controlled trial to evaluate the efficacy and feasibility of an internet-based (telemedicine) smoking cessation support program relative to a face-to-face program among patients with nicotine dependence. We expect that the efficacy of the telemedicine smoking cessation support program will not be clinically worse than the face-to-face program. If this trial demonstrates that telemedicine does not have clinically worse efficacy and feasibility than a conventional face-to-face program, physicians can begin to offer a more flexible smoking cessation program to patients who may otherwise give up on trying such programs.

Trial Registration: University Hospital Medical Information Network Clinical Trials Registry: UMIN000031620; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000035975

International Registered Report Identifier (IRRID): DERR1-10.2196/12701

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KEYWORDS

tobacco use disorder; smoking cessation; telemedicine; smartphone; mobile apps; videoconferencing; digital therapeutics; adult; human; randomized controlled trials as topic

Introduction

Background and Research Question

Smoking is a major public health concern responsible for a diverse range of diseases, such as cancers, heart disease, cerebrovascular disease, and chronic obstructive pulmonary disease [1]. In Japan, the estimated number of smokers is more than 20 million, and smoking accounts for about 129,000 deaths per year; the greatest extrinsic cause of death among noninfectious diseases [2]. Furthermore, the excess medical expenses imposed by smoking may be as high as 1.5 trillion yen (approximately US \$13 billion) [3]. As such, efforts to reduce the prevalence of smoking would not only cut medical costs, but also help prevent the abovementioned life-threatening diseases [4].

A smoking cessation support program is widely available in Japan for patients with nicotine dependence. This program is agreed to be a standard program by related academic societies and reimbursed by national health insurance [5]. This 12-week program mainly consists of face-to-face counseling with a primary care physician, checking exhaled carbon monoxide (CO) concentration, and prescribing smoking cessation medications such as varenicline or nicotine replacement therapies [6,7]. The national survey report on efficacy of nicotine dependence treatment conducted by the Ministry of Health, Labor, and Welfare of Japan showed that there was a linear relationship between the number of patients' visits to the institution or clinic and the treatment success rate. Although the primary care physicians made efforts to have patients complete the 12-week program, as few as 29.81% (390/1308) of the participants could do so [8]. However, the preliminary report showed that as many as 75% of 225 participants could complete the modified 8-week-smoking cessation program when conducted as telemedicine, which was a relatively high completion rate compared with a historical control of 50.79% (1763/3471) completion rate at 8 weeks [9]. This result suggested that telemedicine might have the potential to dramatically improve the completion rate of the standard smoking cessation program.

Recently, telemedicine—or the delivery of health care by remote health care providers via communication technologies—has come to be regarded as a useful method of providing medical care to patients. Telemedicine minimizes a patient's burden of traveling to a health institution and waiting for consultations with their physicians. In addition, it can lead to improved clinical outcomes for patient quality of life [10] and overall quality of

care, which include aspects such as efficiency and patient satisfaction [11].

Telemedicine might also be suitable for delivering a smoking cessation support program, as 71.7% of the patients with nicotine dependence in Japan are under 60 years of age and 66.7% of patients are men, both of who are demographics who are unwilling to spend half their day visiting a clinic for treatment [8]. A well-designed randomized trial of 5800 smokers in the United Kingdom demonstrated that a remote smoking cessation program using motivational text messages and customized behavioral change support could double the quit rate compared with the control group who received short text messages unrelated to smoking cessation [12]. Significant improvement of continuous abstinence rate (CAR) at 6 months in the intervention group was reported, with the intervention group improving by 10.7% vs the control group only improving by 4.9%. Moreover, a systematic review showed that interactive and tailored internet-based interventions for smoking cessation might have a moderate effect compared with nonactive controls [13]. Nowadays, with the advent of smartphone technology, apps, and increasing bandwidth, this has allowed health care providers to interact with patients through real-time video-based communication rather than via text- or audio-based communication [14]. Video-based telemedicine systems can be cost-saving, promote more active self-care, and result in better clinical outcomes in the management of various diseases [15]. For example, researchers of home health care in the United States reported, based on a randomized control trial, that video communication technology could improve the quality indicators of the practice and showed cost effectiveness when it could substitute in-person clinical visits [16]. Another randomized clinical trial suggested that video-based telemedicine specialist consultation was well accepted and cost-effective among nonacute headache patients [17]. Other, previous research showed that video consultation, added to standard care, could improve the glycemic control of diabetes patients who did not respond to standard care [18].

The *CureApp Smoking Cessation (CASC)* is a novel smartphone app paired with a mobile CO checking device that was developed by CureApp Inc, Tokyo, Japan, to improve treatment success of the smoking cessation program for patients with nicotine dependence [19,20]. CASC can provide patients with accurate knowledge of nicotine dependency and tips for changing their behavior, as well as help them monitor their own exhaled CO levels with a personal mobile CO checking device at home. They can then share these data with their primary care physicians remotely. A prospective, single-arm, pilot study demonstrated that a smoking cessation program with a CASC

group showed a higher CAR from weeks 9 to 24 than those without a CASC group [21].

Therefore, telemedicine might have the potential to enhance the smoking cessation success rate and other clinical outcomes among patients with nicotine dependence by helping them achieve easier access to smoking cessation programs. However, it remains unclear whether the smoking cessation program using an internet-based video system is effective and safe relative to a conventional face-to-face program.

Objectives

This is a proof-of-concept study aiming to determine the efficacy and feasibility of a smoking cessation support program using an internet-based video system compared with a face-to-face program, both of which use the CASC, among patients with nicotine dependence.

Methods

Study Design

This study will be a randomized, controlled, open-label, multicenter trial. The study will be conducted in 4 community clinics located in Tokyo, Japan: Tokyo-Eki Center-building Clinic, Shinjuku Research Park Clinic, Fukuwa Clinic and Miyazaki RC Clinic. [Figure 1](#) provides an outline of the trial.

Participants in both arms will undergo the smoking cessation support program used in Japan. For the telemedicine arm, the entire program will be conducted remotely via an internet-based video system except for the first registration visit [22], whereas participants in the control arm will follow the standard program

in the face-to-face manner. Participants in both arms will be asked to download the CASC smartphone app as well as be given a mobile CO checker. These will be used for 24 weeks. The follow-up schedule is shown in [Table 1](#).

Participants

We will recruit nicotine-dependent but otherwise healthy adults from March to July 2018. We plan to follow them up until January 2019 (ie, for 24 weeks). We will include the participants who are diagnosed as nicotine dependent, have smoking history of Brinkman index (BI) >200, and have a determination to quit smoking immediately. Then, we will exclude those participants with severe mental illness and those with any smoking cessation aid, besides prescribed medication at clinics before or after enrollment, based on the subjective questionnaire on the enrollment visit (detail of the inclusion criteria is shown in [Multimedia Appendix 1](#), and the exclusion criteria is shown in the [Multimedia Appendix 2](#)). Not-Burning-Tobacco product users can be included if the participant meets the inclusion criteria of the BI, which was defined as the number of combustible traditional tobacco packs per day multiplied by the number of smoking years. Primary doctors at each study site will obtain written informed consent from all study participants, and the consent forms that will be used have been approved by our institutional review board. We will inform all participants that their medical care will not be affected if they refuse to be enrolled in the trial. In addition, participants will be able to drop out of the study at any time. Clinics participating in this study can provide the smoking cessation support program and have the necessary equipment to conduct telemedicine (eg, Wi-Fi access in the facility).

Figure 1. Scheme of this trial protocol. CASC: CureApp Smoking Cessation.

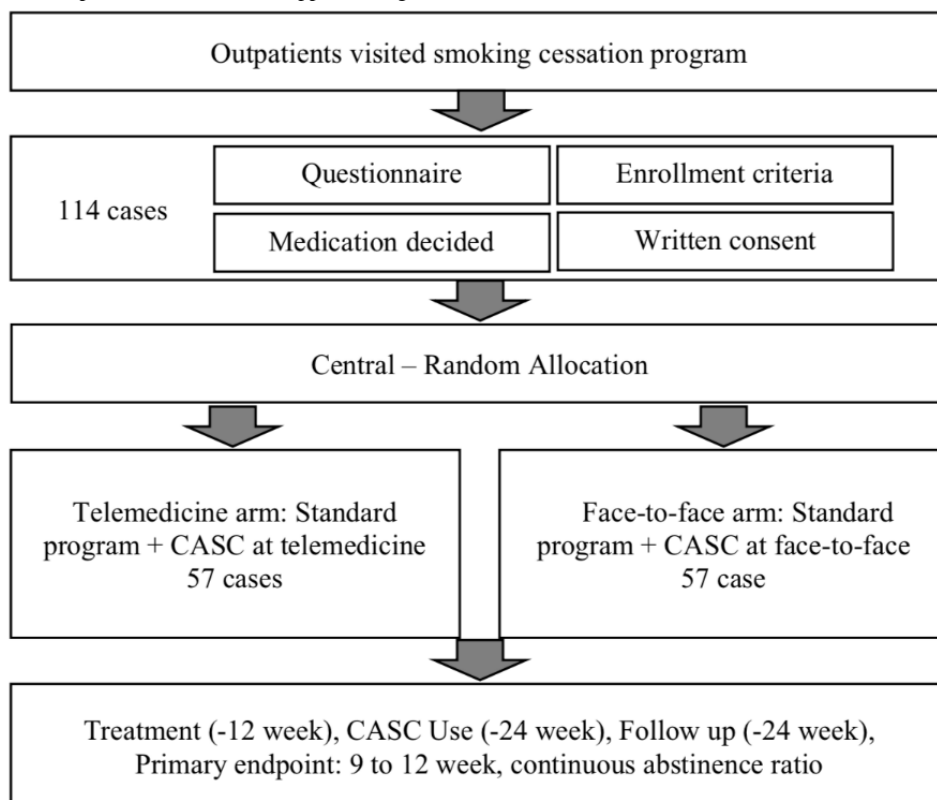


Table 1. Assessment and evaluation schedule of the study.

Variables	Registration	Observation period					
	Day 1	Day 15 (2 weeks)	Day 29 (4 weeks)	Day 57 (8 weeks)	Day 85 (12 weeks)	Day 168 (24 weeks)	At withdrawal
Patients' profile	✓ ^a	— ^b	—	—	—	—	—
Tobacco Dependence Screening Test	✓	—	—	—	—	—	—
Brinkman Index	✓	—	—	—	—	—	—
Fagerström test for nicotine dependence	✓	—	—	—	—	—	—
12-item French version of the Tobacco Craving Questionnaire	✓	✓	✓	✓	✓	✓	—
Kano Test for Social Nicotine Dependence	✓	—	—	✓	✓	✓	—
Mood and physical symptoms scale	✓	✓	✓	✓	✓	✓	—
Nicotine dependence and cognition scale	✓	—	—	—	✓	✓	—
Exhaled carbon oxide concentration	✓	✓	✓	✓	✓	✓	✓
Smoking status	✓	✓	✓	✓	✓	✓	✓
Device use status	—	✓	✓	✓	✓	✓	✓
Adverse events	—	—	—	—	—	—	—

^aInformation collected.

^bNot applicable.

Sample Size

As shown in the findings of a previous pilot study of the CASC, the difference in CAR from weeks 9 to 12 between using a CASC smartphone app group (78%) and historical control groups (not using the application; 54%) is 24% [21,23]. Accordingly, we assumed that the treatment effect of both arms using the CASC in the current study will be 80% and the threshold amount should be 15%, which is smaller than the difference between the CASC group and historical control group in the previous study. The sample size was calculated as 114 (57 per arm) based on the precision of the estimate that the lower limit of the 95% CI of the difference between treatment effects exceeded the threshold amount of 15%. Therefore, we aim to recruit at least 114 participants to allow for this sample size.

Randomization

For randomization, we will use the block randomization method (with 4 blocks) with a 1:1 allocation ratio. Participants will be allocated in this way to either the intervention (telemedicine) or control (face-to-face) arm. The randomization will be performed at the time of participants' registration by a staff member using a computer-generated random sequence for each participating clinic.

Interventions and Control

Participants randomized to the intervention (ie, telemedicine) arm will receive an internet-based support program for smoking

cessation using the CASC. In contrast, participants randomized to the control (face-to-face) arm will receive the conventional face-to-face standard smoking cessation support program, also using the CASC.

The standard smoking cessation support program in Japan consists of 5 clinic visits over 12 weeks, including doctor consultation and exhaled CO check at a registered institution or clinic [5]. All study participants will meet their primary care physicians face to face during the first visit to ensure that they fully understand the study protocol. On this first visit, the physicians will decide on the appropriate treatment drug, provide guidance in accordance with the standard program procedure, and provide participants with the CASC. Following the first visit, control patients are supposed to visit the clinic in weeks 2, 4, 8, and 12, and at each visit, their primary doctors will administer the treatment drug.

Patients in the telemedicine arm will undergo the standard smoking cessation support program with the CASC. However, instead of visiting the clinics, they will meet their physicians to receive counseling via a video-conference system and a standardized telemedicine platform app, in accordance with the guideline for telemedicine in Japan [22]. As in the standard procedure, they will meet with their physicians via internet at each of the planned visits (2, 4, 8, and 12 weeks).

The CASC consists of the following: (1) a CASC smartphone app for patients with nicotine dependence, (2) a mobile CO

checker for patients, and (3) a Web-based patient management software for health care providers [20]. Participants are asked to watch a 5- to 10-min lecture on smoking cessation every day (see [Multimedia Appendix 3](#) for the specifics). They are also asked to write a short comment as a diary and to check their exhaled CO concentration with the device. Primary care physicians can monitor their diaries, physical conditions, lecture progress, and exhaled CO concentration data.

The CASC will be delivered by the study sponsor, CureApp Inc, Tokyo, Japan, and will be carefully managed to avoid being used outside the current study at each institution or clinic. A prescription code specific to each practicing institution or clinic is required to activate the entire system issued by the sponsor, and the sponsor regularly (at least once a year) performs an inventory and confirms the devices are not used outside the research.

Endpoints

The primary endpoint of this study will be the CAR from weeks 9 to 12. We hypothesize that the telemedicine group will not show clinically worse CAR from weeks 9 to 12 than the control group (threshold of 15%). The CAR is defined as the percentage of individuals continuously not smoking during the specified period. We will also evaluate the following secondary endpoints: (1) smoking cessation success rate at the points of 4, 8, 12, and 24 weeks; (2) CAR from weeks 9 to 24; (3) changes in the scores on the mood and physical symptoms scale (MPSS) [24] and 12-item French version of the Tobacco Craving Questionnaire (FTCQ-12) [25]; (4) Kano Test for Social Nicotine Dependence (KTSND) score [26] at 8, 12, and 24 weeks; (5) time to first lapse after the first visit; (6) nicotine dependence and cognition scale (NDCS) score at 12 and 24 weeks; (7) usage rate of the CASC; (8) qualitative questionnaire about the usability and acceptability of telemedicine; and (9) the presence of product problems or adverse events.

The NDCS is a scale for measuring nicotine dependence and cognitive impairment among smokers. It consists of 8 items, each rated on a 4-point scale (ranging from 0 to 3). A higher total score (minimum=0, maximum=24) implies more severe dependency or cognitive impairment.

Follow-Up Schedule and Data Collection

The follow-up schedule is shown in [Table 1](#). Follow-up visits will be conducted in each clinic. At the registration visit, we will record patients' baseline profile, Tobacco Dependence Screening Test [27], BI, Fagerström test for nicotine dependence [28], FTCQ-12, KTSND, MPSS, NDCS, exhaled CO concentration, and smoking cessation status. The baseline profile will consist of age, gender, body weight, years of smoking, number of cigarettes per day, and past medical history. We will check their FTCQ-12, KTSND (after 8 weeks), MPSS, NDCS (after 12 weeks), exhaled CO concentration, smoking status, the frequency of application usage and presence of product problems, or adverse events at 2 weeks (± 1 week), 4 weeks (± 1 week), 8 weeks (± 2 weeks), 12 weeks (± 2 weeks), and 24 weeks (± 4 weeks). The qualitative questionnaire about the usability and acceptability of telemedicine will be asked only for the participants in the telemedicine arm at 24 weeks. Each doctor

at the study site will be responsible for the case report form, and the monitoring staff, who are employees of the sponsor, will visit each study site and check the data quality during the study period.

Statistical Methods

We will compare all endpoints between the telemedicine and the face-to-face arms. Baseline characteristics will be described by means and standard deviations, or medians and interquartile ranges (for continuous variables), or proportions (for categorical variables). We will analyze the primary outcome using the full analysis set (excluding participants who violate the abovementioned inclusion or exclusion criteria). For all outcomes, summary statistics and group difference measures (eg, odds ratios and mean differences) will be presented with 95% CIs and *P* values from 2-sided tests (eg, logistic regression and analysis of covariance).

Patient and Public Involvement

Participants in this study were not involved in the design, recruitment, conduct, or assessment of the study.

Ethics and Dissemination

We will conduct this study in compliance with the Declaration of Helsinki, Medical Device Good Clinical Practice guidelines, and all other applicable laws and guidelines in Japan. This protocol and related documents of all the participating clinics were approved by the Tokyo-Eki Center-building clinic institutional review board. We will always use the latest version of the approved documents. We used the SPIRIT reporting guidelines for submitting this protocol to the journal [29]. We will disseminate the results at national or international conferences and in a peer-reviewed journal.

Results

As of November 2018, 115 participants with nicotine-dependency were already recruited and will be followed up until January 2019 (24 weeks). We expect all study results to be available by the end of March 2019.

Discussion

Rationale

This will be the first randomized control trial to evaluate the efficacy and feasibility of an internet-based video-assisted smoking cessation support program compared with a face-to-face program in patients with nicotine dependence. We expect that the efficacy of the telemedicine smoking cessation support program (in terms of CAR from weeks 9 to 12) will not be clinically worse than the face-to-face program.

Recent advances in mobile technologies have dramatically changed nearly every aspect of our daily lives. Internet services and smartphone apps play a particularly key role because they help us directly communicate with each other even when apart. Nowadays, smartphone and internet-based video communication have been considered useful tools for improving accessibility to smoking cessation programs, thereby improving the outcomes of patients with nicotine dependence. Scott-Sheldon et al

demonstrated in their meta-analysis that a mobile phone short messaging service intervention led to substantial benefits for smoking cessation [30]. Moreover, Carlson et al reported that a group smoking cessation program delivered via video-conference technology in a rural area of Canada was as effective as an in-person group program conducted in an urban area [31]. Thus, we expect that our internet-based smoking cessation support program will have the potential to be comparable to the conventional face-to-face program because it can empower the patients to more conveniently access the relevant medical information and health care providers.

Study Design

Considering that the aim of this study is to compare different ways of delivering a standard 12-week smoking cessation program, a CAR for the last 4 weeks of the treatment period would be the ideal endpoint. It would also be appropriate to compare those 2 groups for CAR from weeks 9 to 12 because a previous phase III clinical trial on smoking cessation aid medications, such as varenicline, evaluated CAR for the same period to assess the efficacy [32].

In this study, we will use the CASC for both arms as it serves to complement the standard smoking cessation program. A previous single arm, prospective pilot study showed that the CASC, in addition to the standard program, led to significantly higher CAR from weeks 9 to 24 when compared with a historical control group [21]. Currently, there is an ongoing Phase III randomized controlled clinical trial to evaluate the efficacy of the CASC [20]. The standard smoking cessation program in Japan requires that patients' exhaled CO concentration be measured at each clinic visit [5], and the information on their CO level is helpful for the primary doctor to give treatment advice on each visit. The CO checker in the CASC enables all patients—even those in the telemedicine group—to monitor their own exhaled CO concentration level at home in the validated way. Therefore, we believe that the CASC must be

used in both arms to fairly evaluate the difference between the telemedicine and face-to-face treatment programs.

Limitations

This study has several limitations. First, this study will be conducted in multiple centers, but participants will be limited to residents in an urban area in Tokyo, Japan, which may limit the generalizability of the study findings. We might need to conduct further investigations to apply the study findings to other cohorts. Second, participants in both groups are going to use the CASC, but this system has not yet been cleared by the Pharmaceuticals and Medical Devices Agency. Therefore, the outcomes for each group must be carefully interpreted because they might be the result of mixed effects of the study intervention and the CASC on the standard smoking cessation program. Nevertheless, since the program in Japan requires evaluation of exhaled CO concentration at each visit, supplying participants with the CASC is the only realistic and validated solution to conduct this study at present. Third, the primary physicians can prescribe treatment drugs, either varenicline or nicotine patch, to support the patients in quitting smoking according to a physician's discretion. Although the institution is an allocation factor for equal randomization, the baseline characteristics of the drug assignment might not be matched between the 2 arms, which could cause the biased results.

Conclusions

In conclusion, we will test whether an internet-based smoking cessation support program does not have clinically worse efficacy and feasibility than a face-to-face smoking cessation program among patients with nicotine dependence. If we obtain the expected findings, physicians can offer a more flexible standard smoking cessation program to patients who might otherwise give up on the idea of trying such programs. In addition, this study could be a milestone to expand the scope of the effective smoking cessation support program, which might contribute to an improvement of public health and reduction of medical expenses.

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Authors' Contributions

TT, AN, MK, TM, and KS designed and conducted the study. EH provided statistical expertise in study design. All authors contributed to the refinement of the study protocol and approved the final paper.

Conflicts of Interest

TT and AN have received consulting fees from CureApp, Inc, Japan. MK and TM are employees of CureApp, Inc, Japan. KS is the founder and a shareholder of CureApp, Inc and patent holder of the CASC. EH has a consultation contract as a biostatistician with CureApp, Inc, Japan.

Multimedia Appendix 1

Inclusion criteria.

[[PDF File \(Adobe PDF File\), 59KB - resprot_v8i7e12701_app1.pdf](#)]

Multimedia Appendix 2

Exclusion criteria.

[[PDF File \(Adobe PDF File\), 61KB - resprot_v8i7e12701_app2.pdf](#)]

Multimedia Appendix 3

List of smoking cessation treatment lectures provided by the application.

[[PDF File \(Adobe PDF File\), 66KB - resprot_v8i7e12701_app3.pdf](#)]

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Abbreviations

BI: Brinkman index

CAR: Continuous abstinence rate

CASC: CureApp Smoking Cessation

CO: carbon monoxide

FTCQ-12: 12-item French version of the Tobacco Craving Questionnaire

KTSND: Kano Test for Social Nicotine Dependence

MPSS: mood and physical symptoms scale

NDCS: nicotine dependence and cognition scale

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Protocol

Virtual Reality and Web-Based Growth Mindset Interventions for Adolescent Depression: Protocol for a Three-Arm Randomized Trial

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Abstract

Background: Depression is the leading cause of disability in youth, with a global economic burden of US >\$210 billion annually. However, up to 70% of youth with depression do not receive services. Even among those who do access treatment, 30% to 65% fail to respond and many dropout prematurely, demonstrating a need for more potent, accessible interventions. In a previous trial, a single-session Web-based growth mindset (GM) intervention significantly reduced depressive symptoms in high-symptom adolescents; however, this intervention did not benefit adolescents uniformly. For instance, the intervention reduced depression in adolescents who reported post intervention increases in perceived control, but it did not lead to significant depression reductions in adolescents who reported no significant post intervention increases in perceived control.

Objective: The goal of this project is to test the acceptability and efficacy of a novel, single-session, virtual reality (VR) depression intervention—the *VR Personality Project*—teaching GM, the belief that personal attributes are malleable rather than fixed. The VR Personality Project was designed to systematically target and increase adolescents' perceived control by offering a more immersive, engaging, user-directed intervention experience than the Web-based intervention can provide. By targeting an identified predictor of intervention response, the VR Personality Project may lead to larger reductions in depressive symptoms than existing Web-based mindset interventions.

Methods: Adolescents with elevated depressive symptoms or a recent history of depression (N=159; ages 12 to 16 years) will be randomized to one of 3 intervention conditions: the VR Personality Project; the Web-based GM intervention tested previously; or an active, Web-based control. Adolescents and their parents will report on the adolescents' depression symptoms, perceived control, and related domains of functioning at preintervention, postintervention, and at 3- and 9-month follow-up assessments.

Results: We predict that the VR and Web-based mindset interventions will both lead to larger reductions in adolescent symptoms than the control intervention. Additionally, we predict that the VR-based single session intervention will lead to larger reductions in depression than the online mindset intervention and that these symptom reductions will be mediated by increases in adolescents' perceived control from pre- to postintervention.

Conclusions: The results may suggest an efficient strategy for reducing adolescent depressive symptoms: One that is mechanism-targeted, relatively affordable (less than US \$200 for a commercially available VR headset, a fraction of the cost of long-term psychotherapy) and potentially engaging to adolescents experiencing mood-related distress.

Trial Registration: ClinicalTrials.gov NCT0385881; <https://clinicaltrials.gov/ct2/show/NCT0385881> (Archived by WebCite at <http://www.webcitation.org/78C3roDgA>).

International Registered Report Identifier (IRRID): DERR1-10.2196/13368

KEYWORDS

mental health; depression; virtual reality; adolescence; ehealth

Introduction

Background

Psychiatric disorders are the leading cause of disability worldwide, and 40.5% of this burden is attributable to depressive symptoms and disorder. Levels of depressive symptoms increase markedly in adolescence with nearly 20% of the youth experiencing a depressive disorder between ages 12 and 18 years [1]. Adolescent-onset depression accounts for 66% of lifetime depression cases and predicts interpersonal problems, substance abuse, and a 20-fold increased risk of attempting suicide. Despite this early onset and protracted course, up to 70% of adolescents with depression symptoms and disorders do not receive services [2-4]. Even among those who do access psychosocial or medication-based treatment, 30% to 65% fail to respond [5] and many drop out of clinic-based services prematurely—after 3.9 sessions on average [6]. These findings highlight the urgent need for more potent and accessible interventions for adolescent depression.

Emerging work suggests that single-session interventions (SSIs) can increase accessibility of potent interventions for youth depressive symptoms and disorders [7]. SSIs include core elements of comprehensive, evidence-based treatments, but their brevity makes them easier to disseminate to diverse settings. Indeed, SSIs can successfully treat youth psychiatric problems: In a meta-analysis of 50 randomized trials [4], SSIs for youth psychological problems demonstrated significant beneficial effects (mean $g=.32$) across various levels of youth problem severity, suggesting the potential of SSIs for youths with diagnosable and subclinical psychopathology. Furthermore, significant effects emerged even for self-administered (eg, Web-based) interventions (mean $g=.32$). Notably, SSIs' overall effects are slightly smaller than those observed for multisession psychotherapy [8]. However, their high potential to render services more scalable and accessible—especially for youths who might otherwise go without services entirely—could magnify their benefits for youth psychological health on a large scale.

One SSI in particular has shown promise in reducing adolescent depressive symptoms: the growth mindset (GM) SSI, which encourages youths to view traits and attributes as malleable (a GM) as opposed to unchangeable (a *fixed mindset*). Youths holding fixed mindsets of personal traits tend to report higher levels of psychopathology [9] and increased internalizing problems over time [10,11]. Recent research suggests that encouraging GMs via brief, targeted interventions can help shift this trajectory: 30- to 90-min self-administered GM SSIs have prevented adolescent depression symptoms in nonclinical samples (OR=.55, with the GM group showing lower odds of reporting clinically elevated levels of depression 9 months later [12]). In a randomized controlled trial (RCT) targeting high-symptom adolescents, a GM SSI led to postintervention increases in adolescents' perceived control over behavior ($d=.34$,

$P<.001$) and emotions ($d=.19$, $P=.03$) relative to a comparison (supportive therapy [ST]) SSI [13]. The GM SSI also predicted steeper 9-month declines in youth depression symptoms per parent ($B=-0.99$, $P=.047$) and adolescent reports ($B=-1.37$, $P=.03$) [14].

Although multiple versions of GM SSIs have been developed to fit varying settings and populations, they are generally self-administered by youths; teach the *brain science* behind why it is possible for a trait (eg, personality, loneliness, and anxiety) to change; include testimonial quotes from peers reinforcing the possibility of personal change; and involve the completion of at least one *self-persuasion* exercise wherein youths write about how change is possible to help a peer who is struggling [15]. Thus, the GM SSI may help remove barriers to adolescents asking for help and for expanding effort rather than withdrawing in the face of setbacks and failure.

Despite its promising effects, it is notable that the GM SSI does not reduce depression in all adolescents. For instance, in the most relevant RCT, the GM SSI reduced depressive symptoms in adolescents who reported postintervention increases in perceived control over their personal behaviors, but it did not lead to significant depression symptom reductions in adolescents who reported small or no increases in perceived control [16]. Thus, the potency of GM SSIs for adolescent depression has yet to be optimized. Such potency may be advanced by developing new iterations of GM interventions (GMIs), which are designed to more systematically target predictors and mechanisms of clinical outcomes, such as low levels of perceived control: a predictor and risk factor for depression [17-21] that GM SSIs have successfully mitigated, both in the short-term [13] and over time [14]. Such efforts may increase the promise of GMIs to produce larger, longer lasting symptom reductions for a greater proportion of youth.

Objectives

Accordingly, the goal of this 3-arm RCT is to evaluate the acceptability and efficacy of a novel, single-session virtual reality (VR)-based GM SSI—the *VR Personality Project*—for depressive symptoms in adolescents compared with both a Web-based GM-SSI and an active, Web-based control program. Immersive VR creates interactive, computer-generated worlds, which substitute real-world sensory perceptions with digitally generated ones, producing the sensation of actually being in new life-sized environments. The last 2 decades have seen a significant increase in the use of VR technology in mental health interventions, with research suggesting benefits of VR-mediated interventions for various anxiety disorders, specific phobias, posttraumatic stress disorder, substance use, and eating disorders [22-27], largely through graded exposure to feared stimuli and situations. VR has also been extended to the adjunctive treatment of psychotic symptoms, delivering cognitive rehabilitation, and social skills training interventions in ecologically valid virtual environments [28,29]. For this study, the VR Personality Project

was designed in collaboration with Limbix Inc to systematically target and increase adolescents' sense of perceived control by offering a more immersive, active, and user-directed intervention experience than Web-based GM SSIs have provided. Within the VR program, participants can exert control over their intervention experience by actively engaging with *characters* in the VR world, autonomously navigating through various environments and speaking directly to (eg, offering verbal advice) same-aged *peers*. By strengthening adolescents' interactions with the program content, lessons, and characters and providing a more ecologically valid environment (relative to that offered by a computer-based program) for youths to rehearse and apply newly acquired skills, the *VR Personality Project* may engage an identified predictor of response to GM SSIs in turn producing larger reductions in depression than Web-based versions. Thus, the *VR Personality Project* may represent a mechanism-targeted, efficient strategy for reducing adolescent depression: one that is both relatively affordable (less than US \$200 for any commercially available VR headset; a fraction of the cost of long-term psychotherapy) and potentially engaging to adolescents experiencing mood-related distress.

Notably, a recent systematic review of studies evaluating VR applications for mental health identified only 2 studies that have tested immersive VR mental health treatment approaches; both were uncontrolled feasibility trials targeting adults [19]. Thus, to our knowledge, this study will be the first randomized trial evaluating a brief VR intervention for adolescent depressive symptoms.

This research has 4 specific aims. Our first aim is to replicate past research suggesting that GM SSIs can significantly reduce depressive symptoms in at-risk adolescents. We hypothesize that adolescents aged 12 to 16 years who participate in a GMI (Web-based or VR-based) will show larger reductions in depression symptoms from baseline through the 9-month follow-up assessment compared with adolescents who receive an active, Web-based control program.

Our second aim is to evaluate new, single-session, VR GMI including a comparative efficacy study. Our second aim is to also evaluate whether the new VR-based GM SSI (the VR Personality Project) can reduce depressive symptoms in adolescents, both relative to an active control program and to the previously tested Web-based GM SSI [13,14]. We hypothesize that adolescents who participate in the VR-based GM SSI will show larger reductions in depressive symptoms from baseline through the 9-month follow-up assessment compared with adolescents who receive the Web-based GMI and compared with adolescents who receive the active Web-based control program.

Our third aim is to test whether shifts in perceived control mediate intervention effects on adolescent depressive symptoms. The VR Personality Project was designed to target and increase adolescents' perceived control by offering a more immersive, active, and user-directed intervention experience than the Web-based GM SSI can provide. Thus, the third goal of this study is to examine whether the VR Personality Project does, in fact, reduce adolescent depressive symptoms by eliciting proximal increases in perceived control. We hypothesize that

the VR Personality Project will lead to larger increases in immediate postintervention perceived control than the Web-based intervention from pre- to postintervention and that these increases will mediate subsequent reductions in adolescent depression across the follow up period.

Our fourth aim is to gauge acceptability of the VR intervention. Adolescents' perceptions of any intervention can impact completion rates, program engagement, and ultimately intervention effectiveness. Thus, an additional aim of this research is to examine whether adolescents view the VR Personality Project as more engaging, helpful, and interesting than the Web-based GMI or the Web-based control intervention.

Methods

Summary of Overall Study Design

This study will be a 3-arm RCT, including 2 active intervention conditions and 1 active control condition. Study procedures were preregistered in ClinicalTrials.gov before enrollment of the first participant (NCT03858881; recruitment start date: March 2019). The Stony Brook University Institutional Review Board (IRB) has approved all study procedures described below. Participants will be randomly assigned to one of 3 conditions in equal numbers. We opted for equal allocation across groups (a relatively conservative approach) rather than weighted allocation to the active intervention groups, owing to the novelty of the VR intervention being evaluated and the resulting need for a rigorous, controlled test of its efficacy. After qualifying for participation based on a phone screen, adolescents (and 1 caregiver per adolescent) will visit the Department of Psychology at Stony Brook University for a 2-hour laboratory visit. Adolescents and parents will complete baseline questionnaires (see below for details). Adolescents will then be randomized to receive one of 3 interventions using a computer-based random number generator: the VR GM intervention (VR GMI), the online GM intervention (online GMI), or an online active control program designed to replicate ST and tested previously [13,14]. Immediately after intervention completion, adolescents will complete a postintervention questionnaire battery. Adolescents and parents will then be asked to complete online follow-up questionnaire batteries 3- and 9-month postintervention.

Subjects, Projected Screen Failure Rate, and Power Analysis

We intend to recruit 159 adolescents aged 12 to 16 years (inclusive). G*Power 3.1 (University of Duesseldorf) was used to calculate the sample size needed to achieve sufficient power, (1- β) to detect mean group differences (based on an omnibus *F* test) of small (.2), medium (.5), and large intervention effects (.8) on depression symptoms, measured continuously, with $\alpha=.05$ and power at 0.80 for a 3-arm randomized trial. Sample sizes calculated were 969, 159, and 66 for effects of .2, .5, and .8, respectively, for an omnibus one-way analysis of variance (ANOVA). Power to detect a small effect size is ideal, but logistical constraints necessitate a more conservative sample size. The sample size of 159 (53 per SSI condition) reflects power to detect a medium ($d=.5$) between-group effect size.

Detailed Study Procedures

Recruitment and Screening

Youth participants will be recruited from community groups, after-school and extracurricular programs, parent organizations, private psychiatric and pediatric primary care clinics, and religious organizations in the Stony Brook area. Eligibility for participation will be ascertained through a parent phone screen conducted by a trained member of the research team. Parents will be informed at the end of the phone screen whether or not their adolescent qualifies for study participation. Youths must be living with at least 1 parent or legal guardian and both must speak English well enough to complete study interventions. Additional inclusion criteria will include the following: (1) the youth is aged 12 to 16 years (inclusive) with 1 parent willing to participate (2) the youth reports elevated depressive symptoms (>80 percentile for age and sex, reflecting subclinical or higher symptom elevations) based on the parent-report version of the Children's Depression Inventory-2 (CDI-2). Exclusion criteria will include intellectual disability (based on parent report) and hospitalization of the adolescent within the past 2 months for suicide attempt or self-harm, as the interventions being evaluated in this study are not designed for youth with acute medical or psychiatric need. Concurrent treatment will not preclude eligibility. Youths prone to seizures will also be eligible to participate; risks of participating will be discussed with prospective participants and families before study participation. This study will focus on youth aged 12 to 16 years because depression increases markedly in adolescence, and youth in this age range have responded well to GMI [13,14].

Laboratory-Based Study Session

On the basis of the parent phone screen, parents of eligible youths will be invited to schedule a laboratory-based study session, which they and their adolescent will attend together. This session will last approximately 2 hours and will be led by 2 research assistants at the postbaccalaureate, master's, or advanced undergraduate level. Before guiding participants through the study, each research assistant will have received individual training from the principal investigator in each step of the study protocol, including 2 start-to-finish *practice runs* with mock participants.

At the start of this laboratory-based study session, the youth and parent will have the opportunity to provide consent or parental permission and youth assent; all study procedures will be explained to the family at this time, and the youth and parent will be reminded that they can choose to leave the study at any time. After providing parental permission and youth assent, study procedures will begin. The youth participant will be escorted to a separate room by a member of the study team to complete study procedures; the parent will remain in the room in which consent and assent was obtained to complete his or her portion of the study procedures (ie, a questionnaire battery). One member of the study team will remain with the youth for the duration of the session; a second member of the study team will provide instructions to the parent and remain available to answer any additional questions the parent has during the laboratory visit.

After consenting, youths will be asked to complete a battery of questionnaires (detailed below) via Qualtrics, a secure collection platform. Subsequently, a random number generator (embedded within the last slide of the Qualtrics survey including youths' baseline questionnaires) will be used to assign youths to one of 3 intervention conditions: VR GMI, Web-based GMI, or Web-based ST. No personally identifying data or information will be collected during intervention administration.

Notably, for youths randomly assigned to the VR GMI, both the youth and experimenter will be aware of the condition assignment (only one of the 3 programs involves VR technology). However, for youths randomly assigned to either of the 2 Web-based interventions neither the youth nor the experimenter will be aware of which Web-based intervention they received; randomization to these 2 conditions will occur without experimenter involvement as part of the youth's Qualtrics survey.

Interventions

Web-Based Growth Mindset Intervention

The Web-based GMI [13,14], called Project Personality, is delivered via Qualtrics and takes approximately 30 min to complete. All intervention activities are self-administered by the youth and delivered in a Web-based format, including illustrations and audio-recordings of text. Intervention content is designed to maximize relevance for youths experiencing symptoms of depression, including excessive sadness and hopelessness. The intervention includes 5 components: (1) an introduction to the brain, including a lesson on the concept of neuroplasticity, describing how and why our behaviors are controlled by thoughts and feelings in their brains, which have potential for change; (2) written testimonials from older youths who describe their beliefs that people's personal traits (eg, sadness and anxiety) are malleable, given the brain's plasticity; (3) additional vignettes written by older youths, describing times when they used *GMs* to persevere through social and emotional setbacks; (4) a summary of scientific studies suggesting that personality can, and often does, change in positive ways over time; and (5) exercises in which the participants write notes to peers, drawing on scientific information to describe the malleability of people's personal traits.

Virtual Reality Growth Mindset Intervention

The VR intervention, called the VR Personality Project, will be administered through an adjustable VR headset that includes a stereoscopic display powered by a Samsung smartphone (Galaxy S6™) mounted on a lightweight (345 g) wireless, off-the-shelf head-mounted display with a 101-degree field of view for users (Samsung Gear Virtual Reality (VR)™). A focus wheel on the VR goggles will be adjusted to find a comfortable focal length for each participant. Sound is delivered through the head-mounted display. A lightweight (295 g) wireless Bluetooth controller (MOGA PRO™ POWER controller) that requires only one hand to operate will be used by each adolescent to interact with the VR environment. For infection control reasons and because the same hardware will be used for all participants, disposable coverings will be used on the head-mounted display.

All equipment will be cleaned between participants using disposable wipes and dried for at least 20 min.

Similar to the Web-based analogue, the VR Personality Project takes approximately 30 min for youths to complete. It contains each of the components included in the Web-based GMI, including a lesson on neuroplasticity (Figure 1); testimonials from older peers; information about research suggesting the malleability of personal traits (Figure 2); and a self-persuasion exercise wherein the participant provides advice to a student in the VR environment who has just experienced a peer-related setback. Content is delivered by *characters* in the VR environment (adolescent and adult actors hired and filmed for the creation of this intervention), who are matched to an adolescent's self-identified gender identity for a more personalized experience (Figure 3). These characters help guide the youth participant through each stage of the program, providing scientific information and personal stories. The primary difference between the VR and Web-based GMI involves the content delivery system and, by extension, the level of immersion each intervention offers. The VR program is designed to be immersive, fun, and interactive; the youth have an opportunity to choose to speak to various scientists and

students within the VR environment and can navigate from one scene to the next; by contrast, in the online program, participants are automatically exposed to a series of text-based activities. Additionally, the VR Personality Projects provides participants the opportunity to provide advice (by speaking aloud to a student) in the VR environment, immediately after the student experiences a setback. Thus, the intervention offers a more self-directed, active experience for participants, as opposed to the passive experience of progressing through a largely text-based online program. Distinctions and similarities in user experience and content between the Web-based and VR GMIs are outlined in Table 1.

Youths who become dizzy or experience discomfort during the VR experience will be permitted to take breaks, or stop participating, at any time. Generally, glasses fit within the VR headset and may be worn during the intervention; however, the choice to wear or remove glasses (for participants who wear them) will be made on a person-to-person basis, based on personal preference and comfort. Youths will be reminded of this at the start of the laboratory session and again before starting the VR experience for those randomized to this condition.

Figure 1. Screen Capture from VR Personality Project – lesson on neuroplasticity.



Figure 2. Screen Capture from VR Personality Project – a “scientist” describes research suggesting the malleability of personal traits.



Figure 3. Screen Capture from VR Personality Project. 3a: Participants select gender identity. 3b: Peer guides for adolescents who are male-identifying. 3c: Peer guides for adolescents who are female-identifying. Adolescents who select “another identity” or “rather not say” encounter peer guides shown in panel 3b.

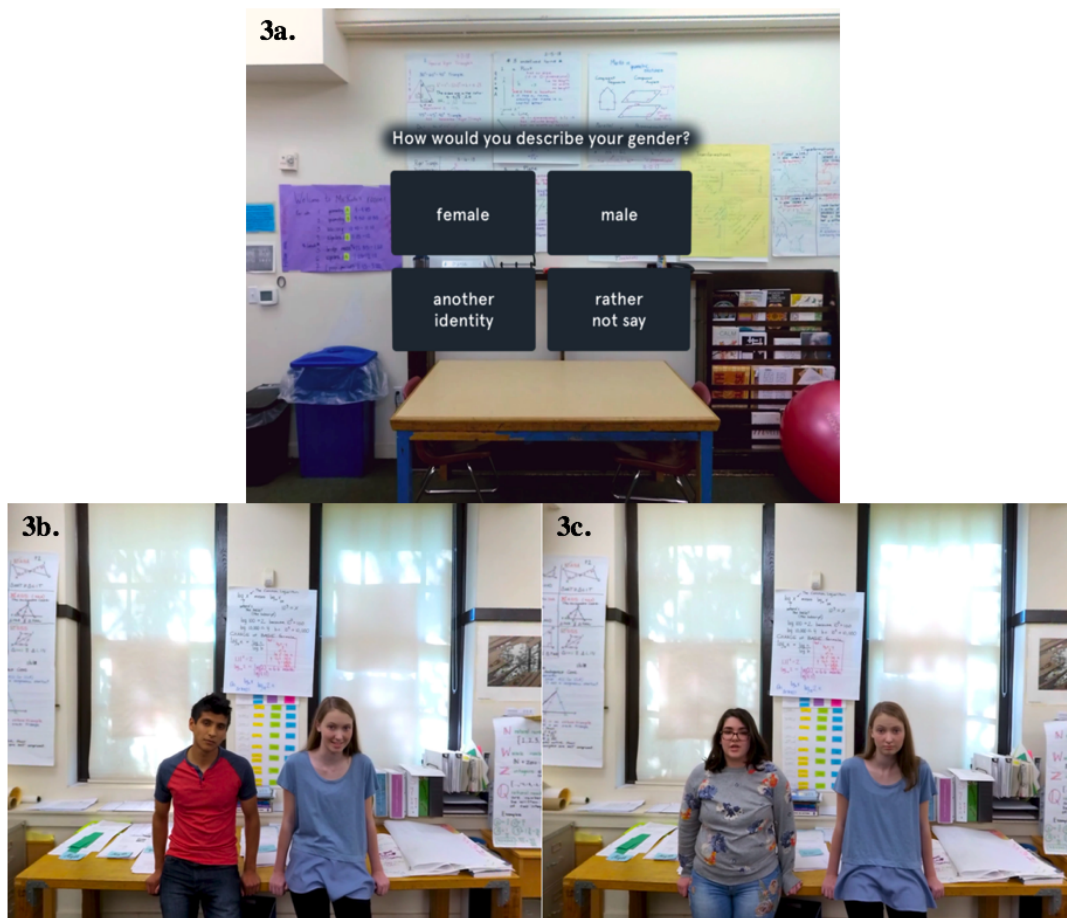


Table 1. Similarities and differences between the virtual reality (VR) and computer-based personality project interventions.

Intervention design feature	Virtual reality personality project	Computer-based personality project
Delivery format	Immersive, 360-degree virtual reality environments	Computer-based program delivered via Qualtrics survey
Personalization of intervention content	Characters in program vary in age, gender identity by participant-selected age and gender identity	Static program content; no personalization by user characteristics
Degree of user choice	Participants select when to proceed to subsequent intervention sections; where to focus attention and which characters to speak to in a variety 360-degree environment; how many questions to ask program <i>characters</i> ; and whether to engage in each intervention activity	Participants select when to proceed to subsequent intervention sections and whether listen to audio-recordings of written intervention text
Core program content	Lesson on neuroplasticity and the brain; psychoeducation regarding links between thoughts, feelings, and actions; peer and scientist testimonials, “saying-is-believing” activities to solidify learning. Delivered by characters and computerized animations in various VR environments.	Lesson on neuroplasticity and the brain; psychoeducation regarding links between thoughts, feelings, and actions; peer and scientist testimonials, “saying-is-believing” activities to solidify learning. Delivered via written text and accompanying audio-recordings of text.
Structure of “saying-is-believing” activity	Participants witness a program character undergo an in-vivo stressor related to depressive symptoms. Participants (a) describe how they themselves would feel, were they to experience a similar stressor, by speaking out-loud to the VR program guide, and (b) offer advice to help this character cope more effectively with the setback, again by speaking out-loud to the program character. Participants select when to begin and stop speaking.	Participants read about a peer undergoing a stressor related to depressive symptoms. Participants (a) write about how they themselves would feel, were they to experience a similar stressor, and (b) offer written advice to help this peer cope more effectively with the setback (using newly-gleaned knowledge about personality and the brain).

Web-Based Supportive Therapy

The Web-based ST [13,14] intervention, called the Sharing Feelings Program, is delivered entirely via Qualtrics, is self-administered by youths, and takes approximately 30 min to complete. It is structurally similar to the Web-based GMI, but it is designed to mimic ST. The goals of the ST intervention are to encourage youths to identify and express feelings to close others; the intervention does not teach or emphasize specific skills or beliefs. In a previous trial, ST led to smaller improvements in adolescent stress recovery, perceived control, and internalizing problems compared with a GM program [13,14]. The ST SSI is designed to control for nonspecific aspects of intervention, including engagement in a computer program. It includes the same number of reading and writing activities as the Web-based mindset intervention; it also mirrors the Web-based mindset intervention’s structure, including vignettes written by older peers describing times when they benefited from sharing feelings with close others. Immediately following intervention completion, all youths (regardless of condition assignment) will be asked to complete the same battery of questionnaires immediately postintervention to index immediate shifts in proximal outcomes.

After both the youth and the parent have completed their respective portions of the study, the laboratory visit will conclude. All study participants will be offered referral information for psychotherapy and/or pharmacologic treatment at Stony Brook and the surrounding community. Participants will not be excluded from completing study procedures if they begin receiving treatment for psychological distress during the study.

Before the youth and parent leave the laboratory, study personnel will inspect the youth and parent questionnaire responses on items inquiring about suicidal ideation. If there is any indication of adolescent suicidal ideation during the laboratory session, risk assessments will be conducted by trained study personnel. In the event that a participant is in imminent danger to themselves or others, their accompanying parent will be informed. Study personnel will meet with the family to establish a safety plan. In the event of reported, active suicidal ideation or plan, the family will be accompanied to the Psychiatric Emergency Program at the nearby University Hospital.

Participant Incentives

Upon completing the 2-hour laboratory-based session, participating families will receive one US \$30 Amazon gift card, for a rate of US \$15 per hour, the standard rate approved by the University IRB and consistent with minimum wage in New York State. When each participating adolescent and parent complete the 3-month follow-up questionnaire, the family will receive a US \$10 Amazon gift card, again based on a US \$15 per hour rate. Similarly, when the adolescent and parent both complete the 9-month follow-up questionnaire, the family will receive a final US \$10 Amazon gift card. Thus, total compensation for participating in this study is US \$50.

Follow-Up Assessments

To enable evaluation of the interventions’ effects on depressive symptoms and secondary study outcomes over time, each adolescent and parent will be invited to complete Qualtrics-based questionnaire batteries, including the same questionnaires as those they completed at their initial laboratory

session. Links to Qualtrics surveys will be sent to families at 3- and 9-month follow-up points. Surveys may be conducted via phone at the family's request. Families who do not complete the follow-up questionnaires within 3 days of receipt will receive up to 3 reminder messages from the research team to encourage survey completion.

Notably, logistical constraints necessitated our limiting the number of follow-up assessments in this study to 2 per family (at 3- and 9-month postintervention), and analyses were planned accordingly (see below for a more thorough description). We elected a final follow-up assessment at the 9-month mark to maintain consistency with previous trials of GMI [13,14].

After the study is complete, an aggregate results summary will be emailed to families. Condition assignment will be revealed at this time, and all youths will receive access to both Web-based interventions. Youths who did not receive the VR program will be invited to complete the intervention at Stony Brook University.

Questionnaires

Table 2 displays a timeline of all study procedures, including points at which each questionnaire will be administered to parents and/or youths. All questionnaires are detailed below.

Family and Treatment History Questionnaire

Parents will report demographic, family, and other background information (eg, age, sex, race, childhood adversity exposure, and mental health treatment history). Parents will also complete the 4-item Pubertal Development Scale [30] with regard to their adolescent, given the well-documented effects of puberty on depression onset.

Children's Depression Inventory-2

Adolescent depressive symptom severity will be assessed using the CDI-2 [31] child form (youth-report) and parent forms (parent-report). The CDI-2 is a reliable, valid measure of youth depression severity, normed for youth age and sex and yielding raw and *T* scores. Changes in youth-report CDI-2 scores from baseline to each of the follow-up assessments (3-month and 9-month) will serve as the primary index of intervention effects. Changes in parent-report CDI-2 scores from baseline to each of the follow-up assessments (3-month and 9-month) will serve as a secondary index of intervention effects. The CDI-2 will not be administered to youths or to parents immediately postintervention, as we do not expect depressive symptom change to occur within the span of 1 study session. Changes in scores on other assessments will serve as secondary outcomes.

Screen for Child Anxiety and Related Disorders

Given high comorbidity between depression and anxiety [32], anxiety symptoms will be assessed at baseline and all follow-ups (except postintervention) using the Screen for Child Anxiety and Related Disorders-Child and -Parent versions (SCARED-C/SCARED-P): a 41-item self-report measure [33,34]. Youths and parents, respectively, rate (0 to 2) the degree to which statements describing anxiety symptoms are true about

them or their adolescent. Higher summed SCARED-C and SCARED-P total scores indicate greater adolescent anxiety severity.

Primary Control Scale for Children

The primary control scale for children (PCSC) [35] is a 24-item scale measuring youths' perceived ability to influence or alter objective events or conditions through personal effort. Youth rate agreement with statements about their ability to exert primary control (eg, "I can do well on tests if I study hard" and "I can get other kids to like me if I try"). The PCSC has shown acceptable internal consistency, 6-month test-retest reliability, and inverse relations to adolescent depression severity.

Secondary Control Scale for Children

The secondary control scale for children (SCSC) [19] is a 20-item scale measuring youths' perceived ability to shape the personal impact of objective conditions on oneself by adjusting oneself to fit those conditions. Youth rate agreement with items reflecting various kinds of secondary control such as adjusting cognition ("When something bad happens, I can find a way to think about it that makes me feel better"). The SCSC has shown acceptable reliability and validity in a large youth sample.

Implicit Personality Theory Questionnaire

The Implicit Personality Theory Questionnaire [36] asks the youth to rate the extent of their agreement with 3 statements linked to the malleability of personality, using a 1 to 7 Likert scale (eg, "Your personality is something about you that you can't change very much"). Higher mean scores on these 3 items indicate a stronger fixed personality mindset, a lower score indicates a stronger growth personality mindset. Both youths and parents will report their mindsets of personality in this study.

University of California Los Angeles Loneliness Scale

The UCLA Loneliness Scale [37] is a widely used self-report scale of loneliness in adolescents. The 20-item version will be used in this study. Adolescents rate how often they experience loneliness in various contexts (eg, "How often do you feel part of a group of friends?" and "How often do you feel there is no one you can turn to?"). Higher scores indicate higher levels of loneliness.

Beck Hopelessness Scale—Short Version

The Beck Hopelessness Scale (BHS)-4 [38] is a shortened version of the 20-item BHS [39] designed for brief psychological screening purposes. The 4 items on this measure are "My future seems dark to me"; "Things just won't work out the way I want them to"; "There is no use in really trying to get something I want because I probably won't get it"; and "I feel that the future is hopeless and that things cannot improve." On each item, participants rate their agreement from 0 to 3, resulting in a maximum of 12 points in total (higher scores indicate higher levels of hopelessness). The short version of the BHS has high internal consistency ($\alpha=.85$) and correlates highly with measures of depressive symptoms, as well as the full-length BHS, in large studies of clinical and community samples [40].

Table 2. Schedule of enrollment, interventions, and assessments.

Schedule	Study period					Close-out (9 months)
	Enrollment	Allocation (baseline)	Post-allocation Intervention ad- ministration	Immediate post- intervention	3 months	
Enrollment						
Eligibility screen	X	— ^a	—	—	—	—
Informed consent/assent	X	—	—	—	—	—
Allocation	—	X	—	—	—	—
Interventions^b						
VR GMI ^c	—	—	X	—	—	—
Web-based GMI ^d	—	X	—	—	—	—
Web-based ST ^e	—	X	—	—	—	—
Assessments						
Youth self-report						
Children's Depression Inventory 2-Youth	—	X	—	—	X	X
Screen for anxiety related disorders-Youth	—	X	—	—	X	X
Primary control scale for children	—	X	—	X	X	X
Secondary control scale for children	—	X	—	X	X	X
Beck Hopelessness Scale-Short form	—	X	—	X	X	X
UCLA ^f Loneliness Scale-Version 3	—	X	—	X	X	X
Implicit personality theories questionnaire	—	X	—	X	X	X
Attitudes toward therapy scale	—	X	—	X	X	X
Program feedback scale	—	—	—	X	—	—
Parent report						
Family demographics, youth treatment history	—	X	—	—	—	—
Children's depression inventory 2-parent	X	X	—	—	X	X
Screen for anxiety related disorders-parent	—	X	—	—	X	X
Implicit personality theories questionnaire	—	X	—	—	X	X
Attitudes toward therapy scale	—	X	—	—	X	X
Brief symptom inventory-18	—	X	—	—	X	X

^aNot applicable.

^bEach ~30 minutes in length; randomized to receive 1 of 3.

^cVR GMI: virtual-reality growth mindset intervention.

^dGMI: growth mindset intervention.

^eST: supportive therapy.

^fUCLA: University of California Los Angeles.

Brief Symptom Inventory 18

The Brief Symptom Inventory (BSI)-18 [41] is a valid, reliable screening tool for adult (here, parental) psychological distress. Adult respondents rate endorsement of 18 physical and emotional complaints on a 0 to 4 Likert scale. The BSI-18 includes 3 subscales for somatic, anxiety, and depressive

symptoms. The total sum score yields an additional total distress score.

Attitudes Toward Therapy

Attitudes toward psychotherapy [42] will be assessed using a single item for youth and parents: "Lots of kids deal with difficult emotions at one time or another. On a scale from 1 (not at all helpful) to 10 (extremely helpful), how helpful do you

think therapy or counseling would be for you (your child) in coping with these kinds of problems?"

Program Feedback Scale (Designed for This Study)

To assess the acceptability of each intervention program, youths will be asked to complete questions regarding their experience with the intervention to which they were assigned. Questions inquire about how much they enjoyed the program; whether

they understood the program; whether they would recommend the program to a friend; and whether they found the program easy to use. The Program Feedback Scale was developed specifically for this study; several items from the Scale were drawn from previous research [13,14] but others are new to this study and have not been used previously. All items are included in [Textbox 1](#).

Textbox 1. Program Feedback Scale items. Items rated on a 0 (really disagree) to 4 (really agree) scale unless otherwise specified.

- I enjoyed the program
- I understood the program
- This program was easy to use
- I tried my hardest during the program
- I think the program would be helpful to other kids my age
- I would recommend this program to a friend going through a hard time
- I agree with the program's message
- What did you like about the program? Please share as many true thoughts and feelings as you would like (*free response*)
- What would you change about the program? Please share as many true thoughts and feelings as you would like (*free response*)

Timeline for Data Collection and Results Reporting

Data collection began in March 2019 and is projected to be complete by December 2021. Thus, we intend to report results by Spring of 2022. Upon completion of data collection and publication of results, deidentified participant-level data will be made publicly accessible.

Results

Aim 1: Attempt to Replicate Past Research

We will use mixed-effects linear models to test the hypothesis that interventions teaching GM (either VR or Web-based) predict reductions in adolescent depressive symptom severity (primary study outcome), per both adolescent and parent reports, relative to Web-based ST. Our study design, including 3 assessment points is structured to allow for detection of linear intervention effects. We will run additional mixed-effects linear models to assess whether interventions teaching GM predict larger improvements in secondary study outcomes (perceived primary and secondary control, hopelessness, loneliness, attitudes toward psychotherapy, and parent psychopathology) versus Web-based ST. Intervention condition will be a binary predictor variable in these models, with the VR GMI and Web-based GMI groups collapsed into a single GM intervention group. Potential covariates will include family income, age, sex, and time (baseline, postintervention where applicable, and 3-month and 9-month follow-up); each possible covariate will be included in analyses if it shows a significant association with a model outcome at baseline or any follow-up point (such associations are unlikely to occur, given randomization procedures, but remain possible). Models will include a random intercept and slope, an autoregressive error structure, and use full information maximum likelihood (FIML) estimation to address missing data. We will create 2 orthogonal planned contrasts for testing intervention effects. One planned contrast

will examine whether the 2 active GM conditions differ from the ST control condition, whereas the other planned contrast will examine whether the VR-based intervention outperforms the Web-based intervention. A significant ($P < .05$) interaction between the first contrast and time would indicate that interventions teaching GM predicted significantly different 9-month change in an outcome relative to the control ST condition. We will also replicate these analyses for the most central symptoms of adolescent depression identified in previous analyses (*sadness*, *self-hatred*, and *loneliness*) and use Holm-Bonferroni corrections for multiple comparisons.

Aim 2: Evaluate New, Single-Session, Virtual Reality Growth Mindset Intervention

As for Aim 1, we will use mixed-effects linear models to test the hypothesis that VR-GMI predicts greater reductions in adolescent and parent-reported depressive symptom severity (primary study outcomes), as well as perceived primary and secondary control, hopelessness, loneliness, attitudes toward psychotherapy, and parent psychopathology (secondary outcomes), relative to (1) the Web-based GM program, (2) the control program, and (3) either program, when combined into a single, *non-VR intervention* group. Models will be structured as described in Aim 1. A significant ($P < .05$) interaction between the second orthogonal contrast mentioned in Aim 1 and time would indicate that interventions teaching GM predicted significantly different 9-month change in an outcome relative to the control ST condition. We will also replicate these analyses for the most central symptoms of adolescent depression identified in previous analyses (*sadness*, *self-hatred*, and *loneliness* [43]) and use Holm-Bonferroni corrections for multiple comparisons.

Aim 3: Test Mediation Through Perceived Control

To test whether the VR intervention and the Web-based GM intervention reduces youth-reported depressive symptoms

through proximal increases in perceived control, we will conduct multiple mediation analyses which involve simultaneous indirect effects by multiple variables [44]. This approach allows for both an analysis of the total indirect effect (the aggregate indirect effect of all the candidate mediators under investigation) and analyses of specific indirect effects (ie, of each mediator under investigation). For mediation models assessing perceived control, we will use postintervention data to assess candidate mediators and 9-month follow-up data to assess depressive symptoms. In each model, the predictor variable will be intervention condition (in Model 1, VR versus Web-based GM intervention; in Model 2, VR versus Web-based ST; and in Model 3, Web-based GM versus Web-based ST); the simultaneous mediator variables will be postintervention perceived behavioral control and postintervention perceived emotional control. We will use bias-corrected bootstrapping to test the significance of specific and total indirect effects within the mediation model. Bootstrapping has the advantage of high statistical power without assuming multivariate normality in sampling distributions, enabling parsimonious analysis of one or several candidate mediators [44,45]. The Iavaan package version 0.5-16 in R version 2.15.1, which is capable of testing both multiple and single mediator models using FIML estimation, will be used for mediation tests [46]. To test for indirect effects of candidate mediators, parameter estimates of total and specific indirect effects are generated, along with their CI, using 1000 to 20,000 random bootstrapped samples. We will specify 5000 resamples in this study per Preacher and Hayes' [32] recommendations. If the 95% bias-corrected CI for a total indirect parameter estimate does not contain 0, then that indirect effect can be considered statistically significant, demonstrating mediation [44,45]. Using this approach, this study will be sufficiently powered to detect significant indirect effects in each model (bias-corrected CIs for a 2-mediator model

show .80 power for samples of 50 and over .90 for samples of 100 [46,47]).

Aim 4: Gauge Acceptability of the Virtual Reality Intervention

A series of between-group ANOVAs will be used to evaluate differences by intervention condition assignment in adolescent-reported intervention acceptability. Specifically, we will examine group-level differences in adolescents' mean ratings on each continuously rated item from the Program Feedback Scale. Specific contrasts comparing groups will be examined, should significant overall mean differences emerge on any item.

Discussion

The objective of this 3-arm randomized trial is to evaluate whether a single-session, immersive VR intervention teaching *GM*—the belief that personal traits and attributes are malleable as opposed to fixed—can reduce depressive symptoms in high-risk adolescents compared with a Web-based GMI and an active Web-based control. Secondary aims are to evaluate the VR program's effects on other types of adolescent symptoms and functioning, including anxiety, perceived control, and hopelessness; to evaluate a possible mechanism through which the VR might reduce depression symptoms (ie, by increasing adolescents' sense of perceived control); and to assess the VR program's acceptability relative to the Web-based interventions. Results will gauge the promise of the *VR Personality Project* as a brief, highly engaging, and mechanism-targeted intervention for reducing adolescent depressive symptoms. Given the increasing levels of adolescent depressive symptoms in recent years [2] and variable efficacy and accessibility of existing interventions [3,8], results of this trial may suggest a promising new approach, using immersive VR technology, to reducing depression in youth.

Acknowledgments

Direct costs for the aforementioned clinical trial will be funded by Limbix; however, no Limbix staff are involved in clinical research procedures.

Conflicts of Interest

None declared.

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Abbreviations

- ANOVA:** analysis of variance
- BHS:** Beck Hopelessness Scale
- BSI:** Brief Symptom Inventory
- CDI-2:** Children's Depression Inventory-2
- FIML:** full information maximum likelihood
- GM:** growth mindset
- GMI:** growth mindset intervention
- IRB:** Institutional Review Board
- PCSC:** primary control scale for children
- RCT:** randomized controlled trial
- SCARED-C:** Screen for Child Anxiety and Related Disorders-Child
- SCARED-P:** Screen for Child Anxiety and Related Disorders-Parent
- SCSC:** Secondary Control Scale for Children

SSI: single-session intervention
ST: supportive therapy
VR GMI: virtual-reality growth mindset intervention
VR: virtual reality

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Protocol

Evaluation of Adaptive Feedback in a Smartphone-Based Serious Game on Health Care Providers' Knowledge Gain in Neonatal Emergency Care: Protocol for a Randomized Controlled Trial

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Abstract

Background: Although smartphone-based clinical training to support emergency care training is more affordable than traditional avenues of training, it is still in its infancy and remains poorly implemented. In addition, its current implementations tend to be invariant to the evolving learning needs of the intended users. In resource-limited settings, the use of such platforms coupled with serious-gaming approaches remain largely unexplored and underdeveloped, even though they offer promise in terms of addressing the health workforce skill imbalance and lack of training opportunities associated with the high neonatal mortality rates in these settings.

Objective: This randomized controlled study aims to assess the effectiveness of offering adaptive versus standard feedback through a smartphone-based serious game on health care providers' knowledge gain on the management of a neonatal medical emergency.

Methods: The study is aimed at health care workers (physicians, nurses, and clinical officers) who provide bedside neonatal care in low-income settings. We will use data captured through an Android smartphone-based serious-game app that will be downloaded to personal phones belonging to the study participants. The intervention will be adaptive feedback provided within the app. The data captured will include the level of feedback provided to participants as they learn to use the mobile app, and performance data from attempts made during the assessment questions on interactive tasks participants perform as they progress through the app on emergency neonatal care delivery. The primary endpoint will be the first two complete rounds of learning within the app, from which the individuals' "learning gains" and Morris G intervention effect size will be computed. To minimize bias, participants will be assigned to an experimental or a control group by a within-app random generator, and this process will be concealed to both the study participants and the investigators until the primary endpoint is reached.

Results: This project was funded in November 2016. It has been approved by the Central University Research Ethics Committee of the University of Oxford and the Scientific and Ethics Review Unit of the Kenya Medical Research Institute. Recruitment and data collection began from February 2019 and will continue up to July 31, 2019. As of July 18, 2019, we enrolled 541 participants, of whom 238 reached the primary endpoint, with a further 19 qualitative interviews conducted to support evaluation. Full analysis will be conducted once we reach the end of the study recruitment period.

Conclusions: This study will be used to explore the effectiveness of adaptive feedback in a smartphone-based serious game on health care providers in a low-income setting. This aspect of medical education is a largely unexplored topic in this context. In this randomized experiment, the risk of performance bias across arms is moderate, given that the active ingredient of the intervention

(ie, knowledge) is a latent trait that is difficult to comprehensively control for in a real-world setting. However, the influence of any resulting bias that has the ability to alter the results will be assessed using alternative methods such as qualitative interviews.

Trial Registration: Pan African Clinical Trials Registry PACTR201901783811130; <https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=5836>

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KEYWORDS

neonatal mortality; education; emergency medical services; global health; smartphone; feedback; health workforce; developing countries

Introduction

Background

In low-income contexts such as Sub-Saharan Africa, the need for health workers to provide care for themselves is more frequent than that in middle- and high-income settings and can be associated with negative neonatal outcomes [1]. Of the estimated 2.9 million neonatal lives (from birth through day 28) lost each year globally, Sub-Saharan Africa has the highest overall risk of death within the first 24 hours of life and accounts for 37% of the global neonatal deaths [1]. This is compounded by severe workforce shortage, coupled with the health workforce skill imbalance and maldistribution, and a lack of training opportunities [2,3]. Additional training is needed to better prepare health providers in these facilities to provide effective emergency pediatric and neonatal care [4,5]; however, unfortunately, face-to-face training costs between US \$80 to \$300 per person per day and is difficult to deliver at scale [6]. A face-to-face course developed in Kenya (Emergency Triage, Assessment and Treatment plus admission care [ETAT+]) [7,8] has been successfully used to provide training in Kenya as well as eight other low-income countries [9]. ETAT+ has already been used to train over 5000 health care workers and 2000 medical students across Kenya, Uganda, Rwanda, Zimbabwe, Zambia, Malawi, Tanzania, Sierra Leone, and Myanmar. It is part of the undergraduate medical training curriculum in medical schools in East Africa [10]. The aim of the ETAT+ is to familiarize health workers with clinical guidelines and the necessary knowledge and skills for triaging all sick children when they arrive at a health facility into emergency cases with priority signs or nonurgent cases and to provide emergency treatment for those with life-threatening conditions [11]. Only a small fraction of trained health providers have received the basic requisite skills training for newborn resuscitation in this context [12,13]. New strategies are therefore required to improve access for over 1 million health providers across Africa, and training approaches need to be updated efficiently as guidelines change and be able to capture data on how many health workers are trained [14,15].

There is little evidence to support the implementation of learning interventions that are relevant to the context of low-income settings, which takes into account health workers' initial and continuing clinical training needs and adapts learning content in light of skill mastery and performance as they continue to develop knowledge through it [15-18]. Within low-resource contexts, investigation of learner models (ie, a cognitive model

that tries to model observed student learning behaviors) needed to support tailored instruction based on predicted learner's skill mastery in clinical settings is required [19], as adaptive instructional support has been shown to significantly outperform teacher-led large-group instruction, nonadaptive computer-based instruction, and paper-based instruction in producing learning gains in high-resource settings outside clinical care [19].

Several health care training apps have been developed to date, and the approaches used therein can broadly be divided into two categories. Some replicate existing teaching strategies "on a screen," for example, by providing questions and answers for exam practice or displaying of textbook graphics. Others take advantage of features specific to mobile devices, examples of which include the ability to respond to user choices with different pathways or the use of animations with which the user can interact [15]. Serious games, which are digital games with a specific, applied purpose (other than entertainment) that can be played on mobile phones, are one such way of providing training with the potential to affect health outcomes [20]. The rationale for using serious games is that, similar to "first-person" computer games, emergency care training should enable health workers to follow highly structured pathways (such as clinical care algorithms) with pieces of information (cues) sought at each step, which determine the correct actions to perform. With both clinical training and performance in computer games, executing cue-response sequences perfectly, rapidly, and automatically demonstrates mastery. This type of mastery has been shown to support effective clinical care delivery, but the required frequency of rehearsal in this approach is difficult and expensive to maintain for face-to-face training [21]. By using a serious gaming approach, users may be more motivated to repeatedly play the serious game, using incentives such as rewards, increasing difficulty, and scores—techniques that have been successfully used to encourage repeated gameplay in nonserious computer games. There is a scarcity of evidence from studies evaluating and assessing serious gaming approaches using smartphones in health care training in low-income settings, but this topic was recently highlighted in the most recent systematic review [22,23].

Efforts to implement innovative educational interventions, which increase the number of well-trained health providers, are yet to capitalize on digital learning approaches that model learners' knowledge states to provide individualized instruction and have been shown to have considerable positive effects on learning outcomes in other subject areas [5,24,25]. The Life-Saving Instruction for Emergencies (LIFE) project is developing an

approach to create serious games for low-cost smartphones initially to provide training for care of very sick newborns and children. The game evolves the scenario-based teaching model that is used in the traditional face-to-face ETAT+ course already described.

The potential for utilizing the digital and reusable nature of interventions such as LIFE, to personalize the way health workers learn and receive feedback on their performance on which they can base future learning, achieve learning objectives, and develop their skills is still underexplored and unknown [18,22]. Additionally, the use of smartphones as experimental tools offers access to a wider pool of study participants due to their ubiquitous nature [26]; can minimize the cost of implementing, evaluating, and scaling an educational intervention such as LIFE in a resource-constrained context [15], and has been shown to raise learners' interest in knowledge interventions [27].

Objectives

The primary objective of this randomized experiment is to investigate whether adaptive individualized feedback is superior to standardized feedback in smartphone-based emergency neonatal care training. We hypothesize that health care providers randomized to receive adaptive feedback will have a significant improvement in learning gains as compared to those randomized to receive standardized feedback.

Methods

Study Design

The study (trial registration: Pan African Clinical Trials Registry PACTR201901783811130) will have a parallel-group double-blinded randomized experiment design with an allocation ratio of 1:1. The participants will be randomized to the intervention or control group when they launch the android-based training app for the first time on their individual smartphone devices.

Eligibility Criteria

Health care workers who are in nursing, clinical, or medical professional cadres that offer bedside patient care are included. Additionally, health care workers in practice and those in training are eligible for inclusion into the experiment. Health care workers who have retired from clinical practice and participants who are not health care workers will be excluded from the study.

Study Setting and Recruitment

This study does not have a specific physical study site; it focuses on low-income countries that stand to benefit from ETAT+ training. Distribution of the intervention is through the Google Play Store, with initial efforts directed toward physical recruitment in Kenya. Recruitment of study participants will be through three main avenues: (1) remotely, by raising awareness of the Android Google app on social media platforms and online health networks forums every couple of weeks during the study duration to promote voluntary, self-enrolment for use of the training tool; (2) use of snowballing sampling by ETAT+ trainers, previous study participants, and lecturers in medical

sciences at local Kenyan universities to suggest that (and encourage) other health workers to self-recruit into the study; and (3) use of a study sample from the purposive selection strategy that will be actively convened once every month, with a unique set of participants to ensure the participant recruitment targets are diverse and met. Snowballing sampling is a type of convenience sampling where a group of people (in our case, already recruited participants) recommend potential participants for the study [28]. The cycle of recommendation of participants for inclusion into the study continues during the study duration. This also serves as an indicator of LIFE intervention adoption. The first avenue includes platforms that are focused on health capacity building in the global south in line with LIFE's focus on low-income contexts. Avenues 2 and 3 will take place at the following sites: Kenyatta National Hospital - Neonatal Nurse Training Unit; College of Health Sciences, University of Nairobi; Kenya Medical Training College (Nairobi); and Gertrude's Garden Children's Hospital Nurse Training School (Nairobi).

Intervention

The intervention in this study involves adaptive, personalized, and immediate feedback that is provided while learning through a smartphone-based serious gaming Android app. The content to be learned is based on ETAT+ guidelines, a course that is already offered in nine low-income countries [7,8,10]. The intervention will be available on the Google Play Store where it will be publicly accessible, downloadable, and installable to any compatible android-based mobile device. All study participants will receive a link to the mobile app hosted on the Android Play Store. The LIFE app was designed for Android's Target SDK 19 as the minimum version of Android supported as of February 2019 (which targets 100% of Android devices) [29]. Given that the intervention has undergone alpha and beta testing on health care providers' smartphones since October 2017 in Kenya, we are confident of the stability of the app.

The personalized immediate feedback to be given to the experimental group participants is designed to arouse meaningful immersive learning experiences from continuous interaction between the learners and the smartphone-based training [30,31]. This adaptive feedback will be provided to experiment group participants after each incorrect attempt at a learning task with three cascading detail levels based on predicted probability that the learner's next attempt is going to be correct. The wording of the feedback provided is dependent on the number of incorrect choices the learner had selected and the actual incorrect choices themselves. The control group study participants will receive standardized nonpersonalized immediate feedback after each incorrect attempt at a learning task, with the feedback on the first incorrect attempt asking the learner to retry and the feedback on the second attempt providing a detailed explanation of the correct choices to select.

The LIFE app is a measurement tool; at the end of successful completion of a learning session, the platform provides performance scores based on whether each learner's response to the learning task was correct on the first attempt.

This methodology mimics a common approach in experimental design known as A/B testing, which is used to optimize concepts

such as feedback or user interface on digital platforms [32,33]. In particular, the experiment described here emulates A/B tests' commonly used Hypothesis Experiment Data - Driven Development model, whose description and use are detailed elsewhere [34]. Such an experimentation approach can be used for digital health interventions where there is need for data-driven decision making on inclusion of features and the data are trustworthy, but assessment of the added value of features on the digital platform is difficult [33].

Outcomes

The primary endpoint for both arms of the experiment will be the presence of two complete rounds of learning sessions using LIFE, the former is the pretest round and the latter is the posttest round. Both scores will be converted into percentages. From the pre-post scores, the study's main outcome—the learning effect size (d), [35]—will be calculated as follows:

$$d = \frac{M_{post,T} - M_{pre,T}}{SD_{pooled}}$$

where the pooled SD is defined as:

$$SD_{pooled} = \sqrt{\frac{SD_{pre,T}^2 + SD_{post,T}^2 + SD_{pre,C}^2 + SD_{post,C}^2}{n_T + n_C}}$$

The bias adjustment is provided by the formula:

$$d_{adj} = \frac{d}{\sqrt{1 + \frac{3}{n_T + n_C}}}$$

where n_T is the sample size of the treatment group, $M_{pre,T}$ is the pretest mean for the treatment group, $M_{post,T}$ is the posttest mean for the treatment group, $SD_{pre,T}$ is the SD of means for pretest in the treatment group, $SD_{post,T}$ is the SD of means for posttest in the treatment group, n_C is the sample size of the control group, $M_{pre,C}$ is the pretest mean for the control group, $M_{post,C}$ is the posttest mean for the control group, $SD_{pre,C}$ is the SD of means for pretest in the control group, and $SD_{post,C}$ is the SD of means for posttest in the control group.

The effect size from equation from (1) is referred to as *Morris G* [35] and represents the mean difference between the study groups. Because of randomization, this calculation allows to control for pre-existing differences among learners (eg, intelligence quotient level), to estimate treatment effectiveness even when the treatment and control groups are not equivalent, and to consider the variances of both pretest and posttest scores. This contrasts with other forms of effect-size calculation such as Hedges G and Becker D, which only use pretest or pooled variances [35]. In this model, the pretest and posttest variances are assumed to be homogeneous.

Secondary outcomes that will be assessed are time difference between each round of learning sessions, the number of times a learner has encountered a learning task up to the current opportunity (ie, cumulative attempts on learning task per learner), the time spent on each learning task, and the level of feedback provided. These calculations will be performed in Python, version 3.6.8 (Python Software Foundation, Wilmington, DE).

Participant Timeline

Enrolment of study participants began on February 1, 2019, and will continue up to July 31, 2019. Because the rollout of LIFE's intervention in this study is based on the principles and outcomes of an implementation study [36] and informed by self-regulated self-directed learning [37-39], it seeks to understand and work within real-world conditions, rather than trying to control for adoption, acceptability, coverage, and sustainability conditions or remove their influence on the study outcome [36]. Subsequently, to optimally maintain fidelity to LIFE's planned scale-up, no training sessions are planned for the study participants. Although LIFE is designed for low-income contexts, we set no limit by geographical coverage for self-directed health care providers who might be interested in undertaking this training. However, for primary outcome analysis, participants from high-income countries will be omitted. Participants without any geographic location data (due to refusal to grant the LIFE app the required Android permissions) will be assumed to be from developing countries, given that our recruitment efforts are directed toward professional groups in these countries.

Sample Size Calculation

Similar interventions in other subject domains have been found to have an mean effect size of 0.22 (95% CI 0.16-0.27) from a meta-analytic fixed-effects model [24]. To detect an effect size of 0.22 with a two-sided 5% significance level and a power of 80%, a sample size of 83 participants per group, who reach the primary endpoint of the study, is necessary. A sample size calculation for a one-way ANOVA, together with one-sample and paired-sample t test analysis using the same effect, power, and significance parameters produce the same required sample size. We anticipate recruiting this number of participants (N=166) in 6 months. The sample size calculation formula is given in the [Multimedia Appendix 1](#).

Based on the alpha and beta tests of the LIFE version, we are assuming a 50% dropout rate of study participants, with drop-out defined as the incomplete or single use of the LIFE smartphone app. We plan to recruit at least 332 participants to account for this dropout rate. To encourage repeated usage of LIFE, participants will receive up to three email reminders from the time they are enrolled into the study, spread over 3 weeks. Demographic data will be collected in the app during its initial use by study participants at the end of the first learning session. Thus, for learners who drop out before completing the first session, or chose not to fill in those data, no demographic data will be available. Logistic regression analyses will be performed on these data to evaluate whether there is a systematic bias caused by attrition of study participants that affects the interaction between the study groups and performance, exposure to previous ETAT+ training, clinical cadre, age of participant, and level of experience. In an effort to ensure participant recruitment is at par with the required study sample size, a monthly target of 30 participants, evaluated at the end of each month, has been set for this study.

Randomization

For allocation of the participants, an in-app algorithm will randomly generate a value of zero or one when the Android-based smartphone app is launched for the first time. This will determine whether the participant is allocated to the control or experiment group. It will also blind both the study participants and intervention staff to the group allocation of participants during the experiment, but not at the analysis stage. Sequence generation for random allocation is a computerized procedure pegged on a single instance (ie, smartphone app installation) that mimics a coin-tossing procedure. Therefore, use of permuted blocks of random sizes to assign participants to either the control or experimental group is not possible and will not be implemented.

Statistical Methods and Planned Analysis

For the primary endpoint, we will use the Morris G effect size to analyze the differences among group means in the study population. This will be assessed after the performance from the second round of training through the mobile app has been recorded. Secondary analysis will be conducted using regression analysis, with learning gains as the dependent variable and the aforementioned secondary outcomes as the independent variables, to evaluate their effect on learning gains. Learning gains, defined as the amount the health care providers learned divided by the amount they could have learned [40], will be calculated with the formula given in Equation 8 in [Multimedia Appendix 1](#).

Due to the definition of the primary learning outcome used in this study, the outcome cannot be computed for study participants whose dropout is characterized by the lack of at least two complete learning sessions. Without a postbaseline assessment, “intention-to-treat” analysis cannot be performed for dropout cases unless we impute outcomes, which tends to produce biased estimates [41]. This study will not be able to conduct an intention-to-treat analysis. However, dropout numbers will be reported in relation to those who reached the study’s primary endpoint, and their implications will be discussed with regard to self-regulated self-directed learning [37-39].

Qualitative interviews will be conducted in parallel with the experiment for participants who have reached the primary endpoint and those who drop out. These interviews will be used to explore how self-regulation in learning affected the use of the smartphone-based learning platform and to provide context for interpreting the observed learning outcomes from this study apart from offering evidence for tool validation.

Data Management

The primary data collected from the study participants’ Android smartphone app will be held on their devices with a backup copy synchronized to *Google Firebase*, a secure distributed online database server, after transmission in an encrypted format. During data collection, transcripts and recordings of interviews after the experiment will be stored on encrypted password-protected USB devices and transferred to secure password-protected servers in Kenya and Oxford. De-identified data will be shared with the Kenya Medical Research Institute

(KEMRI)-Wellcome Trust Research Program and University of Oxford for agreed analyses, with only named investigators having access to the data.

Ethics and Dissemination

The analyses described in this protocol have been approved by the KEMRI’s Scientific and Ethical Review Committee (#3444) and the Central University Research and Ethics Committee of Oxford University (#ED-CIA-18-106). Individual patient consent will be elicited from within the mobile app before collection of any demographic data in addition to using explicit Android permission requests. This approach of obtaining in-app informed consent is not uncommon in medical research; it has been described in detail in a previous systematic review [42] as well as specifically in mobile app-based research [43]. The results of this analysis will be shared with the Kenyan Ministry of Health, submitted to peer-review publications, and presented at international conferences.

Results

This project was funded in November 2016. Data were collected from February 2019 up to July 2019. As of July 2019, we enrolled 541 participants, of whom 238 reached the primary endpoint, with a further 19 qualitative interviews conducted to support evaluation (New-Born Unit in-charge nurses, n=4; Paediatric Intensive Care Unit nurses, n=5, final-year medical students already doing clinical rotations, n=4; and student clinical officers and nurses already doing clinical rotations, n=6). Full analysis will be conducted once the number of required participants is met, and the results are expected to be published by Spring of 2020.

Based on the education literature [24,44,45], an effect size of approximately 0.2, 0.5, and 0.8 will be considered small, moderate, and large, respectively. These thresholds represent the magnitude of effect and reflect our assumption that a statistically significant result is not necessarily important or meaningful; for example, for an effect size of 0.2, the difference between the study groups is trivial even if it is statistically significant [44,46].

Discussion

This study will be used to explore the effectiveness of adaptive feedback for learning in smartphone-based training for health care workers in a low-income setting. This aspect of medical education is a largely unexplored topic. In this randomized experiment, the risk of performance bias across arms is moderate, given that the active ingredient of the intervention (ie, knowledge) is a latent trait that is difficult to comprehensively control for in a real-world setting. However, the influence of any resulting bias’s ability to alter the results will be assessed within this study using qualitative interviews with study participants.

To help minimize attrition in the study, participants in all study arms who have not reached the primary endpoint will receive up to three email reminders to use the smartphone app from the time they are enrolled into the study, every couple of weeks. The email message will also include a running counter of how

many other participants from across the arms of the experiment have successfully played the game so far. The locally accessible study participants will be reimbursed for the mobile data costs incurred when downloading the game if that proves to be a barrier. Whether mobile data charges are a barrier to recruitment of participants and playing the game numerous times will be

evaluated through qualitative interviews on an ongoing basis throughout the study period. In case the participant recruitment does not meet the monthly targets, where possible, nonmonetary incentives (such as provision of clinical guidelines protocol booklets) will be phased in to motivate participation in the study.

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Multimedia Appendix 1

Sample size calculation formula.

[[PDF File \(Adobe PDF File\), 61KB - resprot_v8i7e13034_app1.pdf](#)]

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Abbreviations

LIFE: Life-Saving Instruction for Emergencies

KEMRI: Kenya Medical Research Institute

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Protocol

Designing and Testing a Treatment Adherence Model Based on the Roy Adaptation Model in Patients With Heart Failure: Protocol for a Mixed Methods Study

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Abstract

Background: Adherence to treatment is an important factor to decrease repeated and costly hospitalization owing to heart failure (HF). The explanation and prediction of medication adherence and other lifestyle recommendations in chronic diseases, including HF, are complex. Theories lead to a better understanding of complex situations as well as the process of changing behavior and explain the reasons for the existence of a problem.

Objective: The aim of this study is to report a protocol for a mixed methods study setting out to investigate the empirical validity of the Roy Adaptation Model as a conceptual framework for explaining and predicting adherence to treatment in patients with HF in Iran.

Methods: This mixed methods study consists of an exploratory sequential design to be conducted in 2 phases. The first phase involves identifying the factors associated with treatment adherence in patients with HF through content analysis of the literature and elucidating the perception of participants in the context of Iranian health care where the model of adherence to treatment is designed based on the Roy Adaptation Model. The second phase addresses the interrelationships among variables in the model through a descriptive study using structural equation modeling. Finally, following the summarization and separate interpretation of the qualitative findings and quantitative results, a decision is made about the extent to and ways in which the results of the quantitative stage can be generalized or tested for the qualitative findings.

Results: Content analysis of the literature in part 1 of the first phase was completed in 2017. Collection and analysis of qualitative data in part 2 of the first phase will be completed soon. The results are expected to be submitted for publication in 2019. Then, the second phase—the quantitative study—will be conducted.

Conclusions: The results of this study will provide valuable information about the empirical validity of the Roy Adaptation Model as a conceptual framework for explaining and predicting adherence to treatment in patients with HF, which, to date, have received little attention. The results can be used as a guide for nursing practice and care provision to patients with HF and also to design and implement effective interventions to improve treatment adherence in these patients.

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KEYWORDS

adaptation; treatment adherence and compliance; heart failure

Introduction

Background

Heart failure (HF) is a highly prevalent chronic disease that is considered a global epidemic [1]. A total of 5.1 million people in the United States suffer from this disease, the prevalence of which is anticipated to reach 46% by 2030 [2]. The prevalence of HF in Iran was reported as 8% in 2014 [3]. Despite the significant progress in the treatment of this disease, the mortality and readmission rates associated with this condition have remained high, with a 5-year survival rate of 50% [2] and with rehospitalizations common in HF patients; 83% of patients were hospitalized at least once and 43% hospitalized at least 4 times. These values did not differ in HF with reduced Ejection Fraction (EF) versus preserved EF [2]. These rates lead to increased costs not only for the patients and their family but also for the society and the health care system. Costly readmissions, mortality, morbidity, and progress of the disease can be reduced in these patients through adherence to the treatment regimen [4-8].

Adherence to treatment has been defined as a range of medication behaviors and lifestyle choices that are consistent with the regimen recommended by health care providers [9]. The rate of adherence reported in HF studies has varied within 7% to 90%, depending on differences in methodological approaches such as the type of definition and measurement method of adherence and the criteria for selecting patients in each study [10]. There is little information about the rate of adherence with the treatment regimen in HF patients in Iran. In one study [11], 60.3% of patients and in another study [12], 71.4% of patients had poor self-reported medication adherence. Adherence to treatment in HF is a multidimensional phenomenon influenced by the interplay of several factors, such as socioeconomic factors (age, gender, race, and lack of access to transportation), health care system-related factors (inadequate education of health care providers in chronic diseases, shortened time of visits by the physician, and lack of insurance support), patient-related factors (forgetfulness, improvement or reduction of symptoms, and knowledge deficiency), condition-related factors (severity of illness and depression), and therapy-related factors (side effects and the number of medications taken during the day) [9,13-15]. The explanation and prediction of medication adherence and other lifestyle recommendations in chronic diseases, including HF, are complex and should be understood before intervention [15]. Theories contribute to a better understanding of the complex situations as well as the process of changing behavior and explain the reasons for the existence of a problem [16]. Indeed, theories can provide a framework for explaining or predicting the likelihood of events and facilitate an understanding of various components and behavioral dynamics [17]. There are several social cognitive theories for explaining, predicting, and modifying adherence behavior with treatment regimen [18]. Meanwhile, application of nursing theories as a conceptual framework in research is essential for the development of nursing knowledge [19,20]. The use of conceptual models to guide nursing research seems complicated

because of their abstract concepts. The use of a conceptual model for conducting nursing research requires construction of a conceptual-theoretical-empirical (C-T-E) structure. In this structure, the component C is a conceptual model containing a set of general and abstract concepts and propositions that are used as the basis for research. The component T refers to the theory extracted from the conceptual model, which can be translated into empirical indicators (E) and tested further [21]. Note that the C-T-E structure for nursing is important, as it leads to the structure of the body of nursing knowledge and provides a reference framework for researcher nurses or nurses who take care of patients with a chronic disease on how to observe and interpret the phenomena of interest in the discipline [22]. The relationship between theory, research, and clinical practice is essential for the continuous development of nursing as a profession and science. Ideally, clinical practice should be based on the theory validated by research [23].

The Roy Adaptation Model in nursing is one of the most widely used conceptual frameworks for guiding research, nursing practice, and training. Furthermore, given its scope, it can be used as a conceptual model to generate and test nursing theories [24,25] because adherence to treatment is an adaptive behavior that is essential for coping with chronic diseases [26]. As a conceptual model of adaptation, the Roy Adaptation Model appears capable of explaining adherence behaviors in these patients. The Roy Adaptation Model is an effective guide for nurses' practice across all settings [27] including HF [28]. According to the Roy Adaptation Model, a person is a bio-psycho-social being who is in constant interaction with the physical and social environment and uses adaptive strategies to maintain balance [29]. On the basis of this conceptual framework, the purpose of nursing is to improve adaptation [26] and enhance adherence in patients. Adherence behaviors help people achieve physiological, psychological, and social adaptation [30].

Accordingly, this study was conducted to determine the empirical validity of the Roy Adaptation Model as a conceptual model for explaining and predicting treatment adherence in patients with HF in Iran using a mixed-methods research. Theory testing studies have been designed to examine middle-range theories through the process of deductive reasoning. To this end, concepts and the statement of the middle-range theory were weighed up against those of the conceptual model, and the middle-range theory was then tested using research techniques and empirical indicators [20].

The Roy Adaptation Model

The Roy Adaptation Model has major concepts of nursing theory including health, person, nurse, and environment. In this conceptual model, the person has been viewed in a holistic manner. The main concept in this model is adaptation. Adaptation is considered as a process and an outcome with 3 integrated, compromised, and compensatory levels. The person as an adaptive system uses 2 mechanisms of coping (the cognator and the regulator) to cope with the changing world.

The function of the subsystems is to maintain integrated adaptation. The pooled effect of the focal, contextual, and residual stimuli establishes a person's adaptation level. The focal stimuli are internal or external stimuli that are immediately present in the consciousness of the individual. On the contrary, contextual stimuli are other factors emerging in situations that contribute to the focal stimulus effect. Finally, the residual stimuli are environmental factors in or out of the person, the effects of which are not clear in the current situation. Adaptation levels are present in people's behavior, where the behaviors can be observed in 4 adaptive modes (physiological, self-concept, interdependence, and role function).

Behavior in the physiological mode reflects the physiological processes of cells, tissues, organs, and body systems. The physiological mode has 5 basic physiological needs (activity and rest, nutrition, elimination, oxygenation, and protection) and 4 regulatory processes (senses, fluids - electrolytes and base acid balance, neurological function, and endocrine function). Self-concept is a set of feelings and beliefs about oneself that are shaped by the inner perception and understanding of the reactions of others. The components of this mode include

physical self (such as physical sensation and body image) and personal self (self-consistency, self-ideal, and moral-ethical-spiritual self). The role function is a role-related behavior aiming at achieving social integrity. The role is a set of expectations about how a person functions in the society in relations to others. The interdependence mode includes behaviors related to interdependent relations of individuals. This mode focuses on interactions related to giving and receiving love, respect, and value. The basic need for this mode is relational integrity [31].

Methods

This paper describes the protocol of a mixed-methods study with a sequential exploratory design on the adherence to treatment regimen in patients with HF in Iran. This model starts with data collection and analysis of a qualitative phase, which is then followed by quantitative data collection and analysis [32]. Steps of implementing the study with a sequential exploratory approach adapted from Creswell and Clark are shown in [Textbox 1](#) [33].

Textbox 1. Steps of implementing the study with a sequential exploratory approach.

<p>First phase</p> <ul style="list-style-type: none"> <p>Stage 1</p> <p>Designing the qualitative study</p> <ul style="list-style-type: none"> Objective: Re-designing the model of adherence to treatment in patients with heart failure based on the Roy Adaptation Model Type of research: Directed qualitative content analysis <p>Implementation of the qualitative study</p> <ul style="list-style-type: none"> Content analysis of relevant literature in part 1 based on the modes and stimuli of the Roy adaptation model and re-designing of the model of adherence to treatment in patients with heart failure based on the Roy adaptation model Interviewing patients with heart failure and their caregivers as well as analyzing the data based on the modes and stimuli of the Roy adaptation model in part 2 Presenting the final model of adherence to therapeutic regimen in patients with heart failure <p>Stage 2</p> <p>Strategies of relating the primary qualitative study to the secondary quantitative study</p> <p>Using qualitative findings to:</p> <ul style="list-style-type: none"> Determine research hypotheses for the quantitative phase Designing a study for the quantitative phase <p>Second phase</p> <ul style="list-style-type: none"> <p>Stage 3</p> <p>Objective: Testing the model by determining the interrelationships among variables</p> <p>Type of research: Descriptive-correlational</p> <ul style="list-style-type: none"> Determining sample size based on the number of factors in the model Stratified random sampling with proportional allocation considering the mean number of patients with heart failure in educational health care centers of the selected university of medical sciences Analyzing quantitative data through structural equation modeling <p>Stage 4</p> <p>Interpretation of connected results</p> <ul style="list-style-type: none"> Summarizing and interpreting the qualitative results Summarizing and interpreting the quantitative results Discussing how and to what extent quantitative results match qualitative results
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Table 1. Search strategy.

Database	Search terms
PubMed	("failure" OR "heart failure" OR "myocardial failure" OR "CHF" OR "HF" OR "congestive heart") AND ("patient concordance" OR "patient cooperation" OR "patient adherence" OR "patient compliance" OR "treatment refusal" OR "patient dropouts" OR "self-care maintenance")
Scopus	(ALL("failure") OR ALL("heart failure") OR ALL("myocardial failure") OR ALL("CHF") OR ALL("HF") OR ALL("congestive heart")) AND (ALL("patient concordance") OR ALL("patient cooperation") OR ALL("patient adherence") OR ALL("patient compliance") OR ALL("treatment refusal") OR ALL("patient dropouts") OR ALL("self-care maintenance"))
Web of Science	(TS=("failure") OR TS=("heart failure") OR TS=("myocardial failure") OR TS=("CHF") OR TS=("HF") OR TS=("congestive heart")) AND (TS=("patient concordance") OR TS=("patient cooperation") OR TS=("patient adherence") OR TS=("patient compliance") OR TS=("treatment refusal") OR TS=("patient dropouts") OR TS=("self-care maintenance"))

The First Phase: Qualitative Study

This part of the study is performed in 2 parts: in part 1, factors associated with treatment adherence in patients with HF corresponding to the focal and contextual stimuli of the Roy Adaptation Model affecting the physiologic, self-concept, role function, and interdependence modes are identified and categorized according to a content analysis of the literature. To this end, a search is carried out on articles published between 1970 and 2017 in a number of databases, including Scopus, PubMed, and Web of science (Table 1). In addition, research reports and dissertations are also included in the search to have a comprehensive search. A manual search is also performed in the list of resources extracted from the studies. This literature review examines only studies in which the participants are adult patients with HF (aged 18 years and older) or one of its population subgroups with class I to IV HF according to the New York Heart Association (NYHA) Classification or patients with reduced ejection fraction (HFrEF), preserved ejection fraction (HFpEF), and mid-range ejection fraction (HFmrEF). In addition, studies that have investigated one or more components of adherence to treatment (medication adherence and nonpharmacological (lifestyle) recommendations), have examined adherence as the focal outcome, have reported their results in qualitative and quantitative forms, are in English or Persian, and give access to their full text are considered as eligible. On the contrary, editorials, letters to editors, and summaries of conferences are excluded. Taking into account these inclusion and exclusion criteria, the title and abstract of the articles retrieved through the initial search are examined and articles relevant to the objectives of this content analysis of the literature are then selected. Next, the full text of the eligible articles is reviewed and analyzed using qualitative content analysis with an approach guided by the Roy Adaptation Model modes as well as focal and contextual stimuli. This step also involves identifying and categorizing the features of adaptive and nonadaptive behaviors in each mode. Next, the initial model of treatment adherence in patients with HF is then redesigned based on the modes and stimuli proposed in the Roy Adaptation Model.

In part 2, to redevelop a Roy Adaptation Model-based model of treatment adherence in patients with HF, the factors associated with treatment adherence are examined based on the context of Iranian cultural from the perspective of the patients, their families, and health care providers using qualitative content analysis. This study used directional content analysis, which is a method used when there is an initial theory or a basic research about the phenomenon in question which may be incomplete or can be used in future research. This approach aims to validate or develop the conceptual framework of a theory, where the existing theory or initial research can serve as a guide for investigating the relationship between the codes [34]. In this study, after redesigning and redeveloping the Roy Adaptation Model-based model of treatment adherence in the current Iranian cultural context, the research hypotheses are determined and the quantitative stage of the study is designed.

Study Population and Setting

As in a qualitative study, the study setting is where the phenomenon actually occurs [35], this study is conducted in 6 Referral Cardiovascular Centers affiliated with universities of medical sciences in Tehran with a cardiology unit, cardiac care unit, and heart clinic alongside other places where access to participants is possible (such as cardiologists' offices). This part of the study focuses on patients with HF (NYHA class I-IV or patients with HFrEF, HFpEF, and HFmrEF) coupled with their caregivers and health care providers. The patients' caregivers and health care providers are selected because they are involved in providing care to adults with chronic conditions.

Sample Size and Sampling Method

The sample size is unknown in this part of the study, and sampling continues until the saturation of data, that is, sampling to the point at which no new information is obtained and redundancy happens [35]. After reaching repeated information, interviews are conducted with more participants to ensure no new data are obtained.

The sample was selected using purposive sampling (the researcher purposely selects participants who can act as a rich source of information and can take part in the study and help the researcher better understand the factors related to and affecting treatment adherence—using the strategy of maximal variation sampling). This means that participants are purposefully selected to be diverse in age, socioeconomic situation (level of education, living arrangement, marital status, employment status, and gender), duration of the disease, and illness severity according to class I to IV NYHA Classification (with higher class indicating more severe symptoms).

The patient sample included persons with a primary diagnosis of HF for more than 3 months meeting the following criteria: at least 18 years of age and NYHA Classification I to IV or patients with HFrEF, HFpEF, and HFmrEF. The exclusion criteria included patients suffering from terminal diseases, cognitive impairments, obvious psychiatric disorders with limited capacity to engage in self-care, and candidacy for heart transplantation in the 6 upcoming months. The health care provider sample included cardiologists and nurses providing direct care to adult patients with HF with at least one year of work experience in this field. The patient caregivers' sample included an adult family member, such as a spouse sharing residence with the patient with HF and responsible for taking care of the patient or acting as the patient's caregiver at least twice per week.

Data Collection

The main method for data collection in this part of the research is a semistructured interview using open questions and field notes, but other data collection methods such as observation and existing documents will also be used. Using the directional content analysis, the researcher begins the interviews with general open-ended questions and tries to have the minimum interference in the process of the interviews. The researcher also uses directional questions according to the Roy Adaptation Model and directs the interview such that it covers the study objectives using guiding questions; for example:

1. Please explain about your heart disease.
2. What do you do to take care of yourself concerning your illness? Why?
3. How do you feel about your treatment regimen? Talk about feelings you experience physically or emotionally after taking medication, dietary restriction, or physical activity and other treatment related issues.
4. Have you ever had a chance to forget your diet (eg, you forget to take one or more medication doses)? What was the reason and when this happened to you?
5. Are there any situations that make it easier for you to follow medical treatment regimen (eg, taking medicine, diet, and physical activity)?
6. What is the most difficult aspect of adherence to treatment regimen (eg, the most difficult aspect of medication use)?

Probing questions are then asked for clarifying the subject based on the information provided by the participants. In-depth questions, such as *Please elaborate, What do you mean?*, and *Can you give an example to help me understand better?* are also asked according to the given responses. During the interview, the researcher makes a detailed note of the nonverbal data, such as tone of voice, facial expressions, and state along with their time and place. The duration of the interviews will be between 45 and 90 min depending on participants' ability to answer the questions and all will be audio-recorded. After each interview, the content of the interviews is transcribed verbatim after several times of listening in the first possible instance and is further analyzed and coded as it is being collected using directional content analysis. The interviews continue until data saturation, when no further new data or codes are obtained. After reaching repeated information, interviews are conducted with more participants to ensure no new data are obtained.

Data Analysis

MAX Qualitative Data Analysis software for qualitative data analysis (version 10) was used for data management. Advantages of this software include the ability to handle a large amount of information, saving time, the flexibility, and the possibility of performing more complex analyses. In the qualitative part, data are analyzed as they are being collected using directional content analysis. Directional content analysis has 3 phases including preparation, organizing, and resulting [36]. In the preparation phase, the written material (the text of transcribed interviews and observations) is read several times for data immersion. In the organizing phase, an unconstrained categorization matrix is developed based on the concepts of the Roy Adaptation Model. Then, the researcher reviews the text line-by-line and encodes it. The initial codes are then reviewed several times and then categorized according to the differences and similarities between them. The categorized codes are assigned to larger categories as subthemes (these categories are derived from the concepts of the initial redesigned model based on the Roy Adaptation Model). If the categorized codes are not suitable as a subtheme of the initial model, they are categorized as separate subthemes. Eventually, these categories are categorized as a main theme of the initial model, and the initial model is thus developed according to participants' perceptions of treatment adherence.

Data Rigor

The quality of the data is assessed using Lincoln and Guba's criteria [37]. In this study, the rigor of the data is ensured by member check. The results of the study are presented to some of the participants, and their review ensures consistency and further adds to the credibility of the data. Peer debriefing is another method used to confirm the credibility of data. To this end, the interview texts and the extracted codes and categories are reviewed and assessed not only by advisors and supervisors but also by a faculty member with expertise in qualitative studies to determine the accuracy of the encoding process. Prolonged engagement is another measure taken to enhance the credibility of the study findings. This study also seeks to realize the confirmability of the results by clearly documenting every stage of the study. In addition, the transferability of the results to similar settings becomes possible for other researchers by seeking to cover a wide range of participants in terms of age, occupation, marital status, severity of the disease, duration of the disease, and education as well as by describing the study context and participants.

The Second Phase: Quantitative Study

The model is tested to investigate the relationship between the hypotheses or variables. In this process, all the variables of the model are measured to determine the path between the concepts and develop the conceptual model. In this part of the study, the model is validated through a descriptive study using valid and reliable tools related to the model variables and by applying Structural Equations Modeling. Eventually, the final model developed based on the cultural and socioeconomic characteristics of the Iranian society is presented.

Study Population and Setting

The study setting in this part of the study is similar to part 2 of the first phase including 6 Referral Cardiovascular Centers affiliated with universities of medical sciences in Tehran. The study population consists of all the patients with HF (NYHA class I-IV or patients with HF_rEF, HF_pEF, and HF_{mr}EF) presenting to these centers.

Sample Size and Sampling Method

Determining the minimum sample size required for collecting data related to the structural equation modeling is very important. There is no specific rule for choosing the right sample size, which makes this step more difficult. For instance, some researchers recommend 10 samples per parameter or variable, whereas some references consider 200 as the minimum sample size required for factor analysis and structural equation modeling [38]. This study selects a sample size of 10 per variable.

In the sampling process, proportional stratified random sampling is conducted in the 6 Referral Cardiovascular Centers based on the mean number of patients with HF in each Center. In the next step, the same sampling method is used to choose patients based on their NYHA function classes (I-IV) to ensure the enrollment of equal number of individuals with different classes of HF.

The inclusion and exclusion criteria in this part of the study are similar to characteristics of patients with HF in part 2 of the first phase.

Scales and Data Collection

Treatment adherence has been defined as an adaptive behavior which indicates people's cost-benefit perceptions of treatment manifested as integrated (100% adherence), compensatory (relative or assisted adherence), and compromised (nonadherence) [39]. This study considers treatment adherence as the latent variable which reflects the adaptation system's general response to environmental stimuli (ie, factors related to treatment adherence) and is manifested in the 4 modes of bio-psycho-social response. The data collection tool used for testing the model is, therefore, a demographic form where the instruments used for measuring the concepts of the treatment adherence model are developed according to the Roy Adaptation Model obtained from the qualitative part.

Data Rigor

To ensure the rigor of the data in the quantitative part, valid and reliable tools are used to measure the concepts and variables of the Roy Adaptation Model-based treatment adherence model. To assess the validity of the questionnaires, the face and content validity methods are used. For assessing the face validity of the Persian version of the scales, they are distributed among 10 patients with HF to comment on the clarity and comprehensibility of the items, whereby their corrective views and suggestions are collected and implemented, and the final version is then drafted and approved by faculty members.

To assess the content validity, the questionnaires are distributed among 15 faculty members of schools of nursing and midwifery in Iran who are experts in the field, whose views are collected. After getting the qualitative feedback of the faculty members and making the necessary corrections, content validity is assessed quantitatively using the Content Validity Index [35]. The reliability of the questionnaire is confirmed using the Cronbach alpha coefficient.

Information bias, nonresponse bias, and selection bias are among the potential sources of bias in this phase of study. To reduce information bias, the questionnaires would be completed through face-to-face interviews by interviewers who are unaware of the hypothesis under consideration. To reduce nonresponse bias, a financial reward is offered to participants. Finally, proportional stratified random sampling is used to reduce selection bias.

Data Analysis

In this part, structural equation modeling is used to test the model in linear structural relations. A statistical software package is used to test the validity of assumed models and to illustrate the relationship between variables [40]. Structural equation modeling is a combination of confirmatory factors and path analysis, taking into account the latent variables that cannot be directly measured. Structural equation modeling is used in various cases, for instance, it is applicable when there are latent variables with each having several indices (confirmatory factor analysis) or when the assumed paths between different variables need testing, or when there is a comprehensive approach based on a theoretical model [41,42].

Ethics Approval and Consent to Participate

This research project is approved under the ethics code IR.IUMS.REC.1395.9221199205 by Iran University of Medical Sciences. Before conducting the study, its objectives and methods are explained to the candidates who accept the researcher's invitation to take part. Informed written consent is then obtained from them for participation in the study (including a consent for recording the interviews and completing the questionnaires). The study subjects are ensured of their right to withdraw from the study at any time and their anonymity in all the stages of the publication of the results, and they are later presented with the results of the research if they so wish.

Results

Interpretation of Interrelated Results

The interpretation of interrelated results is referred to as *drawing conclusions or drawing inferences*. Although inferences can be drawn after each stage of the study, meta-inferences are drawn at the end of the study, which include a larger interpretation in the Conclusions or Discussion sections of the study. In an exploratory study, meta-inferences determine whether the quantitative part of the follow-up provides a more generalized understanding of the study subject compared with the qualitative data alone. This interpretation ends in responding to a combination of questions [32]. In this part of the study, following the summarization and separate interpretation of the qualitative findings and quantitative results, a decision is made about the extent to and ways in which the results of the quantitative stage can be generalized or tested for the qualitative findings. Ultimately, the empirical validity of the Roy Adaptation Model as a conceptual model is determined for predicting treatment adherence in patients with HF.

Current Status of the Study

Content analysis of the literature in part 1, the first phase, was completed in 2017. Collection and analysis of qualitative data in part 2, the first phase, will be completed soon. The results are expected to be submitted for publication in 2019. Then, the second phase—the quantitative study—will also be conducted.

Discussion

Summary

There are different theories that provide a framework for the study of nursing requirements and outcomes in different settings as well as for patients in different times of their life. The Roy Adaptation Model is one of the most useful conceptual models in nursing which can be used in research, training, clinical practice, and health care system management [43]. It provides an effective framework for assessing people's adaptation to various environmental stimuli regardless of their age and disease. As a conceptual model of adaptation, the Roy Adaptation Model is applicable to and flexible for different approaches, projects, objectives, settings, and age groups [24]. Nursing knowledge can be developed through research based on Roy Adaptation Model [44]. Fawcett quoted from Roy and Robbert that the theory of person as an adaptive system should

be developed and tested by a systematic program of research [45]. To the researchers' knowledge, this study is the first to determine the empirical validity of the Roy Adaptation Model as a conceptual model for predicting treatment adherence in patients with HF in Iran through a mixed-methods study.

The results of this research will help identify the factors associated with treatment adherence and better understand the perceptions of patients with HF about treatment adherence within the Iranian cultural and socioeconomic context. These results also provide an insight into the perceptions of the families of patients with HF as well as health care providers about treatment adherence and its related factors in HF. By obtaining a more profound understanding of the perceptions of patients with HF and their caregivers as well as health care providers and by conducting studies supported by nursing theories as the road map, researchers will be able to design efficient interventions to improve treatment adherence in these patients and assess them within this conceptual framework. This study can help develop a checklist for assessing the variables responsible for nonadherence behaviors in this group of patients derived from the Roy Adaptation Model stimuli (focal, contextual, and residual) and identify the practical priorities for improving adherence to treatment regimen in this group.

Limitations

Our study has some limitations. First, the aim of this study is to provide a treatment adherence model for patients with different severities of illness (NYHA class I-IV or patients with HF_rEF, HF_pEF, and HF_mrEF). So, one of the potential limitations of the study may be the inability of patients in class III-IV to answer a question. Second, adherence to the treatment regimen is influenced by the health care system, so some of the possible themes associated with these factors may be underreported. Finally, the withdrawal of patients with cognitive impairment and end-of-life diseases from the study leads to exclusion bias, complicating the generalizability of the results for this group of patients.

In the quantitative phase, reliable and valid tools are needed to test the interrelationships between variables. As the concepts of the treatment adherence model based on the Roy Adaptation Model at this stage are not clear, it is difficult to determine the tools required for testing the model in the quantitative phase of the study. On the other hand, it may be necessary designing a new tools or translating existing tools and cultural adaptation of them, which is one of the limitations of this study as the exploratory sequential mixed-methods research design.

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Authors' Contributions

All authors conceived and designed this study. The manuscript was drafted by SS, and all authors contributed to critical revision and approval of the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

C-T-E: conceptual-theoretical-empirical
EF: Ejection Fraction
HF: heart failure
HFmrEF: HF with mid-range ejection fraction
HFpEF: HF with preserved ejection fraction
HFrfEF: HF with reduced ejection fraction
NYHA Classification: New York Heart Association Classification

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Protocol

A Web-Based Therapeutic Program (We Can Do This) for Reducing Methamphetamine Use and Increasing Help-Seeking Among Aboriginal and Torres Strait Islander People: Protocol for a Randomized Wait-List Controlled Trial

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Abstract

Background: Methamphetamine use is of deep concern to Aboriginal and Torres Strait Islander communities, but access to culturally appropriate treatment resources and services is limited. Web-based programs have potential as flexible and cost-effective additions to the range of treatment options available to Aboriginal people. The We Can Do This online intervention is designed to incorporate evidence-based therapies in a culturally relevant format using narratives from Aboriginal people to contextualize the therapeutic content.

Objective: The goal of the research will be to test the effectiveness of the online intervention in a wait-list controlled randomized trial across multiple sites in urban, regional, and remote locations.

Methods: Participants will be Aboriginal and Torres Strait Islander people aged 16 years and over who have used methamphetamine at least weekly for the previous 3 months. They will be recruited online and via health services. During the intervention phase, participants will have access to the online intervention for 6 weeks with optional telephone or face-to-face support provided by participating health services. The primary outcome measure will be the number of days the participant used methamphetamine over the past 4 weeks compared to wait-list controls, assessed at baseline, 1, 2, and 3 months. Secondary outcomes will include help-seeking, readiness to change, severity of dependence, and psychological distress. Any important changes to the protocol will be agreed upon by the trial management committee and communicated to all relevant parties, including trial site representatives and the trial registry.

Results: Recruitment will commence in July 2019, and results are expected in early 2021. This research is funded by National Health and Medical Research Council project grant #1100696. The primary sponsor for the trial is the South Australian Health and Medical Research Institute. A trial management committee with representation from the participating health services, chief investigators, other Aboriginal experts, and consumers will oversee procedures, trial conduct, analysis, and reporting of the results.

Conclusions: The trial of this online intervention builds on existing research supporting the effectiveness of Web-based therapies for a range of psychological and other health-related issues including substance use. If successful, the We Can Do this online intervention will increase the range of options available to Aboriginal people seeking to reduce or stop methamphetamine use. It may provide a pathway into treatment for people who may otherwise be disengaged with health services for a range of reasons and will be a culturally appropriate, evidence-based resource for health practitioners to offer their clients.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12619000134123p; <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=376088&isReview=true>

International Registered Report Identifier (IRRID): PRR1-10.2196/14084

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KEYWORDS

methamphetamine; eHealth; Australian Aboriginal people; Aboriginal health services

Introduction

Background

Methamphetamine use has increased globally over recent years [1]. In Australia, where amphetamine-type stimulants have been a feature of the illicit drug market for many decades, a shift from low-purity powder (speed) to the typically higher purity form of the drug, crystalline methamphetamine (often referred to as ice), has led to an increase in drug-related harms [2,3]. This is indicated by increases in amphetamine-related hospital admissions, drug and alcohol service treatment presentations, and helpline calls [4]. The available evidence indicates that Aboriginal and Torres Strait Islander Australians (hereafter, Aboriginal) use methamphetamine and experience harms at a higher rate than non-Indigenous Australians, with some of the highest recorded rates of use in regional and remote areas [5,6].

In line with national trends, Aboriginal Community Controlled Health Services (ACCHSs) have experienced an increase in amphetamine-type stimulant-related presentations over recent years. The burden of service provision for amphetamines is noted in the 2014-2015 Aboriginal and Torres Strait Islander Health Organizations Online Service Report, where the proportion of organizations that reported amphetamine as one of their most important issues, in terms of staff time and organizational resources, increased from 45% in 2013-2014 to 70% in 2014-2015. At the same time, social and emotional well-being (incorporating mental health within a unique set of culturally informed well-being domains [7]) and substance use services were identified as among the top five service gaps, and

access to evidence-based treatments provided by qualified staff remains variable [8].

A systematic review of psychological treatments applied specifically to methamphetamine use concluded that good clinical outcomes are achieved with cognitive-behavioral therapy (CBT) [9]. Further, CBT with or without motivational interviewing appears to be associated with reductions in methamphetamine use and other positive changes [9]. A preliminary randomized controlled trial comparing acceptance and commitment therapy (ACT) and CBT indicated that these two therapeutic modalities produce comparable results; therefore, ACT may be a viable alternative to CBT for treating harmful methamphetamine use [10]. This is relevant in an Aboriginal context where written, worksheet-based CBT approaches are not always preferred for a range of reasons including literacy and a cultural preference for approaches incorporating yarning and story-telling [11].

Internet interventions have shown effectiveness for some substance use problems, including methamphetamine use. For example, Breaking the Ice was a fully automated, participant self-guided, Web-based intervention consisting of six self-administered modules incorporating components of CBT and motivational interviewing [12]. The program was effective at increasing help-seeking and participant motivation to reduce their methamphetamine use and reducing days out of role, relative to a wait-list control (at 3 to 6 months from baseline). Effect sizes were small to moderate (relative risk 0.5-0.74) [13]. The program participants who completed the Web-based modules, predominantly non-Aboriginal and male, showed a nonsignificant reduction in their methamphetamine use [13].

Feedback on the acceptability of Breaking the Ice was generally positive in relation to the use of fictional case stories as an engaging approach, but participants reported that the program was also too text-heavy, which may have contributed to attrition (less than half [48%] completed all three modules).

Other evidence from evaluations of online interventions developed specifically for Aboriginal people, such as the Stay Strong App for setting goals relating to social and emotional well-being [14,15] and the iBobbly app for suicide prevention [16], indicates that electronic and Web-based therapeutic approaches may be feasible and acceptable to Aboriginal people. These treatment options may also have the potential to increase access to evidence-based therapies by overcoming barriers to health service access stemming from physical distance, cultural, or other barriers.

The We Can Do This online intervention is being developed as part of a larger project seeking to better understand and address deep concerns in Aboriginal communities about methamphetamine use through the development and trial of prevention and treatment strategies. Early quantitative and qualitative findings from the larger project indicate that access to health services does not currently match self-reported need and that barriers to health services exist, including stigma, shame, and a lack of culturally appropriate services. The online intervention may provide a pathway for people using methamphetamine to overcome such barriers to health service access or an alternative support option for people in the community.

Objective

Our primary hypothesis is that participants who complete the We Can Do This online intervention will have significantly reduced days of methamphetamine use in the last 4 weeks at 1, 2, and 3 months from baseline compared with wait-listed participants with access to treatment as usual. Our secondary hypothesis is that the program will increase intended and actual help-seeking, including attendance at participating health services.

Methods

Trial Design

A 2-group randomized controlled trial will be used. The intervention group will receive the We Can Do This online intervention with the option of telephone or face-to-face support provided by their local ACCHS staff. The wait-list control group will undertake the same assessments as the intervention group and have access to treatment as usual at the participating health services until the 3-month control period is complete, at which point they will receive access to the online intervention. They will receive reminders to log in but no further research assessments. Nonidentifiable use data will continue to be monitored. Treatment as usual will involve referral to online harm minimization information and access to alcohol and other drug counseling at the participating health service. The flow of participants through the trial is shown in [Figure 1](#).

Study Setting

The trial will take place in trial sites in geographically remote, regional, and urban locations in Australia. ACCHSs will provide telephone or face-to-face support to participants as required according to the research protocol.

Participant Eligibility, Recruitment, and Consent

Participants will be Aboriginal and Torres Strait Islander people aged 16 years and over who have used methamphetamine at least weekly in the past 3 months. They will be recruited online through advertising and established social media channels in each of the trial sites. Recruitment will be restricted to those areas covered by ethical approval. Advertising material (posters, postcards) directing people to the project website will be available at participating sites and relevant alcohol and other drug services including needle exchange programs. Online screening questions will identify participants who meet the eligibility criteria and invite them to proceed to the online consent process. All participants will be presented with written plain-language information about the trial. The same information will be available online in audio-visual format, and the contact details of researchers and participating health service staff will be provided should participants wish to request further information or require assistance in any way. Participants will provide consent online. All participants will then complete the baseline assessment before being randomized to support via the online intervention or wait-list control ([Figure 1](#)).

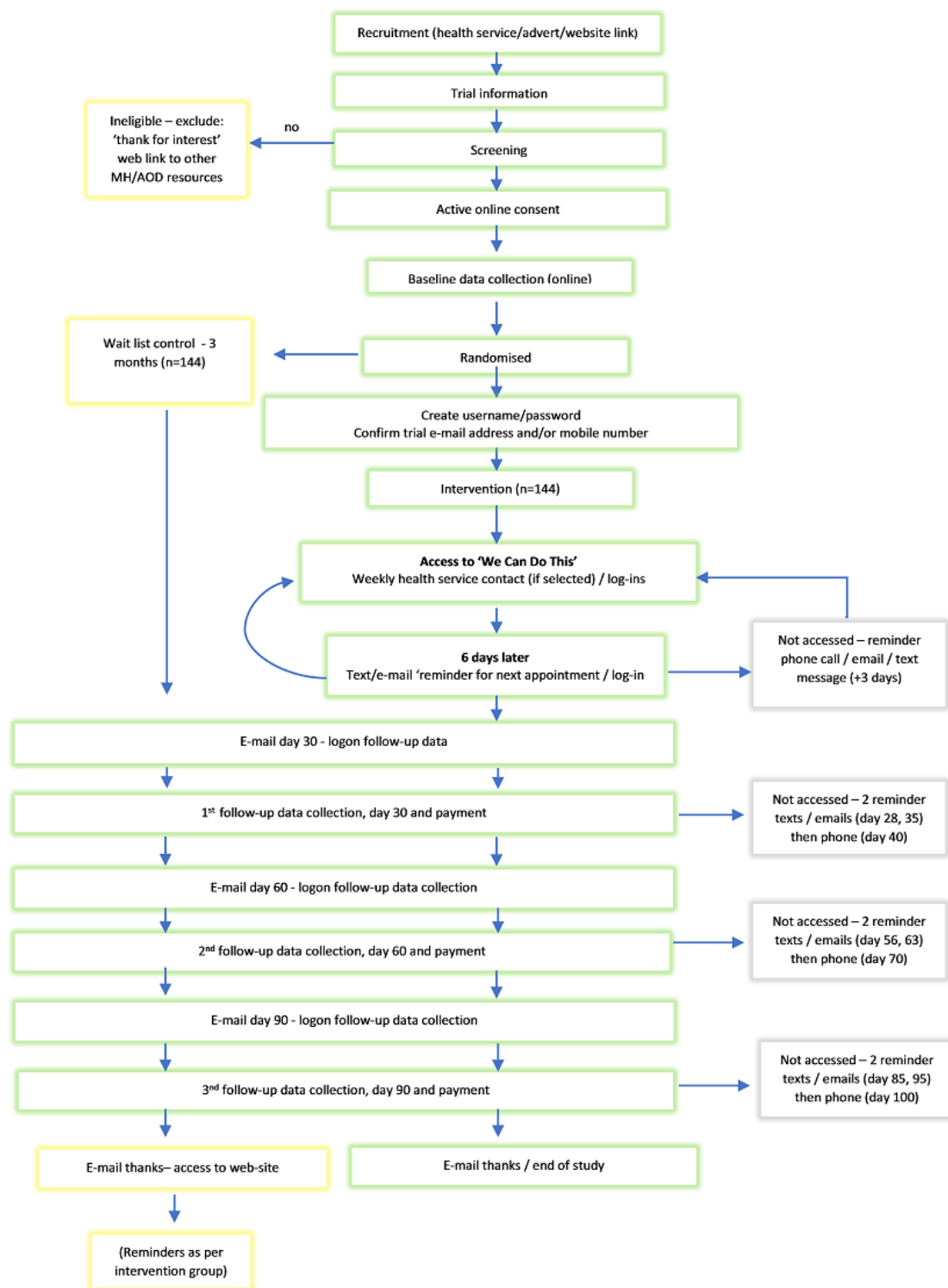
Randomization

The randomization scheme will be developed by a statistician who is not involved with study participants. Subjects will be randomly allocated to the online intervention or the wait list with 1:1 ratio. Random numbers will be generated using the statistical software Stata 14.0 or higher version (StataCorp LLC).

Implementation

The online intervention may be accessed on any digital device (mobile phone, electronic tablet, or desktop computer) and requires continuous internet access to function during the trial. Video quality will adjust automatically according to available internet speed, and when the internet speed is too slow, a still image will appear and the participant will hear the audio track. Instructions will recommend that participants access the online intervention once a week for 6 weeks; however, they are free to access it as frequently as they wish during this time. Based on feedback from advisory groups, participants will not be required to complete modules in a set order but will be able to select modules based on preference. Participants may withdraw from the trial at any time. Data collected until that point will be included unless specifically requested otherwise. All participants will be paid Aus \$20, \$30, and \$40 (US \$14, \$21, and \$28) as reimbursement for their time completing the first, second, and third follow-up assessments, respectively. This payment will not be affected by participant level of engagement with the intervention.

Figure 1. Flow of participants through the We Can Do This trial. AOD: alcohol and other drugs; MH: mental health.



Participants will have the option of receiving health practitioner support via weekly phone calls from trained staff at the participating health service in their geographical area. If this option is selected, participant contact details will be forwarded to the relevant health service, and they will receive an introductory phone call during which the health practitioner will explain their support role and schedule the weekly contact. Alternatively, participants will have the option to proceed without practitioner contact. In either case, participants will be

prompted to consider the option of talking to someone at several points within the online intervention.

At the end of each module, printable summary pages of their inputs may be emailed to participants, their support people, and members of their Healing Circle as attachments according to participant preferences. With the participant's permission, this summary may also be emailed to their allocated practitioner, if they have one. Participants will be sent an email or text to remind them to log in each week regardless of which modules

have been completed. If all modules are completed early, participants may repeat modules. All online interactions will be monitored and inputs recorded but de-identified prior to analysis.

The online intervention has been developed so that a range of health practitioners may provide optional clinical support as an adjunct to the program. Health practitioners providing support will have received face-to-face training from the research team and a training manual with detailed instructions in the use of the online intervention and how it may be used as the basis for supportive conversations that consolidate the online intervention content. The manual contains examples of scripts to guide conversations. If issues arise in these conversations that fall outside the practitioners' professional boundaries, they will have clear referral pathways available to them. Ongoing support for health practitioners will be provided throughout the trial by the research team and senior clinicians in each organization.

Intervention

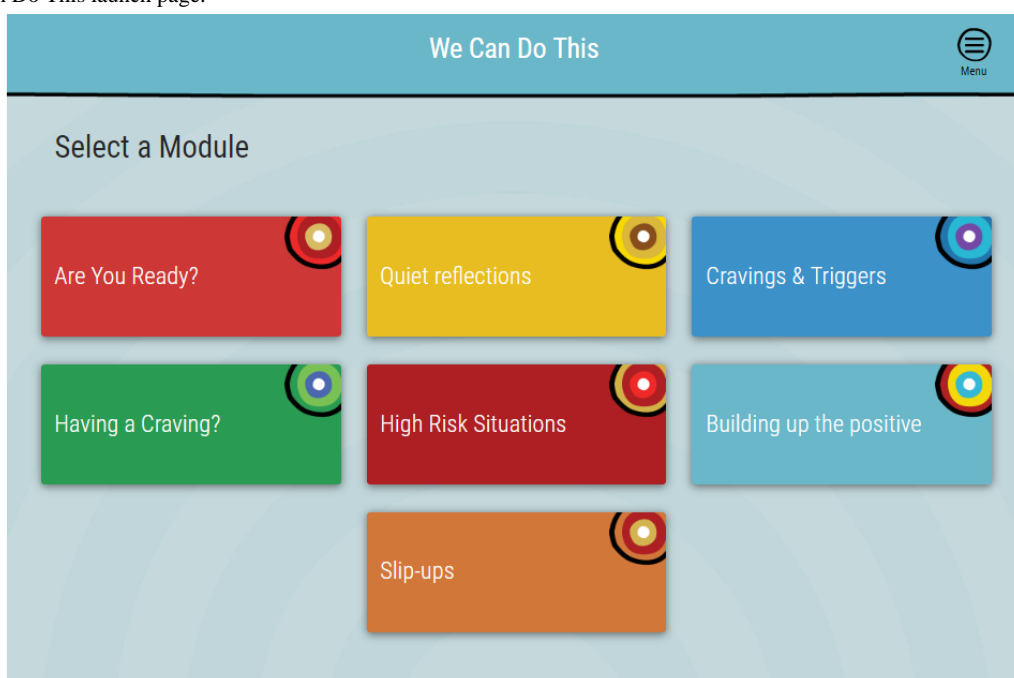
Web-Based Therapeutic Program

The We Can Do This online intervention comprises 7 modules (Figure 2) that attempt to balance adherence to the strongest evidence-base, which points most clearly toward CBT and

motivational interviewing treatment approaches, and advice from clinical and cultural advisors who steered the development toward ACT and narrative approaches. Achieving this balance required input from a range of experts. Three advisory groups were established: (1) a clinical advisory group comprising the research team and Aboriginal and non-Aboriginal clinicians working in drug- and alcohol-related fields, (2) a cultural advisory group comprising a senior representative from the diverse Aboriginal regions represented in the We Can Do This online intervention trial, and (3) a lived experience group comprising Aboriginal people with experience of methamphetamine use, either currently or in the past, who provided feedback on the online intervention acceptability and usability.

With a view to making the online intervention less text-heavy, films narrated and acted by Aboriginal actors that depict the lived experience of Aboriginal people are embedded within the online intervention to engage the participant and provide illustrations of the various issues covered. The films provide narratives that link modules together and an inviting way to engage with the content. The fictional characters depict different experiences with methamphetamine, as described in [Textbox 1](#).

Figure 2. We Can Do This launch page.



Textbox 1. Descriptions of fictional characters embedded within the We Can Do This online intervention.

- Clinton used ice for 10 years but has not used for over 12 months. He has a supportive family, which is now his main focus, but he lost his relationship with his partner as a result of his use. He now has regular access to his young daughter and is motivated to keep healthy for her sake.
- Tanisha is a young woman whose use has been mainly recreational, with her boyfriend. She's started noticing that she's using more but it doesn't feel as good anymore. In fact, she's starting to wonder if it's affecting her thinking. She's also noticing that the drive to score ice has led her to do some things she regrets, including forgetting to pick up her little brother whom she takes care of.
- Joshua works hard and parties hard. He doesn't really see his use as a problem, although his friends and family might beg to differ. Joshua has a full-time job in an office and has received a couple of warnings recently for turning up late. He's also showing some physical effects from a lack of sleep, eating poorly and sometimes picking his skin.
- Auntie Rosie has a couple of nephews who are into ice; Rosie pulls no punches in letting them know what she thinks about it. She sees the ripple effect that using ice can have—not just on the person who uses but on the family, their friends, and the whole community.

Scripts for these films were developed from interviews undertaken for other parts of the larger Novel Interventions to Address Methamphetamine Use in Aboriginal and Torres Strait Islander Communities (NIMAC) project and informed by the findings of focus groups conducted in each of the 10 partner sites. Clinical and cultural advisors emphasized the importance of the visual aesthetic of the online intervention being both culturally appropriate and inviting, so artwork by an Aboriginal artist provides the backdrop for all modules. The modules are designed as stand-alone activities that do not have to be completed in a set order (Textbox 2). To increase accessibility for those with limited English literacy, set text within the modules is audio-recorded so that participants can choose to listen to rather than read the text. Some literacy will nonetheless be required to complete the program as at this stage participants' own inputs are necessarily in written text.

At first log-in, participants will enter names of relevant support people into their Healing Circle. The participant may enter personal contacts or their own professional contacts with whom they would like to share their healing journey or whom they might contact for support. Helpline numbers and other relevant services will be automatically entered into this section of the online intervention and may be accessed at any time during use of the program from the menu icon in the top right-hand corner of each page, as shown in Figures 2 and 3. Some general instructions on the use of the online program are provided before the participant reaches the launch page, where they can access the 7 modules (Figure 2).

Modules

Are You Ready?

This module is an online adaptation of the decisional balance exercise frequently used with motivational interviewing,

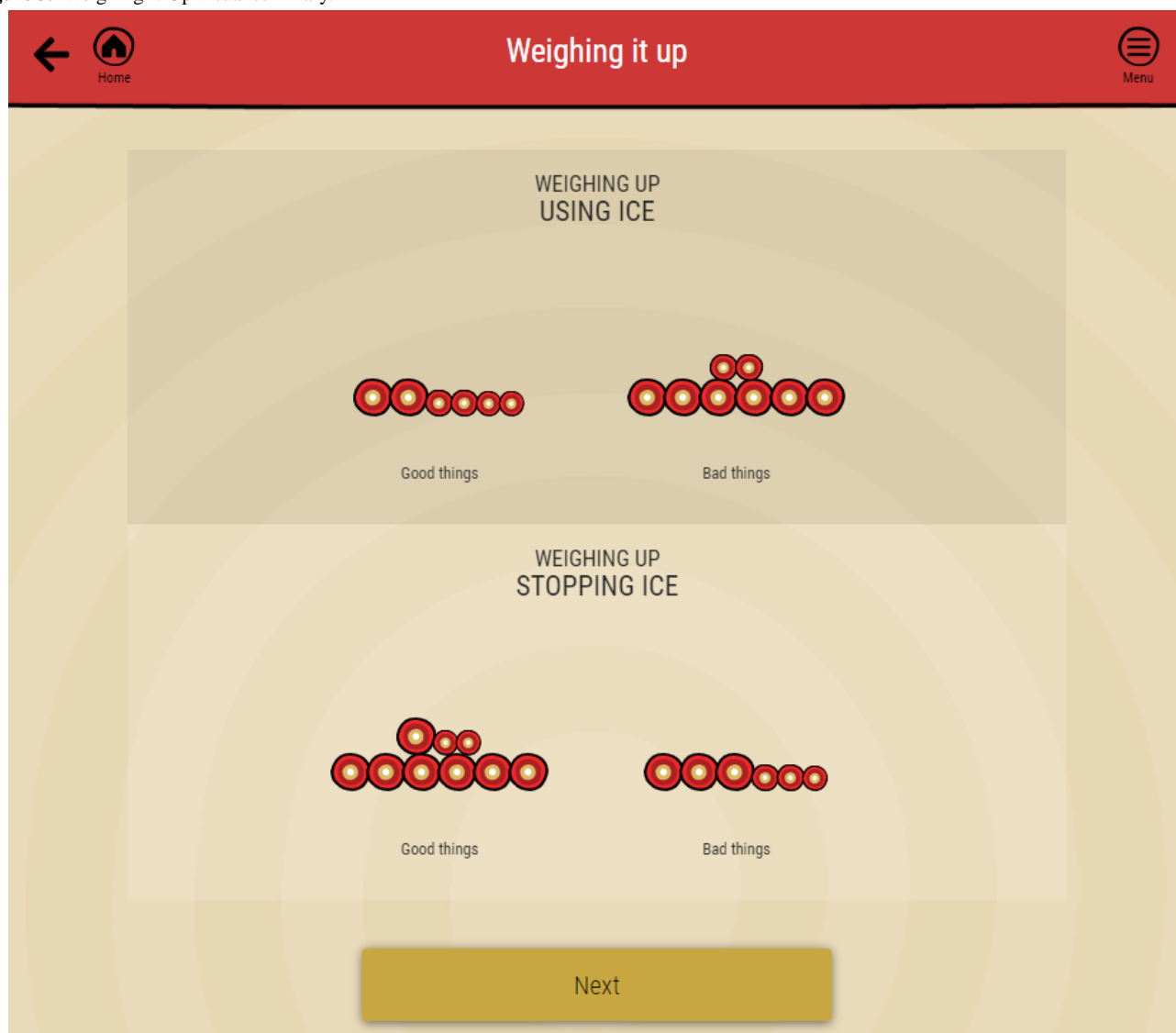
although the exercise is commonly included in treatment manuals for substance use from different therapeutic modalities [17-19]. The exercise proceeds in 4 sections corresponding to good things about using ice, bad things about using ice, bad things about stopping ice, and good things about stopping ice. The choice of language—good versus bad things rather than the traditional good versus not so good—was made based on user feedback. A brief video illustrating relevant issues for one of the characters introduces each section. Within each section, participant is presented with up to 10 items (one per page) that they rate on a slide bar as not true for me, a little bit true for me, or true for me.

After rating the final item in each section, all items are presented in a list in order of relative weighting, and the participant can add further items to the list via a textbox. The weighting for each group of items is represented visually by a pile of stones, and the relative weighting given to each item is represented by the size of the stone (larger stones for those items rated as true; smaller stones for those rated as a little bit true). By the end of all 4 rating exercises, the good and bad things about using ice and stopping ice are represented visually by 4 piles of stones (Figure 3). Participants are then asked to identify the primary good thing about stopping ice that is most important to them and to pause to visualize the difference that stopping ice would make to this important area of their lives. Using mental imagery is known to promote goal-directed behaviors in a range of health-related domains [20,21] and has a long history as an important component of CBT [22]. Participants then have the option of scheduling a text message to themselves to arrive later in the week reminding them of this important motivator. The complete set of items selected, with relative weightings and all other inputs, is summarized in a PDF document that may be emailed or printed.

Textbox 2. We Can Do This modules and content.

- Are You Ready? (10-20 minutes): aims to help participant resolve ambivalence and make a decision about what change (if any) they wish to make to their use.
- Cravings and Triggers (10-15 minutes): provides psychoeducation about the psychological and physiological processes involved in addiction. Exercises assist participant in making a behavioral change plan.
- Having a Craving? (5-20 minutes): behavioral experiment where participant rates the intensity of the craving; sets a timer for 10, 20, or 30 minutes; and is prompted to do other things and then sent a text message with a link back to the program after the specified time to rerate the craving.
- High-Risk Situations (10 minutes): participant identifies high-risk situations and makes a plan for coping with them with the option of receiving a supportive text message at their nominated high-risk time.
- Slip-Ups (10 minutes): reframes slip-ups as opportunities to learn. Participants are prompted to reflect on their experience and plan for next time.
- Quiet Reflections (5-15 minutes): participant may choose to engage with Rosemary Wanganeen's approach to grief and loss, Joe Williams' healing journey, or a simple mindful breathing exercise.
- Building Up the Positive (10 minutes): participant identifies the values that are most important to them and sets goals that will help them move closer to living a life that is aligned with their most important values.

Figure 3. Weighing It Up visual summary.



Cravings and Triggers

The Cravings and Triggers module contains cognitive-behavioral exercises designed to assist the participant to identify their own triggers (situations, thoughts, and feelings that can lead to urges to use) and cravings (actual urges to use) with a view to making a plan for how to deal with them. The section begins with an informational video providing psychoeducation on the nature of addiction and withdrawal. This psychoeducation provides the rationale for subsequent exercises, which prompt the participant to reflect what cravings feel like for them and identify the internal (thoughts/feelings) and external (situations) triggers that lead them to use. The first exercise presents the participant with an image of a person, and they are invited to tap on various body parts to read about common symptoms of cravings, alongside strategies that can help to cope with that symptom. For example, tapping on the nose will bring up the message: “Smell can bring on strong cravings. You can interfere with them by smelling something else, lemon, coffee, soaps—anything that you find calming and not related to using ice.”

The next exercise is introduced with written information defining external triggers, followed by a video of Clinton describing triggers for him (eg, driving past a house where I used to party). The participant is then presented with a list of common external triggers that they can select from a list, with free text boxes to add detail. Aunty Rosie then suggests in a video that stopping ice use will require avoiding certain people and places, and the participant is asked to identify those triggers that may be simply avoided, including getting rid of any ice and equipment they may have left. Tanisha then introduces the idea of internal triggers, and the participant is again asked to select those that apply to them. Participant is then prompted to make a plan to reduce stress and practice identifying and responding constructively and compassionately to unhelpful thoughts using structured questioning. Again, all entries are summarized in a PDF to be printed or emailed.

Having a Craving?

This module is a brief behavioral experiment in which the participant is prompted to rate the intensity of their craving on a scale from 0 to 10 and set a timer for 5, 10, or 20 minutes, during which time they are instructed to do something else. Participant has the option of playing Tetris on their device, as

there is some evidence that playing Tetris acts as visual cognitive interference and reduces the incidence and intensity of cravings in real-world settings [23]. When the timer finishes, the participant receives a text message prompting them to return to the exercise and rerate their craving, after which they can repeat the exercise or move on to another module.

High-Risk Situations

This module includes a series of questions designed to assist the participant to identify potential high-risk situations and make a plan to cope with them without using methamphetamine. Possible strategies include avoiding the situation altogether when possible, making a plan to leave if things get hard, rehearsing how to say no to people when drugs are offered, preparing by letting people know that they have decided not to use, having support people nearby/contactable, and reminding themselves of their primary motivation for reducing or stopping use.

Slip-Ups

In this module, slip-ups are differentiated from relapse and reframed as an opportunity for learning and getting stronger for next time. Unhelpful and helpful thoughts are articulated, and then a series of questions prompts the participant to reflect on how they were feeling and what they were doing and thinking to enable them to respond differently next time.

Quiet Reflections

This module contains a series of reflections and mindfulness exercises that may be selected from a launch page within the module. These reflections emphasize connection to culture, community, and identity and provide pathways for addressing culturally situated grief and loss and connecting with cultural programs. The module also contains a basic introduction to mindfulness via psychoeducation and a brief breathing exercise taken from Smout and Lazicki [19].

Building Up the Positive

Building up the Positive is an adapted version of the Bullseye Values Survey developed by Lundgren et al [24] and further popularized by Harris [25]. This exercise does not focus on drug use specifically and is intended to help the participant build a valued life outside of their use. In our adapted version, the participant is presented with three baskets labeled less important, important, and very important. Values appear on the screen and the participant sorts them into the appropriate basket. In the next stage of the exercise, those values rated as very important appear one by one and can be placed on a stylized image of a dartboard—close to the center if the participant feels they are living well in accordance with that value and further away from the center if they are not living in line with that value. Once all the values have been placed on the board, participant is encouraged to select a value placed further from the center to work on in the next section. Participant is then asked to write a specific, achievable action that would help them move closer to living out that value. This is followed by three questions: What would be the first step toward this goal? Who could help you do this? When will you do this? After nominating a day and time, participant has the option to send a text message to themselves reminding them to take the first step. Participant

can then choose to work on another value, print their plan, or select another module.

Incorporation of Feedback From Focus Testing

The modules were focus tested in two phases. The first module developed (Are You Ready?) was focus tested with Aboriginal people with past or current experience of methamphetamine use recruited via organizational networks in urban and regional locations in South Australia and Victoria. Feedback from these groups was incorporated into the WBTP and informed the further development of subsequent modules. Later modules were focus tested with participants recruited via the same networks. Feedback was generally positive and supported the use of films to convey key messages. Participants found the content credible and useful and provided advice to improve the clarity of terminology, imagery, and usability. They also noted that while films are a powerful medium for conveying positive messages, the emotive nature of some stories could be triggering for some people, which prompted a greater focus on building safety measures into the online intervention—for example, ensuring timely access to face-to-face support when needed.

Outcome Measures

Primary Outcome

The primary outcome measured will be the number of days the participant used methamphetamine during the treatment phase, assessed using questions from the Australian Treatment Outcome Profile (ATOP) [26]. The ATOP has been validated in treatment settings across Australia.

Secondary Outcomes

Differences in help-seeking will be assessed with the General Help-Seeking Questionnaire [27] and by the rate of referral and frequency, type, and duration of health service contact resulting from use of the online intervention. Other outcomes will include readiness to change (Readiness to Change Questionnaire) [28]; psychological distress (Kessler 10) [29]; poly-drug use during the past month (ATOP) [26]; severity of dependence (Severity of Dependence Scale) [30]; days out of role (referencing methamphetamine use rather than depression) [31]; and usability and acceptability (Internet Intervention Adherence Questionnaire [32], which includes questions about barriers and facilitators to using the program and optional free-text to report any criticisms or other feedback). Feasibility of the online intervention will be assessed overall by demographics of participants, general uptake and use of the online intervention (modules completed, time spent, etc), and number of participants who complete the program. Qualitative interviews with health service staff and at least two online intervention users will be conducted to explore positive and negative experiences.

Sample Size and Power

Based on our previous research, we expect a baseline mean of 16 days methamphetamine use in the past 4 weeks [33]. We aim to detect a reduction to a mean of 8 use days in the past 4 weeks, as this will have a significant clinical impact in terms of reducing the risk of psychotic symptoms and violence (reduction from odds of 10-11 to 2-3) [33,34]. To detect this difference at each of the follow-up points with 90% power at a

$P < .01$ level, we will require a sample of 100 participants per group. Based on our previous research, with assertive follow-up (ie, by phone as well as by email/text) we expect up to 30% attrition at follow-up, meaning that we will need to recruit 144 participants into each condition (intervention and treatment as usual) or a total of 288 participants. Treatment sites will be ACCHSs and other relevant services with Aboriginal clients.

Data Collection and Management

Data will be collected online at baseline, and at 1, 2, and 3 months postbaseline. Participants will be invited to complete follow-up assessments online via a link sent by email and/or text message in the first instance and followed up by telephone thereafter. For analysis, participants will be assigned a unique patient identifier. De-identified data on rate of referral and frequency, type, and duration of health service contact resulting from use of the online intervention will be provided by the health service using the unique patient identifier allocated to each participant. Data collected online will be de-identified and uploaded automatically to a secure server managed by the primary sponsor (South Australian Health and Medical Research Institute) in accordance with strict research governance protocols [35]. Contact details are necessary for the successful operation of the online intervention but will not be stored with data collected for research purposes. Access to data will be limited to research staff named on the ethics protocol.

Statistical Analyses and End Points

An intention-to-treat analysis will compare the primary and secondary outcomes for the intervention versus placebo conditions at 1, 2, and 3 months from baseline. Main effects will be evaluated using a mixed effect model that accounts for site-specific clustering effects.

Safety and Security

The safety and security of participants is of paramount concern at all stages of the research process. To address issues of safety, the participant information sheet provided to participants will include emergency numbers of appropriate providers in the local area and the contact numbers of the relevant researchers. These will also be included online at the end of baseline and follow-up assessments. Adverse events or unintended effects of the trial reported by participants or clinicians involved in the trial will be assessed by the trial management committee and reported to the ethics committees and other parties as required.

Ethical Approval

Approval from Aboriginal human research ethics committees at each of the participating sites and the Flinders University Human Research Ethics Committee has been obtained. Any modifications to the protocol will be approved by the trial management committee and communicated to all investigators, ethics committees, and the trial registry. The trial was registered at the Australian New Zealand Clinical Trials Registry [ACTRN 12619000134123p].

Dissemination

Trial results will be reported to all participating sites and to the public via the Australian New Zealand Clinical Trials Registry and NIMAC websites. Topics suggested for presentation or publication in the peer-reviewed literature will be agreed upon by the chief investigators, and authorship will be based upon the four criteria outlined by the International Committee of Medical Journal Editors [36].

Results

Funding for this trial was awarded from the National Health and Medical Research Council in 2016 (APP#1100696). Recruitment will commence in July 2019 and proceed for 12 months. Results are expected in early 2021.

Discussion

Early identification of problematic methamphetamine use and access to timely and effective treatment options is critical to enhance opportunities for successful outcomes for people who use the drug; however, treating methamphetamine use and dependence is a health priority that has not been fully addressed. This will be the first trial of a culturally appropriate online therapeutic program for addressing methamphetamine use specifically among Aboriginal people. We believe that, if effective, the online intervention will provide benefits to Aboriginal people and health services in three main ways.

First, it will be a much-needed resource for Aboriginal people seeking to change their methamphetamine use. Importantly, it has the potential to reach those who face barriers to attending drug treatment and other health and social support services. The anonymous nature of an online intervention helps to overcome such barriers. Second, the online intervention incorporates basic referral mechanisms to professional support, such as the inclusion of links to and prompts to make contact with health services; therefore, it has the potential to link people using methamphetamine with appropriate face-to-face support. Third, the WBTP is a resource that may be used by counselors and other workers within ACCHSs and mainstream services who work with Aboriginal people. Access to alcohol and other drug counselors and registered psychologists is not always readily available; therefore, the WBTP will increase the range of clinicians who, with appropriate training, can deliver evidence-based and culturally appropriate therapeutic content to clients.

At present, barriers to accessing care for people using methamphetamine include physical distance from services, a lack of culturally appropriate health services, and the stigma associated with use. Online interventions have the potential to overcome these barriers and reduce methamphetamine-related harm for Aboriginal people, their families, and communities. Our trial will determine whether access to the internet is a barrier to use of such interventions. While the reliance on text has been reduced as far as possible, the study will also assess the extent to which this material is accessible to the intended user.

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Conflicts of Interest

None declared.

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Abbreviations

ACCHS: Aboriginal Community Controlled Health Service

ACT: acceptance and commitment therapy

ATOP: Australian Treatment Outcome Profile

CBT: cognitive-behavioral therapy

NIMAC: Novel Interventions to Address Methamphetamine Use in Aboriginal and Torres Strait Islander Communities

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A Web-Based Therapeutic Program (We Can Do This) for Reducing Methamphetamine Use and Increasing Help-Seeking Among Aboriginal and Torres Strait Islander People: Protocol for a Randomized Wait-List Controlled Trial

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Protocol

An Online Mindfulness-Based Cognitive Behavioral Therapy Intervention for Youth Diagnosed With Major Depressive Disorders: Protocol for a Randomized Controlled Trial

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Abstract

Background: About 70% of all mental health disorders appear before the age of 25 years. When untreated, these disorders can become long-standing and impair multiple life domains. When compared with all Canadian youth (of different ages), individuals aged between 15 and 25 years are significantly more likely to experience mental health disorders, substance dependencies, and risks for suicidal ideation and death by suicide. Progress in the treatment of youth, capitalizing on their online responsivity, can strategically address depressive disorders.

Objective: We will conduct a randomized controlled trial to compare online mindfulness-oriented cognitive behavioral therapy (CBT-M) combined with standard psychiatric care versus psychiatric care alone in youth diagnosed with major depressive disorder. We will enroll 168 subjects in the age range of 18 to 30 years; 50% of subjects will be from First Nations (FN) backgrounds, whereas the other 50% will be from all other ethnic backgrounds. There will be equal stratification into 2 intervention groups (INT¹ and INT²) and 2 wait-list control groups (CTL¹ and CTL²) with 42 subjects per group, resulting in an equal number of INT¹ and CTL¹ of FN background and INT² and CTL² of non-FN background.

Methods: The inclusion criteria are: (1) age 18 to 30 years, FN background or other ethnicity; (2) Beck Depression Inventory (BDI)-II of at least mild severity (BDI-II score ≥ 14) and no upper limit; (3) Mini-International Neuropsychiatric Interview (MINI)-confirmed psychiatric diagnosis of major depressive disorder; and (4) fluent in English. All patients are diagnosed by a Centre for Addiction and Mental Health psychiatrist, with diagnoses confirmed using the MINI interview. The exclusion criteria are: (1) individuals receiving weekly structured psychotherapy; (2) individuals who meet the Diagnostic and Statistical Manual of Mental Disorders criteria for severe alcohol/substance use disorder in the past 3 months, or who demonstrate clinically significant

suicidal ideation defined as imminent intent, or who have attempted suicide in the past 6 months; and (3) individuals with comorbid diagnoses of borderline personality, schizophrenia, bipolar disorder, and/or obsessive compulsive disorder. All subjects are provided standard psychiatric care defined as 1 monthly session that focuses on appropriate medication, with session durations of 15 to 30 min. Experimental subjects receive an additional intervention consisting of the CBT-M online software program (in collaboration with Nex J Health, Inc). Exposure to and interaction with the online workbooks are combined with navigation-coaching delivered by phone and secure text message interactions.

Results: The outcomes selected, combined with measurement blinding, are key features in assessing whether significant benefits regarding depression and anxiety symptoms occur.

Conclusions: If results confirm the hypothesis that youth can be effectively treated with online CBT-M, effective services may be widely delivered with less geographic restriction.

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KEYWORDS

intervention study; telemedicine; mobile phone; mhealth; fitbit; depression; cognitive behavioral therapy

Introduction

A total of 70% of all mental health problems appear before the age of 25 years. If untreated, these problems can become long-standing disorders that impair multiple life domains [1]. When compared with all Canadian youth (of different ages), the cohort between 15 and 25 years is significantly more likely to experience mental health disorders and substance dependencies and risks for suicidal ideation and death by suicide [2-5]. The current economic costs of mental health are vast, estimated at Can \$51 billion annually, with Can \$20.7 billion annually due to lost labor force participation [6]. Innovations in internet and smartphone technologies provide opportunities to deliver mental health care in ways that improve outcomes, reduce costs and overcome the geographic barriers that obstruct service equity.

Cognitive behavioral therapy (CBT)—the best-validated psychotherapy [7]—has, in recent years, been integrated with mindfulness meditation (MM), resulting in strong evidence supporting their combined effectiveness [8-14]. Research with this combination, with student populations, by our group, has resulted in psychometric and neurophysiological [9-17] benefits in online single-arm and randomized controlled trials (RCTs). Another online intervention, tested in an RCT, demonstrated significant reductions in glycosylated hemoglobin blood levels in patients with type 2 diabetes [18-20].

Mindfulness interventions gained notice due to the efficacy and low costs of easily learned procedures that fostered attentional skills and present-time awareness ([21-31]; Kirk et al, in press). For over three decades, in-person mindfulness-based stress reduction and acceptance and commitment therapy programs [17-24,32] have reduced mental and physical symptoms, summing in a significant accumulation of evidence supporting their effectiveness in nonclinical [28] and clinically diagnosed populations [29-31]. A recent review of mindfulness-based cognitive behavioral therapy (CBT-M) suggests that internet-based approaches have effects similar to in-person approaches [33] with evidential support from a systematic review of studies published between 2000 and 2018 [33-43]. The reviewed studies (all RCTs) assessed internet-delivered

CBT-M programs in terms of changes in anxiety and depression (as primary or secondary outcomes) in adults (mean age ≥ 18 years) with a clinical diagnosis of depression or anxiety (using the Diagnostic and Statistical Manual [DSM]-IV protocol) [34-43]. In this review of 11 RCTs, a mean Hedges' g of -0.47 was calculated based on a 45.6% reduction in depression symptoms when compared with the control populations. These reductions are similar to those found in a systematic review reported by Karyotaki et al who calculated a mean Hedges' g of -0.27 (for depressive symptom reduction) in online, self-guided treatments that solely implemented CBT [44].

Online programs, altogether, can track usage and transmit text or email prompts to motivate adherence, resulting in higher motivation levels [45-48]. Access to a virtual mindfulness-based navigator-coach at greater frequencies than possible with face-to-face communication [45-49], and improved outcomes. The RCT described here combines these features and assesses them with youth with diagnosed major depressive disorders.

Methods

Aim

The study aims to evaluate the efficacy of CBT combined with MM to treat youth (aged 18-30 years) diagnosed with major depressive disorder. We will enroll 168 subjects, where 50% of the subjects will be from First Nations (FN) background, while the other 50% will be from all other ethnic backgrounds, stratified in 2 intervention groups and 2 (wait-list) control groups (42 subjects per group, where INT¹ and CTL¹ are from FN background and INT² and CTL² are from non-FN background). The intervention groups will be compared with the control groups at baseline, 3 months (mid intervention), and 6 months (post intervention), using validated outcome measures.

Recruitment and Randomization

Subjects are identified from the wait-lists for services at the Centre for Addiction and Mental Health (CAMH) and through contacts with multiple Toronto-based clinics. Eligible patients interact with a research coordinator who reviews and explains the study. Eligibility is ascertained in person followed by written consent before randomization. The identification of most

subjects follows CAMH procedures where research coordinators identify potential participants by prescreening new clinic referrals and notifying the investigative team and the client's clinician about potential study eligibility. The clinician then asks the client if she/he is willing to meet with a study team member to explore participation. Only when a client agrees, is she/he approached.

A biostatistician at the Department of Biostatistics at University Health Network (G Tomlinson) performed an electronic randomization of participants with study IDs to the different groups (INT¹, INT², CTL¹, and CTL²). The information regarding each study ID with its respective group allocation was transferred onto cards and placed in individually sealed envelopes. After a participant had completed the baseline questionnaires, the research coordinator opened the next envelope in the series to determine participant group allocation and their respective study ID.

On the basis of a careful review of previously successful studies [38,39,41], we determined a sample size of 42 participants per group in 4 groups (total of n=168). Type I error was set at $\alpha=.05$ and power at 80%. Our projected sample size of 168 participants is deemed more than adequate for the detection of small to medium effect size. With an anticipated drop-out rate of up to 20%, we will recruit 208 participants (54 per group).

Inclusion Criteria

The inclusion criteria are as follows: (1) age 18 to 30 years, FN background or any other ethnicity; (2) Beck Depression Inventory (BDI)-II of at least mild severity but no upper limit (BDI-II score ≥ 14) [50]; (3) Mini-International Neuropsychiatric Interview (MINI)-confirmed psychiatric diagnosis of major depressive disorder [51]; and (4) fluent in English. All patients are diagnosed by a CAMH physician, and the diagnoses are confirmed using the MINI interview administered at the screening visit [51].

Exclusion Criteria

The exclusion criteria are: (1) individuals who are currently receiving weekly structured psychotherapy; (2) individuals who meet the DSM-V criteria for severe alcohol/substance use disorder in the past 3 months, or who demonstrate clinically significant suicidal ideation defined as imminent intent, or who have attempted suicide in the past 6 months; and (3) individuals with comorbid diagnoses of borderline personality, bipolar disorder, schizophrenia, and/or obsessive compulsive disorder.

Intervention

All subjects are provided standard psychiatric care, involving 1 monthly session that focuses on appropriate medication, with session durations from 15 to 30 min. Experimental subjects receive the additional intervention, consisting of a CBT-M software program (in collaboration with Nex J Health, Inc), which is accessed online. Interactions with the online workbooks is combined with navigation-coaching (total 24 hours duration), primarily delivered in phone and text message interactions. In addition, each participant is given a Fitbit-HR Charge 2 that assesses physical steps and 24-hour heart rate in 5-second (averaged) durations (the software permits daily monitoring).

The intervention content builds on 2 prior successful Web-based CBT-mindfulness RCTs with students [9,10,13,15-17] and on effective methods with other populations demonstrated in previous RCTs [52-55]. The online workbook content includes 24 chapters reflecting multiple topics (eg, Living By Your Truths, Overcoming Wired-ness and Tired-ness, Mindfulness and Relationships, Loss and Grief, and Resilience, Befriending Ourselves, Befriending Your Body with Exercise, Body Image and Mindfulness, Intimacy, Forgiveness, Overcoming Procrastination, Dealing with Negative Moods, Stress Resilience, Overcoming Performance Anxiety, and Cultivating Inspiration) covered sequentially on a weekly basis with the navigator-coach. In summary, the key intervention features are 24-hour access and CBT-mindfulness contents that address specific symptoms and generic depressive experiences.

Hypothesis

The CBT-M online intervention will be associated with statistically and clinically significant between-group differences (benefits) when treatment groups and control groups are compared, using both intention-to-treat (ITT) and per protocol analyses (PP). The ITT will proceed in a standard manner, whereas the PP will be based on the 24-week and 24-session structure of the intervention. All subjects who fail to attend 50% of the sessions (ie, <12 sessions) will be excluded from the PP.

Outcome Measures

Primary Outcome

The primary outcome measure is the BDI-II [50].

Secondary Outcomes

The secondary outcomes assess anxiety (Beck Anxiety Inventory) [56], depression (ie, Quick Inventory of Depressive Symptomatology) [57], 24-item Hamilton Depression Rating Scale (HDRS-24; with a blinded interview-rater) [58], mindfulness (5-Facet Mindfulness Questionnaire) [59], and pain (Brief Pain Inventory) [60].

All self-report measures and the HDRS-24 interview are carried out at the same CAMH Mood and Anxiety research clinic in identical assessment rooms. The HDRS-24 interview-rater is blinded to intervention and control conditions for the trial duration.

Results

Analyses

Data obtained from participants during the study visits are de-identified and stored as electronic case reporting forms (CRFs) on the CAMH REDCap system and physical CRF paper copies in a locked cabinet. Participant characteristics are summarized via descriptive statistics. Group equivalence at baseline in terms of demographic and clinical variables is assessed.

Primary and Secondary Outcomes

The monthly rate of recruitment is calculated and the level of retention will be presented in the proportion of enrolled participants completing study outcomes at each time point.

The effect of the intervention on the primary clinical and secondary outcomes will be assessed through separate analysis of covariance (ANCOVA) models that have changed from baseline to 6 months as the dependent variable, the baseline value of the outcome as a covariate and the group assignment as a categorical variable. The treatment effect, its effect size (Hedges' g), and 95% CIs for the treatment effect and within-group changes from baseline to one year will be calculated from the ANCOVA model. The sensitivity of results to missing data will be evaluated by running a purely data-based multiple imputation procedure, as well as the imputation of

missing values on a case-by-case basis using expert opinion and patient history.

Discussion

If hypothesized results are obtained, this intervention may be an important option for depressed youth. As it can be accessed wherever internet-based services are available, geographic barriers to high-quality treatment could be minimized. Acknowledged study limitations include the lack of blinding regarding administration of self-report measures other than the blinding maintained for the HDRS-24 assessment.

Conflicts of Interest

None declared.

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Abbreviations

ANCOVA: analysis of covariance
BDI: Beck Depression Inventory
CAMH: Centre for Addiction and Mental Health
CBT: cognitive behavioral therapy
CBT-M: mindfulness-based cognitive behavioral therapy
CRF: case reporting form
DSM: Diagnostic and Statistical Manual of Mental Disorders
FN: First Nations
HDRS-24: 24-item Hamilton Depression Rating Scale
ITT: intention-to-treat
MINI: Mini-International Neuropsychiatric Interview
MM: mindfulness meditation
PP: per protocol
RCT: randomized controlled trial

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Protocol

Motivational Interviewing to Reduce Drug Use and HIV Incidence Among Young Men Who Have Sex With Men in Relationships and Are High Priority for Pre-Exposure Prophylaxis (Project PARTNER): Randomized Controlled Trial Protocol

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Abstract

Background: Men who have sex with men (MSM) currently account for more than two-thirds of new HIV diagnoses in the United States and, among young MSM (YMSM) aged 20 to 29 years, as many as 79% to 84% of new infections occur between primary partners. Contributing to HIV risk, YMSM use drugs at comparatively high rates. To date, no interventions have been developed that specifically address the unique needs of partnered YMSM or incorporate a focus on relationship factors in addressing personal motivation for change.

Objective: The study's primary aim is to evaluate the efficacy of the PARTNER intervention and evaluate potential moderators or mediators of intervention effects. The study's secondary aims were to gather ideographic data to inform a future effectiveness implementation study and develop a novel biomarker for pre-exposure prophylaxis (PrEP) adherence by analyzing PrEP drug levels in fingernails.

Methods: PARTNER is a 4-session motivational interviewing-based intervention that integrates video-based communication training to address drug use and HIV prevention among partnered YMSM. This study utilizes a randomized controlled trial design to compare the PARTNER intervention with an attention-matched psychoeducation control arm that provides information about HIV-risk reduction, PrEP, and substance use. Participants are randomized in a 1-to-1 ratio stratified on age disparity between partners, racial composition of the couple, and relationship length. Follow-up assessments are conducted at 3-, 6-, 9-, and 12-months postbaseline. The study recruits and enrolls 240 partnered YMSM aged between 18 to 29 years at a research center in New York City. Participants will be HIV-negative and report recent (past 30-day) drug use and condomless anal sex with casual partners; a nonmonogamous primary partner (regardless of HIV status); or a serodiscordant primary partner (regardless of sexual agreement). Primary outcomes (drug use and HIV sexual transmission risk behavior) are assessed via a Timeline Follow-back interview. Biological markers of outcomes are collected for drug use (fingernail assay), sexual HIV transmission risk (rectal and urethral gonorrhea and chlamydia testing), and PrEP adherence (dried blood spots and fingernails for a novel PrEP drug level assay).

Results: The study opened for enrollment in February 2018. Anticipated completion of enrollment is October 2021. Primary outcome analyses will begin after final follow-up completion.

Conclusions: Existing research on partnered YMSM within the framework of Couples Interdependence Theory (CIT) has suggested that relationship factors (eg, dyadic functioning and sexual agreements) are meaningfully related to drug use and HIV transmission risk. Results pertaining to the efficacy of the proposed intervention and the identification of putative moderators and mediators will substantially inform the tailoring of interventions for YMSM in relationships and contribute to a growing body of relationship science focused on enhancing health outcomes.

Trial Registration: ClinicalTrials.gov NCT03396367; <https://clinicaltrials.gov/ct2/show/NCT03396367> (Archived by WebCite at <http://www.webcitation.org/78ti7esTc>).

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KEYWORDS

HIV; pre-exposure prophylaxis; substance-related disorders; sexual behavior; sexual partners

Introduction

Background

Young men in same-sex relationships are confronted with a unique constellation of challenges specifically related to drug use and HIV risk. Men who have sex with men (MSM) accounted for 67% of all new HIV infections in the United States in 2016 and approximately two-thirds (64%) of those infections among MSM were observed in the youngest age cohorts (13 to 24 years and 25 to 34 years) [1]. Although rates remained largely stable among 13 to 24-year-old young men who have sex with men (YMSM), they rose by 21% among men aged 25 to 34 years [1]. Collectively, these data point to the early years of adulthood as a time of emerging and potentially escalating risk for HIV infection.

MSM in same-sex relationships are particularly vulnerable to HIV infection, with risk again concentrated in the early years of adulthood. Main partners accounted for 35% to 68% of new HIV infections among MSM [2,3]. Estimates suggest that rates of main partner transmission may be as high as 79% to 84% among YMSM aged 20 to 29 years [2], and this risk of main partner HIV transmission increases with discrepancy among the partners' ages [2,3]. Sullivan et al [2] suggested that the increased risk for partnered men arises from the fact that men in relationships have sex more frequently with each other, with high rates of condomless anal sex (CAS).

The vulnerable age range defining YMSM corresponds largely to the developmental period of emerging adulthood. The transition from adolescence to adulthood has lengthened over time, with experts suggesting that emerging adulthood lasts from age 18 to 29 years with implications for both physical and mental health outcomes [4]. During this developmental period, emerging adults develop an increasingly firmer sense of sexual identity, solidify mechanisms to regulate emotions, and learn to develop romantic relationships [5-7]. Therefore, it is important to note that behaviors emerging adults adopt during this critical period not only affect current health but also have substantial implications for behaviors and health outcomes later in adulthood [5,7].

Drug Use and Emerging Adult Young Men Who Have Sex With Men in Relationships: A Covariate of HIV Infection Risk

YMSM use drugs at higher rates than their heterosexual counterparts [8,9]. The most common drugs reported include cocaine, crystal meth, and other *party drugs* (eg, ketamine and gamma-hydroxybutyrate [GHB]) [10,11], as well as marijuana [12]. Drug use among YMSM is of particular concern because of its established association with HIV transmission risk behavior (ie, CAS with a partner of serodiscordant or unknown status) [13]. The fact that YMSM use drugs at higher rates than older MSM [14] and their heterosexual same-age counterparts [15,16] potentially compounds their risk for HIV infection.

A number of factors contribute to the need to develop tailored intervention strategies to address drug use among YMSM in relationships with other men. Unlike their heterosexual counterparts, being partnered is not associated with reductions in drug use among MSM [15]. Meanwhile, associations between drug use and HIV transmission risk behavior with casual partners remain significant among partnered MSM [17-19]. Sexual aspects of the relationship contextualize drug use for partnered men. Drug use covaries with sexual agreements [17,18], the understandings couples have about sex with partners outside their relationship [20]. Men in nonmonogamous relationships are significantly more likely to use drugs [17,18], and nonmonogamous relationships are characterized by more between-partner variability in use [17].

Motivational Interviewing: A Basis for Intervention Development

Motivational interviewing (MI) is a client-centered approach to discussing a target issue: understanding that issue from a client's perspective, enhancing individual motivation for change, and subsequently developing plans to achieve identified goals [21]. MI provides a framework for delivering information regarding the target behavior and specific strategies to cultivate personal motivation for change. It emphasizes the individual's self-efficacy and autonomous capacity to make well-informed health decisions [21].

Brief MI-based interventions have shown efficacy in targeting substance use and sexual health among youth, including sexual minority youth [22-25]. Specifically, Parsons et al found empirical support for a 4-session MI-based intervention—termed

the Young Men's Health Project (YMHP)—to reduce both substance use and HIV transmission risk behavior among YMSM [25]. Secondary analyses of YMHP outcome data underscored the need to tailor interventions for YMSM in relationships. Starks and Parsons found that those YMSM who were partnered when they received YMHP showed essentially stable drug use over time, whereas a matched comparison sample of single men who also received the intervention showed significant and stable reductions in drug use [26]. Thus, although MI represents an adaptive and multipurpose platform with a proven record of success in integrated interventions focused on sexual health and substance use among YMSM, existing brief MI interventions may benefit from adaptations that specifically address relationship factors relevant to YMSM in relationships, particularly with regard to effects on drug use.

Couples Interdependence Theory: Tailoring Motivational Interviewing for Partnered Young Men Who Have Sex With Men

CIT [27] has been applied to understand how relationship factors influence individual health outcomes for men in relationships with other men [28]. Through a process termed accommodation, partners within a relationship arrive at a shared goal or vision. When successful, the creation of the shared goal leads to a transformation of motivation, wherein partners consider the long-term effects of their decisions on their partner and their overall relationship [27,29-31]. This allows joint goals to draw on both individual-level and couple-level resources and increases the likelihood of goal accomplishment [30,31]. Notably, individual-level factors related to better dyadic functioning—including elements such as relationship satisfaction, commitment, communication, and relationship investment—facilitate the accommodation process [30].

CIT would suggest that an intervention tailored for partnered YMSM should incorporate components of relationship skill building. Male couples with better dyadic functioning will be better able to create shared sexual health goals and be more successful at the accomplishment of these shared goals once formed. However, dyadic interventions alone are insufficient to meet the diverse needs of partnered YMSM. For some couple-focused interventions, concurrent participation is required. This type of participation poses a logistical barrier for many couples as coordination of schedules is needed. Moreover, there is a possibility that one partner of the couple may be less able or motivated to participate. In addition, the implementation of couple-focused interventions may strain resources with providers as clinical skills and administrative-level concerns may arise [32]. Furthermore, researchers have indicated that participation in a couple-focused intervention may bias participation toward couples with higher relationship functioning [33,34].

Biomedical Prevention for HIV Infection and Partnered Young Men Who Have Sex With Men

Daily use of Emtricitabine/Tenofovir Disoproxil Fumarate, FTC/TDF (Truvada), or PrEP reduces the risk of HIV infection substantially among those at risk. Recommendations from the US Centers for Disease Control and Prevention (CDC) [35] identify MSM in nonmonogamous relationships or relationships

with an HIV-positive partner as high-priority candidates for PrEP. Despite this recommendation, research on gay male couples suggests that partnered YMSM face unique barriers to PrEP uptake.

Partnered men report being fearful that their primary partner may perceive them to be having sex with outside partners if they were to go on PrEP or discuss PrEP with their primary partner [36]. At the same time, the incorporation of HIV risk reduction plans (eg, PrEP use and consistent condom use) into sexual agreements can significantly reduce HIV transmission risk [37-39]; however, such inclusion requires the couple to be open to discussing PrEP. Gay men's willingness to persuade a relationship partner to use PrEP was associated with their own willingness to take PrEP [38]. Collectively, these findings point to the need to facilitate communication between YMSM and their relationship partners about PrEP. Having an interventionist—a neutral party outside the relationship—introduce the topic may reduce anxiety related to initiating the conversation about PrEP and provide an opportunity for partners with some interest in PrEP to encourage less-interested partners to consider it.

Novel Assessment of Pre-Exposure Prophylaxis Adherence

The extent to which PrEP achieves reductions in HIV risk is highly contingent upon adherence. Estimated reductions in infection risk are as high as 96% with full adherence to daily PrEP [40]. The assessment of adherence constitutes an inherent methodological challenge in PrEP studies. Behavioral measurements (eg, self-reports of missed doses and pill counting) are generally considered acceptable proxies for adherence but they can be influenced by participant biases such as social desirability or recall bias [41]. Testing for PrEP metabolites in dried blood spots (DBS) has emerged as a leading method for the objective assessment of adherence [42], although obtaining and storing high-quality samples is challenging [43]. Hair analysis can also be used to measure PrEP adherence [44-46]; however, the analysis requires a particular length of hair and therefore poses challenges for some participants—particularly males with very short hair [45].

Fingernail assays are a promising alternative approach to measuring PrEP adherence. Fingernail collection has high rates of acceptability and can be implemented with minimal training, with lower associated costs than blood collection. Fingernail assays have become increasingly used in the detection of illicit drug use [47-51]. Studies demonstrate that fingernail analysis may be more sensitive to detecting substances relative to hair assays [49,52,53]. Thus, developing a fingernail assay to measure Tenofovir (TFV) and FTC levels as biomarkers of adherence has potential utility for community-based and public health providers over DBS or hair adherence metrics in terms of acceptability and feasibility.

Objective

The purpose of this study is to test the efficacy of a tailored MI-based intervention that specifically addresses factors relevant to drug use and HIV prevention for partnered YMSM who are high-priority candidates for PrEP. The study has 2 primary

objectives. The first is to evaluate the efficacy of PARTNER with regard to 3 primary outcomes: (1) PrEP uptake and adherence, (2) sexual HIV transmission risk behavior, and (3) drug use. The second is to identify individual and relationship factors that moderate and/or mediate intervention effects. The study also has 2 secondary objectives: (1) gather ideographic data to inform a future effectiveness-implementation study and (2) validate the use of fingernail assays as a biological marker for PrEP adherence. In this study, the research team will collect both DBS and fingernail samples to assess the concurrent validity of PrEP drug or metabolite levels in each matrix.

The primary hypotheses are that YMSM receiving the PARTNER intervention will be more likely to initiate and/or be adherent to PrEP throughout the follow-up period than those in the education condition. It is hypothesized that they will have a lower probability of HIV transmission risk behavior at follow-up. In addition, it is hypothesized that the PARTNER intervention will be associated with lower levels of drug use

(number of use days) at follow-up compared with the education condition. Secondly, we hypothesize that levels of TFV/FTC observed in the fingernail assay will correlate highly with levels of TFV-diphosphate (TFV-DP) and FTC-triphosphate (FTC-TP) in DBS, providing evidence for the validity of this novel biological marker of adherence.

Methods

Trial Design

This study utilizes a randomized controlled trial design to evaluate the efficacy of the PARTNER intervention relative to an attention-matched psychoeducation control condition. Baseline assessment is conducted before randomization and receipt of intervention. Follow-up assessments are conducted at 3, 6, 9, and 12 months post baseline. Table 1 presents the study schedule for participation consistent with Standard Protocol Items: Recommendations for Interventional Trials guidelines (SPIRIT).

Table 1. Recommended content for the schedule of enrollment, interventions, and assessments.

Research activity	Study period					
	Enrollment	Allocation	Post-allocation			Close-out
Time point in months	0	0	3	6	9	12
Enrollment						
Eligibility screen	X ^a	— ^b	—	—	—	—
Informed consent	X	—	—	—	—	—
Baseline	X	—	—	—	—	—
Allocation	—	X	—	—	—	—
Interventions						
PARTNER	—	X	—	—	—	—
Education	—	X	—	—	—	—
Assessments						
Demographic; HIV status; pre-exposure prophylaxis uptake; Drug use; Relationship length;	X	—	—	—	—	—
Drug Use Events; Positive drug assay; pre-exposure prophylaxis uptake/adherence, HIV transmission risk events; and Positive sexually transmitted infection test	X	—	X	X	X	X
Dyadic functioning and sexual agreements	X	—	X	X	X	X

^aDenotes that the research activity was conducted or data was collected at a particular time point.

^bIndicates that the research activity was not conducted or data was not collected at a particular time point.

Study Setting

All study assessments and intervention sessions are conducted at the Promoting Resilience, Intersectionality, Diversity, & Equity (PRIDE) Health Research Consortium affiliated with Hunter College of the City University of New York. PRIDE is located centrally in Manhattan with easy access to a mass public transportation hub linking it to the larger metropolitan area. Assessment and intervention sessions are conducted in private rooms.

Eligibility Criteria

Participants must fulfill the following inclusion criteria to be enrolled in the study: (1) be aged 18 to 29 years, (2) have a main partner, for 1 month or longer, who is male and is aged 18 years or older, (3) be HIV negative (as confirmed by the rapid test), (4) have used drugs in the past 30 days, (5) have engaged in HIV transmission risk behavior in the past 90 days, (6) live in the New York City metropolitan area, and (7) be able to speak and read in English. Participants will be excluded from the study if they indicate any of the following: (1) any signs of serious mental illness or cognitive deficit and (2) history of intimate partner violence with their main partner.

Interventions

PARTNER Intervention (Experimental Condition)

The PARTNER intervention comprises 4 sessions of MI to address 3 target behaviors that correspond to the study's primary outcomes: drug use, PrEP uptake/adherence, and HIV transmission risk. Miller and Rollnick [54] suggested that 4 processes are ongoing during an MI session: engagement (establishment of a therapeutic alliance), focusing (clarification of session goals), evoking (eliciting speech in favor or change while softening arguments for the status quo), and planning (the identification of action steps that can be taken toward the accomplishment of an identified goal). The salience of these various processes is dependent upon the duration of the relationship between the interventionist and the participant as well as the client's stage of change.

The first session emphasizes the engaging process. It begins with an introduction to the participant followed by an exploration of participant's primary relationship, understanding how he and his partner handle sex outside their relationship, and enhancing motivation to reduce both drug use and HIV infection risk. This conversation then focuses on what strategies, if any, the participant and his partner use to manage their HIV risk. The interventionist then seeks to evoke motivation to reduce HIV related risk, potentially through PrEP uptake or adherence. The values card sort activity is utilized midway through the session to integrate a conversation about how the participant's values are expressed in his relationship and the decisions made around HIV prevention. The second session engages the participant in a review of the previous week and then transitions to focus on drug use. The interventionist seeks to evoke motivation to reduce drug use, with particular attention given to how the participant's relationship partner feels about use. The third session integrates a focus on the links between drugs and CAS with main and casual partners, PrEP, and presents video-based modeling to enhance communication skills. This facilitates a longer discussion about planning toward any identified goals. The interventionist gives particular attention to the role of relationship partners during the planning phase. The final session engages the participant in a review of the previous week. The session then proceeds to review the participant's perception of the overall intervention process with emphasis on successes and challenges. The session emphasizes the planning process by inviting the participant to identify long-term goals related to the target behavior and develop plans to accomplish these goals. A discussion of relevant resources and referrals occurs during this time.

PARTNER incorporates a video-based approach to relationship skill building with a structured series of debriefing questions asked by the MI provider after the video is viewed. The video utilized was comprised 3 scenes, each depicting a different couple. It is integrated into Session 3 of the intervention and serves a dual purpose. First, it provides information specific to PrEP. Each scene depicts either a nonmonogamous or serodiscordant couple discussing PrEP and HIV prevention. In this way, participants viewing the video see men in relationships with men talking about reasons why PrEP might be relevant, while also receiving basic information about PrEP and its

efficacy. Second, the videos directly teach communication skills through modeling. Each scene is divided into 2 parts. In the initial portion of the scene, the couple makes a specific communication error. Midway through the scene, a narrator interrupts the couple, explains their error, and suggests an alternative strategy. The scene then continues, and the couple communicates more effectively.

Education Intervention (Control Condition)

The education intervention is administered one-on-one by a health educator. The sessions are guided by a PowerPoint presentation that helps to insure fidelity of delivery while also increasing the participant's engagement through the integration of pictures, animation, and video. The presentation is viewed on a personal computer located in the intervention room. Dual monitors are used to ensure that both the educator and participant can readily view material.

The condition comprises 4 sessions of health education addressing sexual risk and drug use. The sessions utilize a mixture of modalities including lecture, question and answer, and video. Session 1 focuses on HIV risk and prevention. Lecture content is supplemented by videos focusing on HIV transmission generally and HIV prevention strategies among gay and bisexual men specifically. Session 2 is focused on drug use. Information about the biological effects of drug use is largely provided through videos. Lecture content and discussion questions focus on the impact of drug use within the local gay community. Session 3 examines the intersection of drugs and sex in the local gay community. Education content also focuses on mitigating the risks associated with having sex while intoxicated. Session 4 again focuses on drug use with video and lecture-delivered content describing the signs and warnings of potential substance use disorders.

Training of Interventionists

Experimental Condition

Initial intervention training includes a 2-day workshop for the interventionists employed by the study on MI delivered by a member of the Motivational Interviewing Network of Trainers (MINT) followed by a day long workshop on the structure of the PARTNER intervention. Ongoing coaching and supervision will occur, in addition to training on new interventions, as required. The training of the interventionists (experimental condition) is led by a clinical psychologist (principal investigator) who is a member of MINT and is from PRIDE. The training procedure consists of (1) a 2- to 3-month training period of role-play practice, coding and feedback, and supervision modeling, including mock sessions with *standardized participants* role-played by PRIDE research assistants; (2) weekly 1-hour supervision sessions with interventionists individually; (3) weekly group supervision with all the interventionists collectively; and (4) ongoing quality assurance and feedback using Motivational Interviewing Treatment Integrity (MITI) coding.

PARTNER will be delivered by postdoctoral fellows with formal training in mental health counseling, doctoral students in the Health Psychology and Clinical Science program at the City University of New York Graduate Center, and Masters level

mental health clinicians employed at PRIDE. They will be trained in MI—and on the specific PARTNER protocol—by the principal investigator.

Education Condition

Training in the control condition (education intervention) is led by a postdoctoral fellow with extensive experience in the delivery of brief and structured intervention protocols. Educators delivering the education intervention will be project coordinators or graduate students with specific training in the delivery of the educational content related to drug use and sexual health. The training procedure consists of a 2- to 3-month training period of role-play practice, coding and feedback, and supervision modeling, including mock sessions with *standardized participants* role-played by research assistants.

Fidelity Monitoring and Supervision

All PARTNER (experimental) and Education (control) sessions will be audio recorded. MI fidelity in PARTNER will be evaluated using the MITI coding system [55]. We will randomly select 25% of sessions by each interventionist to be coded. PRIDE maintains a team of trained MITI coders utilized in all of PRIDE's National Institutes of Health-funded studies involving MI-based interventions. The educators will undergo similar fidelity procedures in which 25% of their education sessions will be evaluated for fidelity. These recordings will be reviewed and matched to a fidelity checklist that outlines the content of the Education session. Successful Education sessions will have accurately discussed at least 90% of the content.

Outcomes

Drug Use Events

The number of drug use events is measured using a self-report interview commonly known as the timeline follow-back (TLFB [56]). Participants complete an interviewer administered 30-day TLFB interview of their drug and alcohol use [56]. Using a calendar, a research assistant coded whether any substance use occurred on a given day. On days when substance use occurred, the research assistant codes the presence of heavy drinking (ie, 5 or more alcoholic drinks) and/or the type of drug used (ie, marijuana, ketamine, methylenedioxy-methamphetamine (MDMA) or ecstasy, GHB, cocaine/crack, opiates or prescription drugs, or methamphetamine). In addition, this method will allow researchers to determine the number of days a particular drug was used and the total number of days in which any drug was used. Drug use is assessed at baseline, 3-, 6-, 9-, and 12-month follow-up appointments.

Positive Drug Assays

Positive drug tests via validated and commercially available fingernail assays will determine if a particular drug was used in the past 3 to 6 months. The assays are derived from a 5-panel detection system that detects the consumption of amphetamines/ecstasy/MDMA, cannabinoids, cocaine, opiates, and phencyclidine. The nail samples will be sent to the US Drug Testing Laboratories Inc for processing.

Pre-Exposure Prophylaxis Uptake/Adherence

PrEP uptake will be measured using self-report and PrEP adherence (among those on PrEP) and will be assessed using a TLFB interview approach analogous to that described earlier for drug use. Self-reported adherence will be verified by measuring PrEP metabolite concentrations in DBS via liquid chromatography/tandem mass spectrometry (LC-MS/MS). The results of the assays that analyze TFV-DP and FTC-TP in DBS quantify how many PrEP doses are taken over an average of 6 weeks as a metric of PrEP adherence. If participants did not report PrEP use at baseline, but report it at follow-up assessments, we will record their response to indicate that they initiated use and assess PrEP adherence via TLFB and DBS. With regard to the study's secondary aim, PrEP adherence will also be assessed via nail samples. Levels of TFV-DP and FTC-TP observed in nail samples will be correlated with DBS results as a validation metric in accordance with the study's secondary aim.

Number of HIV Transmission Risk Events

Self-report of CAS acts is measured using the TLFB. Using the TLFB calendar, the research assistant codes whether CAS occurred on a given day and how many times, and with what type of partner (main or casual and the partner's HIV status). This method will allow researchers to determine the number of occurrences of CAS within the specified period. CAS is assessed at baseline, 3-, 6-, 9-, and 12-month follow-up appointments.

Positive Sexually Transmitted Infection Test

Positive sexually transmitted infection (STI) tests for urethral and rectal gonorrhea and chlamydia will be used as a supplemental proxy for HIV transmission risk behavior. STI tests used in addition to self-report have increasingly been used in studies focused on PrEP to measure CAS [57,58]. STI testing occurs at baseline, 3-, 6-, 9-, and 12-month follow-up appointments.

Participant Timeline

See [Table 1](#).

Sample Size

We utilized the *Test for the Ratio of Two Negative Binomial Rates* module in PASS 19 [59] to evaluate power to detect between-condition differences in drug use frequency at any one follow-up time point. Power (1-beta) was set to .80 and the probability of type II error (alpha) was set to .05. The number of exposures was set to 30 (the number of days of use assessed in the TLFB). The rate of use in the education condition was set to 3, 6, and 9. Meanwhile dispersion values of 1, 2, and 4 were tested. Power was highest at low levels of dispersion and high base rates of use in the education condition. Under these circumstances, the study has power=.80 to detect a rate ratio of 0.70 or a 30% reduction in drug use instances. At high levels of dispersion and low base rates, the study would be expected to detect a rate ratio of 0.48.

Power to detect differences in HIV transmission risk behavior was calculated in 2 ways. First, using procedures similar to those described for drug use, the study has power to detect a rate ratio between 0.48 and 0.69 in the number of CAS events

in the absence of PrEP. This calculation tested average rates of CAS in the absence of PrEP in the education condition of 1, 3, and 5 instances and dispersion was tested at values of 1, 2, and 4. Power to detect significant differences in the odds of a positive STI test was calculated using the *inequality tests for 2 proportions in a repeated measures design* module [59]. Analyses specified 4 waves of data, power (1-beta) was set to .80, and the probability of type II error (alpha) was set to .05. Autocorrelation (rho) was permitted to vary between .25 and .75. The proportion of positive STI diagnosis in the education condition was tested at values of .13, .10, and .07. Power declined as rho increased. Power increased with the proportion of positive diagnoses in the education condition. Analyses suggested that the study is adequately powered to detect large effects, associated with an odds ratio between 0.20 (under the least favorable conditions) and 0.32 (under the most favorable).

Power to detect differences in PrEP uptake was similarly calculated using the *inequality tests for 2 proportions in a repeated measures design* module [59]. Analyses specified 4 waves of data, power (1-beta) was set to .80, and the probability of type II error (alpha) was set to .05. Autocorrelation (rho) was permitted to vary between .25 and .75. We estimated that on average 35% of the education condition would be on PrEP during the follow-up period. The proposed sample is sufficient to detect an odds ratio of 1.90 even at the highest values of rho, which corresponds to approximately 51% of the PARTNER condition initiating PrEP. With regard to adherence, assuming approximately 100 participants (45% of the sample assuming 80% retention) are on PrEP at any follow-up point and 75% of the control condition is adherent to their PrEP medication (Cronbach alpha=.05; and rho=.25 to .50), results suggested that the study has power=.80 to detect an odds ratio of approximately 3.0.

Recruitment

We will utilize a multifaceted recruitment effort including both active and passive approaches. Our previous research focused on MSM has indicated that Web-based recruitment is particularly efficient at reaching those who use substances and engage in sexual HIV transmission risk behavior [60,61]. We anticipate enrolling 6 new participants each month. Contacts for prescreened eligible participants obtained through the online screener will be contacted by email and phone and will be rescreened for project eligibility over the phone. If eligible, participants will have their baseline appointment scheduled and have their home-based survey emailed to them.

Assignment of Interventions

Randomization

Participants will be randomly assigned using a stratified block randomization procedure using responses from the participant's baseline questionnaire programed in Qualtrics. Specifically, randomization will account for: (1) age discrepancy: participant age difference with his partner (3 years or less/greater than 2 years); (2) relationship length with his main partner (2 years or less/greater than 2 years); (3) race/ethnicity makeup of the participant and his partner, for example, both partners identify as white and non-Hispanic/one or both partners identify as

non-white or Hispanic. Thus, random assignment will occur only after participants have completed a baseline questionnaire. The random assignment will be performed by the Qualtrics system that has been programmed by the onsite data team. Participants will be randomized to 1 of 2 conditions, PARTNER (experimental condition) or education (control condition).

Blinding

Study staff delivering the intervention and education conditions cannot be blinded to the condition they are delivering. To minimize contamination, these staff are cleared to only deliver one of the study conditions. Assessment staff are blinded to the condition at baseline as participants are not randomized until after the baseline assessment is completed. Assessment staff are not blinded to the condition at follow-up. Participants cannot be blinded to their assigned arm as participants will either be receiving an MI-based intervention in a modality analogous to psychotherapy or a control condition which is highly structured and educational in nature.

Data Collection for Primary Outcomes

Dried Blood Spots Adherence Assays

Plasma levels of TFV only represent recent use, whereas PrEP drug or metabolite levels in DBS and hair represent long-term measures of adherence. DBS measurements of TFV-DP have proven useful in the evaluation of PrEP efficacy [62] and hair and DBS measures are highly correlated [63]. The DBS adherence assay allows for an estimate of the average number of PrEP doses taken using validated methods [64]. Blood samples for DBS preparation will be taken intravenously by a licensed phlebotomist.

Fingernail Assay for Tenofovir /Emtricitabine

The hair analytical laboratory (HAL) at the University of California San Francisco (UCSF) has developed expertise in the analysis of TFV/FTC concentrations in small hair samples using LC/MS-MS. The UCSF HAL will attempt to develop and validate a fingernail-based assay for PrEP adherence by measuring TFV/FTC levels in fingernails collected in the PARTNER study for the first time. Similar to the processing of hair samples, the fingernail samples will be pulverized using an Omni Bead Ruptor and weighed. TFV and FTC in the pulverized fingernail samples will then be extracted with 50% methanol/water containing 1% trifluoroacetic acid, .5% hydrazine dihydrochloride, and internal standard in a 37°C shaking water bath overnight (>12 hours) and then analyzed by LC-MS/MS. The DBS assays in the Antiviral Pharmacology Laboratory at the University of Colorado and the hair assays at UCSF are both peer validated and approved by the Division of AIDS Clinical Pharmacology and Quality Assurance (CPQA) program [65]; the fingernail assay, once developed and validated in year 1 of this proposal, will be similarly peer-reviewed by CPQA before testing during years 2 to 4. This specific fingernail assay will only be completed with fingernails collected from participants who report taking PrEP. Thus, a distinct fingernail drug assays will be analyzed with a separate set of fingernails collected from participants with the goal of measuring PrEP adherence. In addition, regardless of PrEP uptake, a nail sample

will be collected from all participants for the purpose of drug testing.

Fingernail Assay for Drug Testing

Although studies have consistently supported the validity of self-reported drug use data [66-69], concurrent biological assessment enhances self-report accuracy [70]. Drug testing will be completed using the Nail Testing Panel from the US Drug Testing Lab. Participants will clip 100 mg of nail (approximately 10 clippings of 2 mm each). Clippings will be weighed on a jeweler's scale to ensure the collection of an adequate sample. Clippings are transferred to a foil packet, stored at room temperature, and shipped to US Drug Testing Lab in a secure envelope. The assay detects amphetamines/MDMA, cannabinoids, cocaine, opiates, and phencyclidine use over a period of 3 to 6 months [71]. Results will be available in 5 to 7 business days [71].

Urethral Sexually Transmitted Infections

Urethral STIs (chlamydia and gonorrhea) are being tested with a kit from Identigene [72] and processed by Sunrise Laboratories. The kit uses the Gen-Probe Aptima Combo 2 Assay [73], which detects both chlamydia and gonorrhea. Participants will collect a urine sample and then place the specimen tube into a clear plastic biohazard bag.

Rectal Sexually Transmitted Infections

Participants will also perform a self-administered testing for rectal chlamydia and gonorrhea using a test kit from Sunrise Laboratories. The swab is approximately the size of a cotton swab and is grasped between the thumb and forefinger about an inch from the base. The swab is inserted until the fingers touch the anus and then it is rotated as it is removed. Swabs are stored in a specimen tube that is placed in a clear plastic biohazard bag. Specimens will be sent to Sunrise Labs who will provide us with test results, which we will then share with our participants. We will comply with New York City Health Department Reporting Requirements [74]. The purpose of STI testing is to provide a proxy assessment of HIV transmission risk behavior. We omit syphilis testing because it can be transmitted by a variety of behaviors, not all of which carry the risk of HIV infection.

HIV Testing

HIV testing will be conducted during the baseline assessment for those participants not on PrEP. Testing will be performed using Determine Ab/Ag 4th Generation Rapid HIV Test. A research assistant trained in couples HIV testing and counseling will utilize a lancet to collect a sample of blood from the participant's finger. This drop of blood is then placed on the test paddle, and the paddle is placed in the test solution to culture. Test results are available in 20 min and delivered to participants immediately during the baseline assessment. For participants on PrEP, HIV testing occurs using an ARCHITECT HIV Ag/Ab Combo assay. This assay is a 2-step immunoassay to determine the presence of HIV p24 antigen and antibodies to HIV-1 (Group M and Group O) and HIV-2 in human serum and plasma using chemiluminescent microparticle immunoassay (Chemiflex) technology with flexible assay protocols. Blood samples are sent to and processed at Sunrise Laboratories.

Data Management

Data will be collected onsite at baseline and at 3-, 6-, 9-, and 12-month follow-up periods. All survey instruments are administered using a Qualtrics-based computer-assisted survey instrument interface. To reduce the time required to attend the in-office baseline appointment, participants have the option of completing a portion of the baseline survey at-home Web-based before the appointment through a Qualtrics link. TLFB data are gathered by a trained interviewer using a data-entry system programmed in Microsoft Access (see below for additional details). The following sections also provide specific details related to the handling of biological specimens and related results. Study procedures have been reviewed by the Institutional Review Board of Hunter College. In addition, we have set up a Data Safety Monitoring Board consisting of leading experts in YMSM with particular specific expertise in randomized controlled trials, epidemiology statistical analysis, and clinical research broadly.

Data Analysis Plan

Analyses will be conducted on both self-report and the biological metrics of adherence. Using self-reported data taken from TLFB interviews, we will utilize a latent growth curve (LGC) model to examine between treatment-group differences in PrEP uptake and adherence over the follow-up period. To do this, we will utilize a 0-inflated binomial distribution to model uptake (whether a participant is on PrEP) and adherence (whether the participant has maintained 4 or more doses of PrEP [75] weekly as prescribed) during each follow-up period. Separate growth processes (intercepts and slopes) will be specified for both the 0-inflated (PrEP uptake) and adherence portions of the model. Treatment condition will then be entered as a predictor of these growth factors. Separately, we will conduct analyses in which DBS data (estimated weekly doses) are used to determine dichotomous adherence to PrEP. Consistent with our secondary aim, exploratory analyses will compare results obtained using TFV/FTC levels assayed in fingernails to TFV-DP and FTC-TP concentrations measured in DBS via mixed-effects regression analysis calculated on log-transformed PrEP drug or metabolite concentration data from both matrices.

We define the occurrence of HIV transmission risk behavior using self-reported data as any CAS with a casual partner, serodiscordant main partner, or nonmonogamous main partner in the absence of adequate PrEP adherence (maintenance of at least 4 doses per week). Biologically, we will also consider a positive test result for either gonorrhea or chlamydia in the absence of PrEP adherence as an indicator of HIV transmission risk behavior. We will utilize an LGC model to examine between group differences on both of these 2 outcomes simultaneously. Mplus allows for the application of LGC modeling to dichotomous outcomes through the use of a log-link function. For each variable, a latent intercept and slope will be calculated. This will allow us to calculate the covariation between self-reported HIV transmission risk behavior and biological indicators of transmission risk over time. Treatment condition will then be entered into the model as a predictor of intercept and slope factors for each outcome.

Analyses will be conducted on both self-reported drug use instances (the total days of use reported for all drugs assessed on the TLFB, a count outcome) and drug use data from fingernail assays indicating the dichotomous occurrence of use during the assessment window. In this way, the rigorous biological measure of drug use is supplemented by self-reported data which provides information about a wider array of drugs and amount of use during the assessment period. Similar to the proposed analysis of HIV transmission risk behavior, we will model self-report and biological outcomes in the same LGC model. This will allow an examination of their covariation over time. Treatment condition will be entered into the model as a predictor of intercept and slope factors for each outcome.

Data Monitoring

This current study protocol was approved by the City University of New York's Human Research Protection Program (HRPP; Protocol Number 2017-0630) and is registered with Clinicaltrials.gov (NCT03396367). All participants undergo consent twice, first via an internet platform during the recruitment process, and second in-person at the baseline appointment

Results

Recruitment was initiated in February 2018, and the first participant was enrolled on February 14, 2018. Enrollment is ongoing with the first 25% of the sample enrolled as of March 7, 2019. We anticipate completion of sample enrollment approximately in October 2021. Final follow-up assessments will be completed over the following year. Primary outcome analyses will commence therefore in October 2022 with the dissemination of findings anticipated over the following 6 months.

Discussion

This study aims to address a critical gap in HIV prevention and drug use intervention options for partnered YMSM by developing an individually delivered intervention which incorporates a focus on relationship factors. The intervention therefore circumvents the demands of dyadic intervention delivery and is potentially useful with YMSM who are unable

or unwilling to participate in couple-focused interventions but can still benefit from an intervention that addresses HIV and drug use within the context of romantic relationships.

Similar to existing dyadic interventions tailored for partnered YMSM, the PARTNER intervention incorporates a focus on communication skills training. The rationale for this focus is derived from CIT and premised on the assumption that enhancing communication skills will increase the likelihood that YMSM are able to engage with their partners in the formation and maintenance of HIV prevention and drug use goals. To minimize demands on interventionists while also facilitating individual delivery (which precludes a facilitated conversation between partners in session), the PARTNER intervention incorporates a novel video-based approach to communication skills training, which can be delivered by the MI providers with a minimum of additional training.

Finally, the proposed project tests an intervention aimed at addressing PrEP uptake in a high-priority population for whom no existing interventions are tailored (partnered YMSM meeting CDC criteria for PrEP candidacy). Furthermore, the secondary aims of this study include the development and validation of fingernail assays to assess PrEP adherence. This innovation has broad implications for the examination of PrEP adherence across research and service delivery settings.

The absence of data from relationship partners precludes the direct observation of dyadic influences on outcomes and potential cross-partner effects of the intervention. The use of individual (rather than dyadic) assessment was selected to enhance feasibility and is consistent with the focus on developing an individually delivered intervention for partnered men that removes the demands of dyadic participation. Participants will report relationship functioning and their perception of their partners' drug use, sexual behavior, and PrEP uptake. This will provide proxy data that can inform future studies. In addition, generalizability is limited by a focus on cisgender MSM who are aged 18 to 29 years. This relatively narrow focus was chosen to reflect the epidemiology of a high-risk group and also to facilitate the tailoring of video-based modeling content. The sample is further limited to men living in the New York City metropolitan area.

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Authors' Contributions

TJS serves as the principal investigator of this research project and oversaw the completion of this manuscript. GR was a major contributor in writing the manuscript and served as a lead trainer for the control arm (education) interventionists. MP was a contributing author and specifically provided content for the research methodology and additionally serves as the project director, overseeing the implementation of the PARTNER study. RHJ was a contributing author, providing information related to the recruitment of participants and also served as the Director of Recruitment. MG provided translational science content for the manuscript and served as the study's coinvestigator. JTP provided scientific guidance in the development of the PARTNER

intervention and the research protocol, assisting in the completion of this manuscript. BMM contributed content and helped with editing the manuscript.

Conflicts of Interest

JTP's spouse is the owner of Mindful Designs, which received a contract to produce the communication skills training video used in the PARTNER intervention.

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Abbreviations

- CAS:** condomless anal sex
- CDC:** Centers for Disease Control and Prevention
- CIT:** couples interdependence theory
- CPQA:** clinical pharmacology and quality assurance
- DBS:** dried blood spot
- FTC:** Emtricitabine
- FTC-TP:** FTC-triphosphate
- GHB:** gamma-hydroxybutyrate
- HAL:** hair analytical laboratory
- LC-MS/MS:** liquid chromatography/tandem mass spectrometry
- LGC:** latent growth curve
- MDMA:** methylenedioxy-methamphetamine
- MI:** motivational interviewing
- MITI:** motivational interviewing treatment integrity
- MSM:** men who have sex with men
- PrEP:** pre-exposure prophylaxis
- PRIDE:** Promoting Resilience, Intersectionality, Diversity, and Equity (PRIDE) Health Research Consortium
- STI:** sexually transmitted infection
- TFV:** Tenofovir
- TLFB:** timeline follow-back
- UCSF:** University of California San Francisco
- YMHP:** young men's health project
- YMSM:** young men who have sex with men (aged 18-29 years, unless otherwise specified)

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Protocol

Receipt of Curative Resection or Palliative Care for Hepatopancreaticobiliary Tumours (RICOCHET): Protocol for a Nationwide Collaborative Observational Study

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Abstract

Background: There are variations in the management of patients with suspected pancreatic and periampullary cancers and/or malignant biliary obstruction. These differences may be due to a number of organizational, institutional, and patient factors that could affect outcomes for those with curable or incurable disease. The Receipt of Curative Resection or Palliative Care for Hepatopancreaticobiliary Tumours (RICOCHET) study will be the first to provide a snapshot of investigative pathways across the United Kingdom to reflect the real-world practice in these patients. The RICOCHET study is contemporary to new national and international clinical guidance and can potentially inform future local and national strategic planning to optimize care for patients with suspected hepatopancreaticobiliary (HPB) malignancies.

Objective: The aim of this study is to define national variation in the investigative and management pathways of patients with suspected HPB malignancies and to determine the effect of these variations on patient outcomes.

Methods: The RICOCHET study is a nationwide, multicenter, prospective study. It is led by trainees through collaboration between surgical and medical specialties. Patients with suspected pancreatic cancer, other periampullary cancer, or extrahepatic cholangiocarcinoma presenting to hospitals in the United Kingdom will be identified over 90 days. Each case will be followed up for 90 days to collect data on the mode of presentation, investigations, interventions, use of local and specialist multidisciplinary team meetings, and transfer of care between hub and spoke sites. Furthermore, the study will define dates and intervals between key points in the patient pathway.

Results: The RICOCHET study results and analyses will be subject to peer review by presenting them at international cross-specialty conferences and by submitting them for publication in open-access journals. Moreover, our findings will be presented to patient groups and sponsoring charities (eg, Pancreatic Cancer UK), who in turn will disseminate key findings to the primary beneficiaries of the results: the patients. The RICOCHET study was funded in September 2017. Data collection started in April 2018 and the planned end date for data upload is spring 2019. Data analysis will take place in the summer of 2019 and the first results are expected to be published in late 2019 or early 2020.

Conclusions: The RICOCHET study is a multidisciplinary, prospective, observational study that aims to highlight variability in practice and to determine whether these affect the outcomes of patients with HPB malignancies. This is a trainee-led initiative that utilizes a novel design to achieve full coverage of the differences in diagnostic and management pathways. The RICOCHET study may provide evidence to develop a more standardized approach to managing patients with suspected HPB malignancy.

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KEYWORDS

ERCP; malignant jaundice; palliative; pancreatic cancer; PTC; patient pathway

Introduction

Pancreatic cancer is the twelfth-most common cancer worldwide, but ranks fifth in its contribution to cancer-related deaths [1,2]. While the prognosis of most solid-organ cancers has improved over the last decade, the outcomes of patients with pancreatic cancer remain poor with an overall 5-year survival rate of 18% and 3.5% for patients with resectable and nonresectable disease, respectively [1,3]. This poor prognosis is partly explained by patients often presenting with advanced disease or distant metastases, due to the incipient nature by which pancreatic cancer develops and the absence of an effective screening tool [4,5]. Like pancreatic cancer, the other periampullary malignancies and extrahepatic cancers—herein collectively termed hepatopancreaticobiliary (HPB) malignancies—also have poor prognoses [6-8].

Due to the complex anatomy of the pancreas and biliary tract, the investigation of HPB malignancies requires multimodal approaches for diagnosis and staging. These tumors may involve local vascular structures and currently there is a lack of evidence regarding the optimum management of borderline and locally advanced tumors. Consequently, there is wide variability in the investigation and management of HPB malignancies between countries, but also on a national level [9,10]. It has been recognized that variability in the patient pathway can have a dramatic impact upon outcomes among these patients with regard to the time required to come to a diagnosis and referral to a specialist resectional center [11-15]. The need for better diagnostic pathways and faster access to surgery have recently been incorporated into the UK National Institute for Health and Care Excellence (NICE) guidelines for the diagnosis and management of pancreatic cancer [16]. Furthermore, the European Society for Medical Oncology recognized the rising number of deaths from pancreatic cancer in Europe and has also outlined recommendations for screening and diagnosis of pancreatic cancer [17].

In this paper, we describe the protocol of the Receipt of Curative Resection or Palliative Care for Hepatopancreaticobiliary Tumours (RICOCHET) study. This prospective study aims to define variations in diagnostic and management pathways for patients with suspected HPB malignancies, determine factors associated with these variations, and test the hypothesis that these variations have an impact on patient outcomes.

Methods

This national, multicenter, prospective observational study will be coordinated and delivered by a cross-specialty, trainee-led research network in collaboration with surgeons, physicians, and allied health care professionals.

Objectives

This study will define the pathways that patients with suspected HPB malignancies take from presentation to the completion of treatment, in terms of times between key diagnostic tests, multidisciplinary team (MDT) meetings, management of jaundice, treatments, and outcomes. Furthermore, it aims to define the variation in these practices and the potential effect of this variation in observed outcomes. The intention of therapy for patients with an HPB malignancy is determined by whether the primary lesion is deemed surgically resectable or not. The secondary objectives of the study are sectioned by intent of therapy (ie, resectable or nonresectable). The details of the primary and secondary objectives can be found in [Table 1](#). Audit standards of the RICOCHET study are shown in [Table 2](#). While patients will be analyzed by resectional status, outcomes from palliative management, which may occur concurrently, will also be collected. Therefore, referrals to a palliative care team, rates of palliative chemotherapy, and reviews by a clinical nurse specialist (CNS) have been included in our data collection.

In undertaking a cross-specialty national study, we aim to develop a lasting collaborative research network that will provide a framework for future clinical research.

Table 1. Primary and secondary objectives of the RICOCHET^a study.

Objectives and outcomes	Outcome measures
Primary objective: To describe the management pathways and 90-day outcomes for patients who are investigated with suspected resectable and nonresectable cancer of the pancreas, periampullary tissues, and the major bile ducts	
Management pathway domains	
Presentation to secondary care	Presentation to outpatient clinic, emergency admission, referral from spoke center, incidental radiological finding, etc
Principal care point	Whether first presentation was at a hub or spoke center ^b
Utility of MDT ^c	Whether case discussed at MDT meeting Timing with reference to presentation and frequency
Investigation domains	
Imaging	Timing of imaging with reference to presentation Modality and frequency USS ^d , CT ^e , MRI ^f , and PET CT ^g
Diagnostic tissue sampling	Timing of diagnostic sampling with reference to presentation Modality and frequency EUS FNA ^h , ERCP ⁱ , PTC ^j brushings, and tissue biopsy
Intervention domains	
Biliary decompression	Utility: describing indication for decompression Modality: ERCP, PTC, or other Safety: decompression modality-specific complication rates Success rates as defined by successful biliary drainage ^k
Neoadjuvant chemotherapy	Utility: rates of use Safety: chemotherapy-specific complication rates
Nutritional supplementation	Utility of specialist nutrition team input: rates of referral Utility of pancreatic enzyme replacement: rates of prescription
Intention domains	
Curative surgery	Time from presentation to surgery Rates of completion of surgery with curative intent or awaiting surgery Histological staging Rates of adverse events
Palliative and end-of-life care planning	Rates of referral to hospital or community palliative care team if appropriate Number of patients seen by a CNS ^l Number of patients where ceiling of care and resuscitation status has been discussed
Other outcomes	Number of inpatient days Number of unplanned admissions Death: time and cause
Secondary objectives: resectable	
Subgroup comparison of patients with obstructive jaundice who undergo preoperative biliary decompression versus patients who do not have decompression	
Decision making	Recording reasons why biliary decompression withheld in patient with obstructive jaundice
Management pathway, investigation, intervention, and intention domains	Comparison of outcome measures, as in primary objective, between patients who did and did not undergo biliary decompression
Subgroup comparison of patients who primarily attend a hub center compared to a spoke center	
Management pathway, investigation, intervention, and intention domains	Comparison of outcome measures, as in primary objective, between subgroups
Secondary objectives: nonresectable	
Subgroup analysis of cohort who undergo biliary decompression^k	

Objectives and outcomes	Outcome measures
Management pathway, investigation, intervention, and intention domains	As in primary objective, with intention to determine associations with adverse events and "other outcomes"
Additional intention domain: palliative chemotherapy	Rates of starting palliative chemotherapy
Determine whether observed practice meets expected standards as defined by audit standards	
See Table 2	–
Other objectives	
Comparison of institutional factors and hepatobiliary services in hub and spoke centers	
Institutional factors and HPB^m services	
Hospital capacity	Number of inpatient beds
Critical care capacity	Number of beds available for patients requiring intensive care or organ support
	Number of HPB surgical resections
Interventional management of obstructive jaundice	Availability of biliary decompression services
	Number of decompression sessions per week
Assessment of data collection tools	
Hospital technological facilities	Proportion of sites with access to electronic reports of patient data
National research network development	
Promotion of collaborative research	Size of geographical region
	Number of sites in geographical regions
	Number of regional leads, local leads, and data collectors

^aRICOCHET: Receipt of Curative Resection or Palliative Care for Hepatopancreaticobiliary Tumours.

^bHub-and-spoke design: network consisting of an anchor establishment, the hub, complemented by secondary establishments, the spokes.

^cMDT: multidisciplinary team.

^dUSS: ultrasound scan.

^eCT: computed tomography.

^fMRI: magnetic resonance imaging.

^gPET CT: positron emission tomography-computed tomography.

^hEUS FNA: endoscopic ultrasound fine-needle aspiration.

ⁱERCP: endoscopic retrograde cholangiopancreatography.

^jPTC: percutaneous transhepatic cholangiography.

^kSuccessful decompression is defined as the successful deployment of a stent as stated on the latest procedure report.

^lCNS: clinical nurse specialist.

^mHPB: hepatopancreaticobiliary.

Table 2. Audit standards of the RICOCHET^a study.

Audit standard	Standard compliance, %
Patients proceeding to surgery for pancreatic cancer should be found to have metastatic disease [9]	<25
For patients undergoing first biliary decompression, stent should be placed and cytology or histology taken where appropriate [18]	>80
Patient survival after biliary decompression in palliative disease	
7 days [19,20]	>90
30 days [21]	>75
Ability to proceed to palliative chemotherapy in patients with unresectable malignancy [22]	25

^aRICOCHET: Receipt of Curative Resection or Palliative Care for Hepatopancreaticobiliary Tumours.

Case Identification, Inclusion, and Follow-Up

Aspects of health care in the United Kingdom are modelled on a hub-and-spoke design, which arranges service delivery assets into a network consisting of a tertiary care provider, the hub, complemented by secondary care providers, the spokes. The hub offers a specialist service, including resection, whereas the spokes offer a more limited service, routing patients needing specialist treatment to the hub [23].

Adult patients with a newly suspected HPB malignancy will be identified and screened for inclusion at participating sites over a 90-day, case-identification period. A patient will be included according to one of the three inclusion criteria: (1) suspected malignant pancreatic lesion, (2) suspected periampullary lesion, or (3) suspected malignant biliary obstruction caused by a primary malignancy of the liver hilum or extrahepatic biliary tree (see Figure 1). Exclusion criteria include the following: less than 16 years of age, recurrent HPB malignancy, suspected secondary malignancy (ie, metastatic disease of an origin outside of the HPB anatomical area), and gallbladder or intrahepatic lesions. Cases will be identified at four nodes: MDT meetings,

CNS referrals, from biliary decompression lists, and any remaining modes of referral, including through outpatient clinic and ward referrals (see Figure 2). Upon inclusion to the study, each patient's management and investigative pathways will be charted from their initial relevant presentation to hospital care at the participating site. This *day zero* will be defined as the chronologically primary relevant attendance to the emergency department, outpatient clinic, discussion of the case at MDT where a diagnosis of malignancy was first considered, or the date of the radiological or endoscopic imaging that identifies an incidental finding of malignancy. Cases will be mapped by the outcome measures described in Table 1 for 90 days from *day zero*. For cases in which a patient's care is moved between a spoke and hub center, data will be collected from site-specific *day zero* for the following 90 days. For the purpose of analysis, we will primarily assess 90-day outcomes from the first *day zero*. However, we may explore extended time points as part of an exploratory outcome analysis. The differences in treatment and outcomes of patients across centers (ie, hub or spoke) will be analyzed.

Figure 1. Schematic of the liver and pancreas showing the inclusion criteria for the study. To be included, patients must have one of the three indicated inclusion criteria.

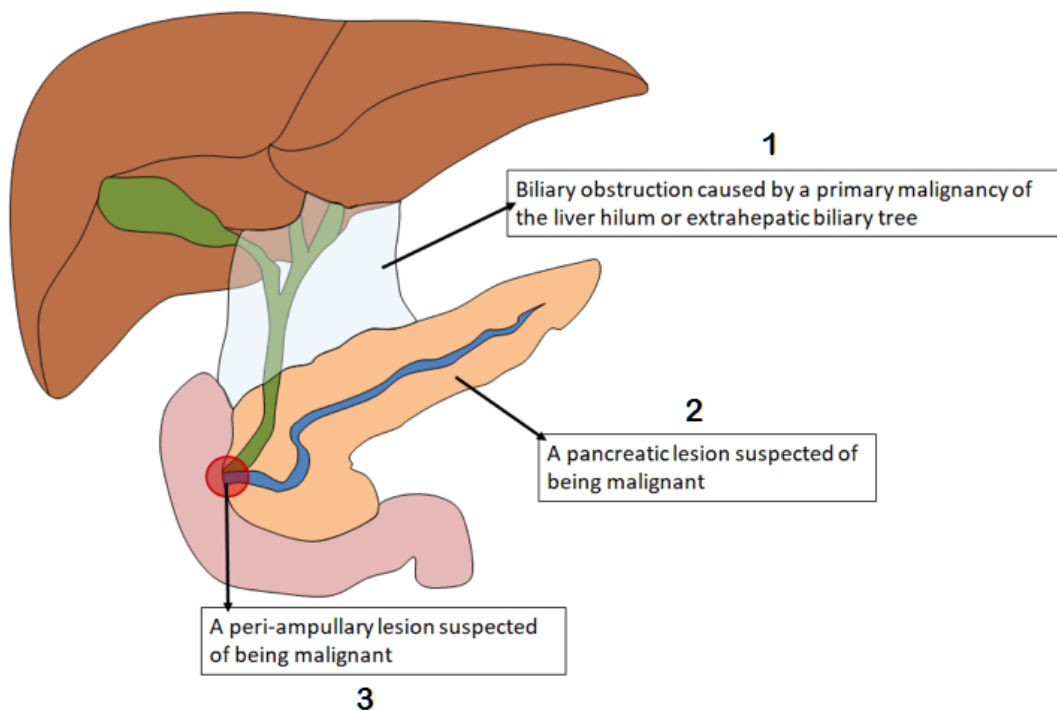
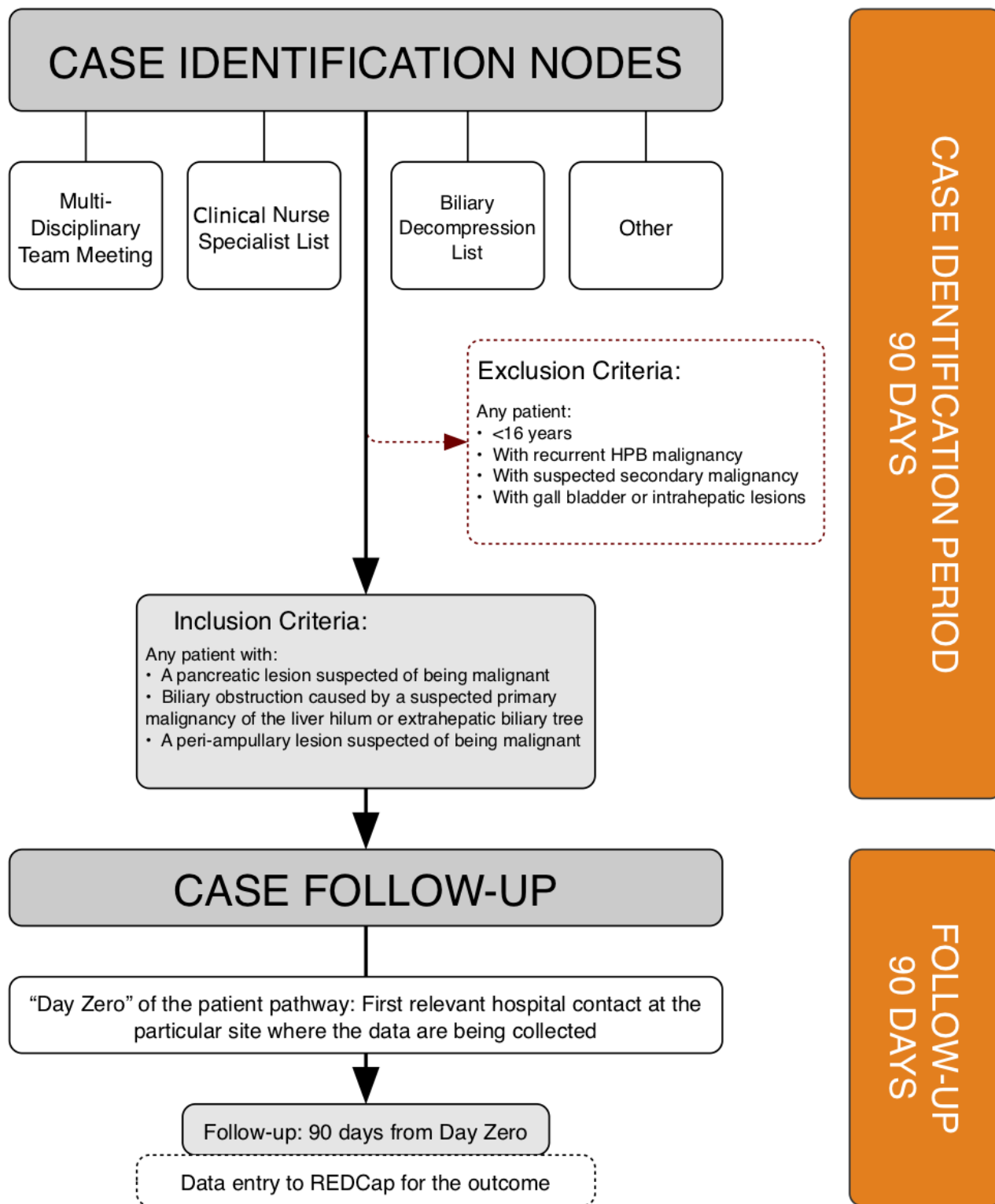


Figure 2. Case identification for the study. HPB: hepatopancreaticobiliary; REDCap: Research Electronic Data Capture.



Sample Size

The RICOCHET study aims to involve all hub and spoke centers across the United Kingdom, and we expect to reach 75% of the cases during our inclusion period. Based on the follow-up period of 90 days and the annual incidence of the included HPB malignancies in the United Kingdom, we project the inclusion of approximately 1835 cases [1].

Center Recruitment and Research Network

All centers that identify or refer HPB malignancies (N=227) are eligible to participate in this study (see Figure 3). The RICOCHET study will be open to all hub and spoke centers across the United Kingdom. Recruitment will take place via conferences, social media, established research contacts, trainee collaborative research networks, and from the use of the RICOCHET website [24].

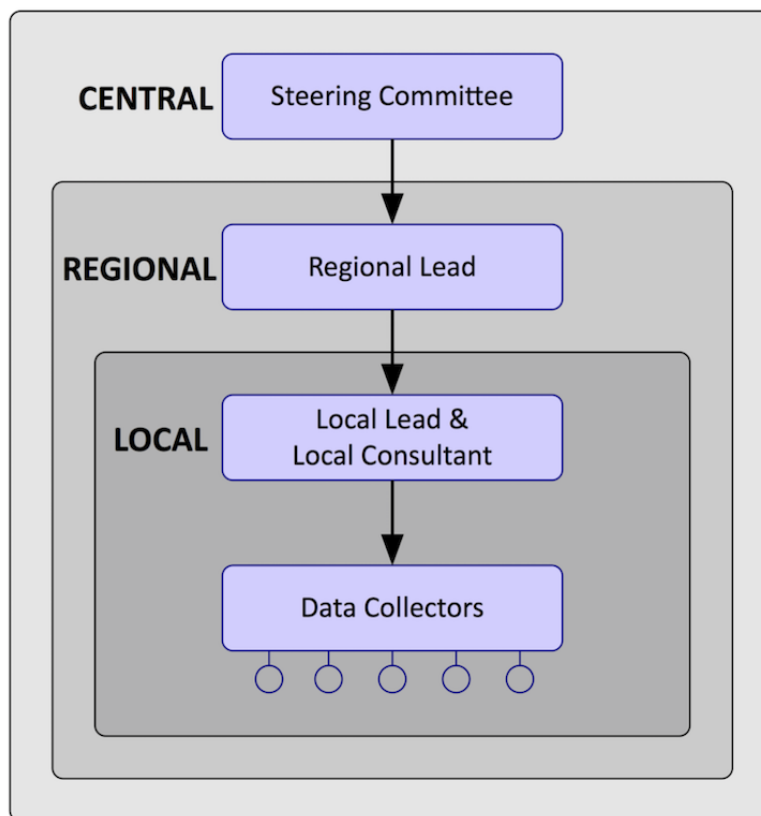
Figure 3. Schematic of the United Kingdom showing the location of all centers eligible for recruitment.



Project Management

A steering committee—formed from doctors in training alongside one medical consultant and one surgical consultant—has designed, implemented, and overseen the study as well as the analysis and dissemination of results on completion. Regional collaborators will be organized as geographical regional leads (1-2 per region; 17 regions) that will support participating sites (up to 227 sites); they consist of

local consultants (1-2 per site), local leads (1 per site), and data collection teams (1-5 collectors per site) (see [Figure 4](#)). It will be encouraged that both consultant surgeons and physicians work together as part of a multidisciplinary approach. The involvement of clinical nurse specialists, research nurses, and MDT coordinators will also be encouraged. Patient representatives are involved in every step of the development of this study.

Figure 4. The Receipt of Curative Resection or Palliative Care for Hepatopancreaticobiliary Tumours (RICOCHET) research network.

Data Collection

Case identification and follow-up will be undertaken in the same manner at all sites. The local data collectors are either medically trained, ranging from medical students to consultants, or specialist nurses in HPB surgery or oncology. Site- and case-specific data will be entered onto Research Electronic Data Capture (REDCap), an established Web application that allows collaborators to enter and store data [25]. The REDCap server for the RICOCHET study is hosted by the Birmingham Surgical Trials Consortium, University of Birmingham, Birmingham, UK, under license from Vanderbilt University, Nashville, Tennessee. REDCap allows electronic data collection and can be accessed via a Web browser or an app on a tablet or mobile phone. REDCap has been used successfully in over 120 different countries and in more than 500,000 projects around the world [26-28].

Data Linkage Across Sites and Pseudonymization

The RICOCHET study will involve a large number of sites across the United Kingdom to include both hub and spoke centers. Patient care may be transferred from spoke centers to specialist hub centers for discussion and/or treatment. In order to record a patient's complete pathway, data will be collected from all sites involved in a patient's care. However, the centers involved in the RICOCHET study have isolated, independent computer and data storage systems, with no means of centralized data access. To overcome this problem, the study will utilize a system of pseudonymization that assigns a case identifier to a patient's REDCap records, which can be used to link REDCap data.

Data collection teams at each site will be sent the OpenPseudonymiser program via individual USB sticks. OpenPseudonymiser is a free, open-source, standalone Windows application [29] that uses the principles outlined by the Information Commissioner's Office on data protection [30]. It has been designed to comply with national information governance requirements for the transfer of unidentifiable confidential data. OpenPseudonymiser checks the validity of the National Health Service (NHS) number within a comma-separated variables file, attaches extra encrypted data to the NHS number, then encrypts the combination using the international standard Secure Hash Algorithm 256 (SHA-256) to produce a string of output characters, known as the digest. The digest can then be used as the case identifier within REDCap. It enables data linkage across sites, as using the same NHS number with the same encryption will produce the same digest. Therefore, pseudonymization of the NHS number for each case can be achieved before being uploaded onto REDCap to maintain confidentiality of patient data and allow data linkage across sites.

A successful pilot study was carried out by the RICOCHET committee and involved testing of the REDCap and pseudonymization systems to allow accurate patient data linkage across hub and spoke sites before being rolled out nationally.

Statistical Analysis

Upon data collection and dissemination, data distribution will be determined and appropriately summarized. Frequencies and percentages will be used for categorical variables. Univariate and multivariate analyses will be assessed by appropriate statistical techniques. A *P* value of less than .05 will be

considered significant for statistical methods used. The analysis will be completed by suitable statistical software.

Ethics, Consent to Participate, and Dissemination

The RICOCHET study is a prospective study mapping patient investigative and management pathways. An intervention involving the patient's health care will not be implemented; therefore, patient consent is not required for the RICOCHET study. This has been confirmed using the national UK decision-making tool of the NHS Health Research Authority and the Medical Research Council [31]. The RICOCHET study will therefore be locally registered as a clinical audit or service evaluation project at all participating sites prior to patient identification and data collection.

Availability of Data and Material

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Results

The RICOCHET study results and analyses will be subject to peer review by presenting them at international cross-specialty conferences and by submitting them for publication in open-access journals. Moreover, our findings will be presented to patient groups and sponsoring charities (eg, Pancreatic Cancer UK), who in turn will disseminate key findings to the primary beneficiaries of the results: the patients. The RICOCHET study was funded in September 2017. Data collection started in April 2018 and the planned end date for data upload is spring 2019. Data analysis will take place in the summer of 2019 and the first results are expected to be published in late 2019 or early 2020.

Discussion

Survival among patients with pancreatic cancer has not improved over the past 40 years, a fact that demands the attention of health care providers, users, and service designers [32,33]. Nevertheless, there are grounds for optimism. Adjuvant chemotherapy is increasingly effective, correction of pancreatic exocrine insufficiency can improve survival, and optimized diagnostic pathways can reduce the time to surgery and improve resection rates [9,34,35]. These are just a few examples of where progress is being made. Optimizing pathways, reducing variation in practice, and national guidance can all help achieve improvement. While more substantial improvements may occur from novel chemotherapeutics, it is clear that outcomes and patient experience can be improved by focusing on optimizing every part of the patient pathway, from diagnosis to treatment [36]. It is therefore essential that current practice and its variation and effect on patient outcomes are evaluated. This study closely follows the publication of the first NICE guidelines for the management of pancreatic cancer in the United Kingdom [16]. Real-world practice may stray from guidelines for a

multitude of reasons, including limitations of local resources and expertise, case-specific vagaries, and, in some cases, perceived equipoise in the available data [9]. There may also be a tendency to overinvestigate patients, with consequent delays to treatment [10]. The RICOCHET study aims to reveal the main bottlenecks in the pathways and identify where improvements can be made.

The 15% of patients with potentially resectable disease are frequently the focus of clinical research, with a limited emphasis on the considerably larger proportion of patients with nonresectable disease [37]. The RICOCHET study is a comprehensive study of practice among all patients with suspected cancer, regardless of stage or treatment options. Analysis of Hospital Episode Statistics data demonstrates a remarkably high 30-day mortality rate among patients with malignant biliary obstruction, but the cause for this high incidence remains unknown [19]. A further benefit of the RICOCHET study is, therefore, to target areas where there is a particular need for more in-depth information.

Collecting patient-level data across hospitals with linkage presents significant ethical challenges. The use of the OpenPseudonymiser tool to link patient data across independent sites overcomes this potential prohibitive barrier to patient-pathway mapping. Successful implementation of this system in an ambitious nationwide study will provide a blueprint for future collaborative research that requires linking patient data from discrete sites.

The RICOCHET study has several limitations. The study has been designed to assess patient pathways against contemporary guidelines [16,17]. The 90-day patient follow-up period reflects this, but denies the assessment of medium- and long-term outcomes. We expect that the data gathered by the RICOCHET study will inform focused cohort studies and randomized controlled trials that are designed to comprehensively answer questions about medium- and long-term outcomes. Furthermore, the nature of this observational study precludes an assessment of quality of life and patient-reported outcomes; these are critical in the meaningful assessment of care in patients with cancer, resectable or otherwise [38]. Over the course of the RICOCHET study, we aim to involve more than 500 collaborators across specialties, creating an extensive network of enthusiastic individuals. It will build a strong foundation for future collaborative research and strengthen interest in improving patient care in the NHS and beyond.

In conclusion, the RICOCHET study is an ambitious, multidisciplinary, multicenter, prospective observational study utilizing a novel design to achieve full coverage of the different patient pathways. It is led by trainees and builds on an extensive national collaborative network. The study aims to highlight the variation in practice and its effect on the outcomes of patients with HPB malignancies. It may then provide evidence to develop a more standardized approach to managing patients with suspected HPB malignancy.

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Authors' Contributions

All members of the steering committee contributed equally to study and protocol development, including the writing of the manuscript. Members of the RICOCHET Study on Behalf of The West Midlands Research Collaborative are as follows: Graham Baker (Department of Gastroenterology, The Royal Wolverhampton NHS Trust, Wolverhampton, UK), Manjinder K Brom (Department of Emergency Medicine, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK), Zahra Brown (Department of Acute Medicine, Walsall Healthcare NHS Trust, Walsall, UK), Debashis Haldar (National Institute for Health Research, Biomedical Research Centre at University Hospitals Birmingham NHS Foundation Trust, and the University of Birmingham, Birmingham, UK; Centre for Liver and Gastrointestinal Research, Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK; Liver Unit, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK), Philip R Harvey (Department of Gastroenterology, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK), Marit Kalisvaart (Liver Unit, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK), Georgia Layton (Department of Cardiothoracics, Birmingham Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK), Alexandra Marley (Department of Gastroenterology, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK), Siobhan C McKay (Department of General Surgery, University Hospitals Coventry and Warwickshire NHS Trust, UK), Rupaly Pandé (Department of General Surgery, New Cross Hospital, Royal Wolverhampton NHS Trust, Wolverhampton, UK), Reeya Patel (Department of General Surgery, Birmingham Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK), Keith J Roberts (Liver Unit, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK), Barney TF Stephenson (Liver Unit, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK), Nigel Trudgill (Department of Gastroenterology, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK), Richard JW Wilkin (Department of General Surgery, University Hospitals Coventry and Warwickshire NHS Trust, UK; Academic Department of Surgery, University of Birmingham, Birmingham, UK).

Conflicts of Interest

None declared.

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Abbreviations

CNS: clinical nurse specialist

CT: computed tomography

ERCP: endoscopic retrograde cholangiopancreatography

EUS FNA: endoscopic ultrasound fine-needle aspiration

HPB: hepatopancreaticobiliary

MDT: multidisciplinary team

MRI: magnetic resonance imaging

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

PET CT: positron emission tomography-computed tomography

PTC: percutaneous transhepatic cholangiography

REDCap: Research Electronic Data Capture

RICOCHEt: Receipt of Curative Resection or Palliative Care for Hepatopancreaticobiliary Tumours

SHA-256: Secure Hash Algorithm 256

USS: ultrasound scan

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Protocol

Effects of a School-Based Health Intervention Program in Marginalized Communities of Port Elizabeth, South Africa (the KaziBantu Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: The burden of poverty-related infectious diseases remains high in low- and middle-income countries, while noncommunicable diseases (NCDs) are rapidly gaining importance. To address this dual disease burden, the *KaziBantu* project aims at improving and promoting health literacy as a means for a healthy and active lifestyle. The project implements a school-based health intervention package consisting of physical education, moving-to-music, and specific health and nutrition education lessons from the *KaziKidz* toolkit. It is complemented by the *KaziHealth* workplace health intervention program for teachers.

Objectives: The aim of the *KaziBantu* project is to assess the effect of a school-based health intervention package on risk factors for NCDs, health behaviors, and psychosocial health in primary school children in disadvantaged communities in Port Elizabeth, South Africa. In addition, we aim to test a workplace health intervention for teachers.

Methods: A randomized controlled trial (RCT) will be conducted in 8 schools. Approximately 1000 grade 4 to grade 6 school children, aged 9 to 13 years, and approximately 60 teachers will be recruited during a baseline survey in early 2019. For school children, the study is designed as a 36-week, cluster RCT (*KaziKidz* intervention), whereas for teachers, a 24-week intervention phase (*KaziHealth* intervention) is planned. The intervention program consists of 3 main components; namely, (1) *KaziKidz* and *KaziHealth* teaching material, (2) workshops, and (3) teacher coaches. After randomization, 4 of the 8 schools will receive the education program, whereas the other schools will serve as the control group. Intervention schools will be further randomized to the different combinations of 2 additional intervention components: teacher workshops and teacher coaching.

Results: This study builds on previous experience and will generate new evidence on health intervention responses to NCD risk factors in school settings as a decision tool for future controlled studies that will enable comparisons among marginalized communities between South African and other African settings.

Conclusions: The *KaziKidz* teaching material is a holistic educational and instructional tool designed for primary school teachers in low-resource settings, which is in line with South Africa's Curriculum and Assessment Policy Statement. The ready-to-use lessons and assessments within *KaziKidz* should facilitate the use and implementation of the teaching material. Furthermore, the

KaziHealth interventions should empower teachers to take care of their health through knowledge gains regarding disease risk factors, physical activity, fitness, psychosocial health, and nutrition indicators. Teachers as role models will be able to promote better health behaviors and encourage a healthy and active lifestyle for children at school. We conjecture that improved health and well-being increase teachers' productivity with trickle-down effects on the children they teach and train.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): 18485542; <http://www.isrctn.com/ISRCTN18485542>

International Registered Report Identifier (IRRID): DERR1-10.2196/14097

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KEYWORDS

anthropometry; cardiovascular; cognitive function; diabetic complications; children's health; marginalization; physical activity; physical fitness; schools; South Africa

Introduction

Background

Children's health and well-being are influenced by cultural, environmental, and socioeconomic factors as well as living conditions and social and community networks [1]. In low- and middle-income countries (LMICs), infectious diseases remain an important public health problem [2-4] with negative impacts on child development [5]. Over 200 million children are infected with parasitic worms (helminths) [6,7] leading to chronic infections causing abdominal pain, diarrhea, and anemia, and may impair cognitive and physical development [8], which in turn might result in reduced fitness and work productivity [9]. In addition, helminth infections can negatively impact children's nutritional status [10].

Although helminth infections and other neglected tropical diseases (NTDs) do not feature prominently in the burden of disease statistics of South Africa, some NTDs are common in disadvantaged populations, especially among children of poor communities [11]. The nutritional status of school children from poor neighborhoods is adversely affected by food outlets in close proximity to the schools. Indeed, many school children routinely purchase unhealthy foods from local vendors and tuck shops that are generally low in nutritional value, often refined, processed, and of low fiber content [12]. In a 12-country study (Australia, Brazil, Canada, Colombia, Finland, India, Kenya, People's Republic of China, Portugal, South Africa, United Kingdom, and United States of America) [13], South African children showed the highest intake of sugar-sweetened beverages [14]. Schools located in poor communities in South Africa are part of the National School Nutrition Program, where members of the community, usually unemployed parents, are employed as food preparers. They do not have any food- or nutrition-related qualification.

A deprived socioeconomic environment can put children at risk of malnutrition resulting in growth retardation [15]. Studies have shown that malnutrition is associated with stunting and poor cognitive development, resulting in a low intelligence quotient, cognitive delays, and negative impact on motor development [15]. This, in turn, negatively affects children's ability to concentrate, process information, and focus on academic tasks [16]. Children from low socioeconomic status (SES) families are also less likely to have access to health care

or health insurance [17]. Together, this leads to a greater risk of illness, school absence, and ultimately poor academic performance and life prospects [18]. These deficiencies, caused mainly by the socioeconomic environment, can prevent school-age children from realizing their full potential and perpetuate a vicious cycle of poverty and poor health.

In addition, noncommunicable diseases (NCDs) are a rapidly evolving public health problem worldwide, especially in LMICs, imposing a growing burden on population health [2,19] including that of children [20]. Urban African populations have moved toward a disease profile similar to western countries, with increasing proportions of deaths attributed to chronic, lifestyle-related diseases [20]. The coexistence of under- and overnutrition has resulted in a double burden of nutrition-related diseases in Africa [21]. Children may, already at a young age, develop risk factors predisposing them to NCDs in adulthood [22,23]. Hence, children are at risk of compromised health because of a dual burden of disease, which may hamper their development and well-being [2,24]. Potential drivers of this double burden may be related to the shift in dietary habits and reduced energy consumption. This dual burden constitutes a large and growing challenge for health systems in African countries.

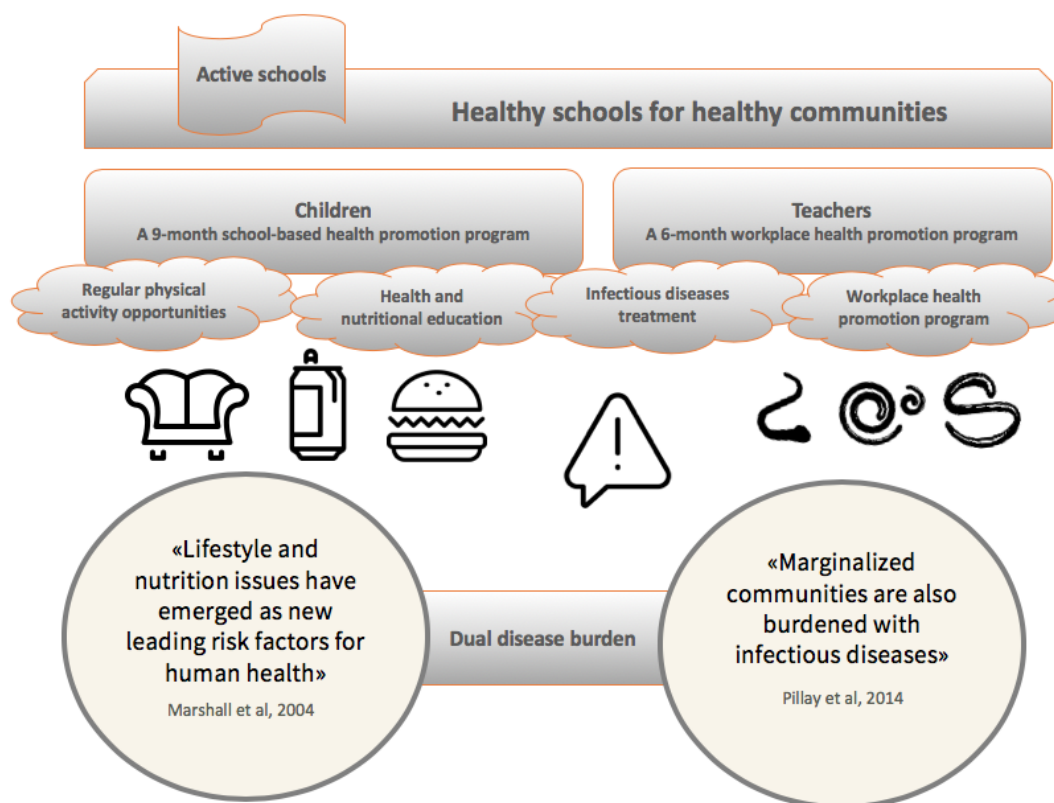
With up to 80% of all chronic diseases, stroke, and diabetes being preventable through healthy nutrition and regular exercise, more emphasis should be placed on prevention and awareness campaigns [25]. Physical education (PE) plays a critical role in holistic health education of the child. A randomized controlled trial (RCT) with Swiss elementary school learners (first and fifth graders) has shown that a 1-year school-based intervention can markedly improve physical activity and fitness, while simultaneously reducing obesity [26]. Regular physical activity contributes to the development of physical competence and fitness, as well as to the cognitive, social, and emotional development of the child [27]. As a rule of thumb, children should undertake at least 60 min of moderate-to-vigorous physical activity (MVPA) daily [28].

The Healthy Active Kids South Africa Report Card (2018) has shown that many children, particularly from marginalized communities, do not achieve the minimal daily requirements of MVPA [14]. Schools play an important role in making a meaningful contribution to the goal of achieving the recommended daily physical activity guidelines by incorporating

PE lessons, among others, into the school curriculum. One plausible strategy to promote children's health is through school-based health promotion programs. An attempt by a Swiss-South African research team to increase health literacy in South African children at school was the *Disease, Activity and Schoolchildren's Health* (DASH) project [4]. The study focused on grade 4 children and the creation of an enabling school environment. The intervention program consisted of 4 main components, including (1) a medical examination and anthelmintic treatment, (2) micronutrient supplementation in the form of a nutrient-dense paste enriched with protein, essential vitamins (vitamin A), minerals, energy, and essential fatty acids, (3) health education (eg, hygiene and healthy nutrition), and (4) physical activity (dancing and playful games).

Our experiences with the DASH project also revealed that many South African teachers are at risk of cardiovascular diseases [29,30]. This insight was confirmed in a representative sample of South African educators (n=21,307) in public schools. Educators reported high stress levels, and there were significant associations between stress, lack of job satisfaction, and stress-related illnesses [31]. In South Africa, NCDs among adults have steadily increased. Indeed, although 42.90% (256,645/598,240) of deaths in 2005 were attributable to NCDs, the proportion rose to 57.40% (262,096/456,612) in 2016 [32]. Furthermore, in 2017, more than 1.8 million cases of diabetes were recorded in South Africa, representing 5.41% (1,826,100/33,762,000) of the adult population [33]. The project *Healthy Schools for Health Communities* presented here addresses this dual burden of disease, both in school children and teachers in South Africa (Figure 1).

Figure 1. A conceptual framework of the *KaziBantu* study.



Rationale

Having identified the potential for health status improvement among teachers and knowing the importance of teachers as role models in the education process of children, teachers will also participate in the proposed research project by involving themselves in a workplace health intervention. We will capitalize on the experiences from the aforementioned DASH project by scaling up the intervention program and monitoring and improving the efficacy and effectiveness of the intervention program. The goal of the *KaziBantu* project is to assess the impact of a school-based health intervention package on communicable diseases, risk factors for NCDs, health behaviors (beliefs and actions relating to health and well-being), and psychosocial health in primary school children in disadvantaged

communities in Port Elizabeth, South Africa. In addition, we aim to test a workplace health intervention targeted at teachers.

Methods

Ethical Approval and Considerations

Ethical approval for the study has been received from the following ethics committees in Port Elizabeth, South Africa: (1) The Nelson Mandela University Ethics Committee (reference #H18-HEA-HMS-001; obtained on 26 March 2018), (2) Eastern Cape Department of Education (obtained on 9 May 2018), and (3) Eastern Cape Department of Health (reference #EC_201804_007; obtained on 5 June 2018). The study is registered at the ethical review board of the Ethics Committee

Northwest and Central Switzerland (EKNZ; reference #R-2018-00047; registered on 1 March 2018).

On the basis of a uniform study information sheet, the investigators will explain to each participant (children and teachers) the purpose of the study, procedures involved, expected duration, and potential risks and benefits. Participation is voluntary, and hence, participants can withdraw at any time without any further obligations. All participants will be provided with an information sheet and a consent form describing the study. Individual medical information obtained during this study will be treated confidentially. Subject confidentiality will be ensured by utilizing subject identification code numbers to correspond to treatment data in password-protected computer files. For data verification purposes, authorized representatives of the EKNZ and the Nelson Mandela University Human Ethics Committee may require direct access to parts of the clinical records relevant to the study, including participants' medical history.

Study Area

The study will be conducted in historically black and colored primary schools in Port Elizabeth townships (Motherwell, Zwide, Kwazakhele, and New Brighton) and northern areas (Schauderville, Bethelsdorp, Windvogel, and Booyens Park), which form part of the Nelson Mandela Bay Municipality (Figure 2). These schools and communities are characterized by poverty and high unemployment rates. They represent the typical institutional and teacher-related PE barriers faced by the schools [34], including (1) shortage of qualified, accountable, and engaged PE teachers; (2) PE is marginalized as priority—it lost its standalone subject status in 1997 and is placed within the life skills and life orientation learning area, as more importance is given to other (examinable) subjects; (3) teachers lack the ability to integrate PE with other study areas within the life skills and life orientation subject (personal and social well-being, creative arts, and PE); (4) large class sizes; (5) insufficient and inadequate infrastructure and equipment; and (6) safety and security challenges.

Figure 2. Study area (Port Elizabeth, South Africa) and location of the 8 schools participating in the *KaziBantu* study. Source: Kartendaten, AfriGID (Pty) Ltd.



Study Design

The intervention arm targeting school children is designed as a 36-week RCT, including an intervention group (4 schools) and a control group (4 schools). The 4 intervention schools, assigned through randomization, will be further allocated randomly to the following intervention conditions: all schools will receive the teaching materials (*KaziKidz* and *KaziHealth*), but the components workshop and coaching will be assigned as follows: (1) teaching materials only, (2) teaching materials plus workshops, (3) teaching materials plus coaching, and (4) teaching materials plus workshops plus coaching (Figure 3).

The 4 remaining schools will be assigned to the control group. In the control schools, there will be documentation of routine PE and sports in school.

The primary comparison will be made between the 4 intervention schools and the 4 control schools to assess the benefit of teaching materials. Secondary comparisons will be between teaching materials plus coaching and teaching materials without coaching or teaching materials plus workshop and teaching materials without workshop. In view of the factorial design of our study, each comparison group consists of 2 schools.

By focusing on change in quantitative outcomes from baseline to follow-up, preexisting differences between schools should play less of a role. Although the intervention covers grades 1 to 7, in each school, 1 class each from grades 4, 5, and 6 will be randomly selected for evaluation of the intervention. After completion of the baseline assessment, children of the intervention schools will take part in a school-based health promotion program (32 school weeks, 1 PE lesson of 40 min per week, 1 moving-to-music lesson of 40 min per week, 3 health education lessons, and 3 nutrition education lessons of 40 min per year across the whole study period). The follow-up will be after 36 weeks (Figure 4). Qualitative data on the feasibility and acceptability of the intervention measures will also be collected from teachers through focus group discussions (FGDs).

For teachers, the study is designed as a 20-week RCT (Figure 5). The baseline assessment will also be offered to the teachers in the control schools. Intervention schools will be randomly assigned to the 4 different combinations of the additional components. After completion of the baseline assessment, all teachers will be informed about their personal health profile, providing an overview of cardiovascular health markers and mental health parameters. For each parameter, established internationally accepted cut-off and normative values will be used to estimate teachers' health risks.

Figure 3. A pictorial display of the *KaziBantu* study design.

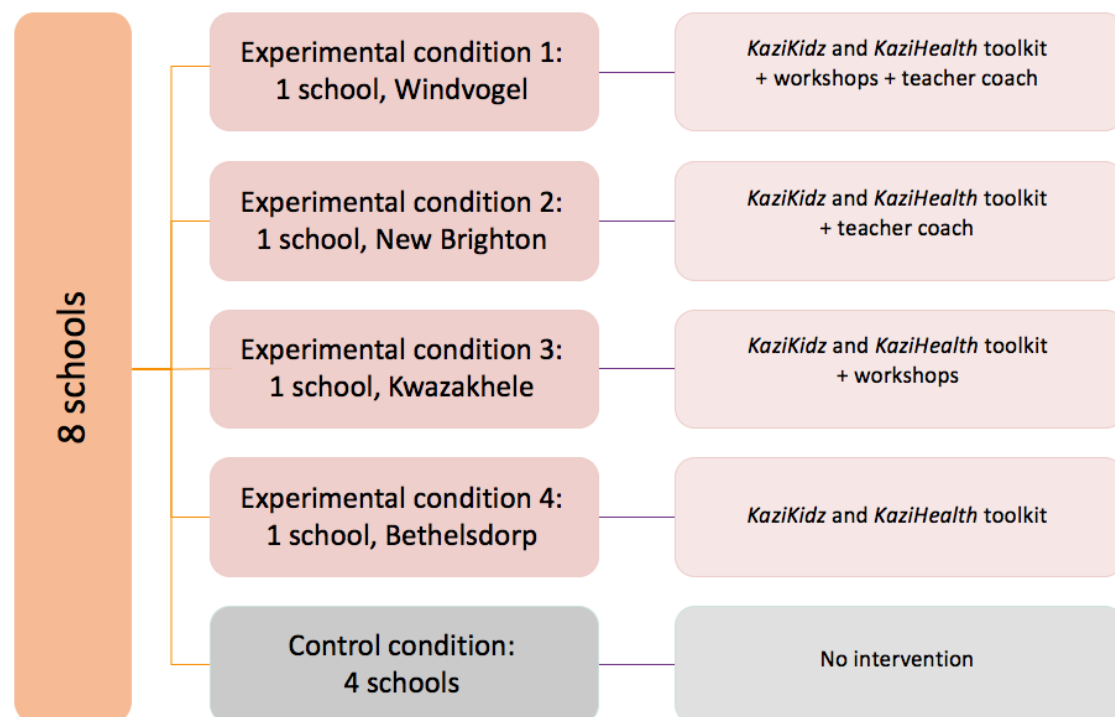


Figure 4. *KaziBantu* study design of testing the *KaziKidz* teaching material.

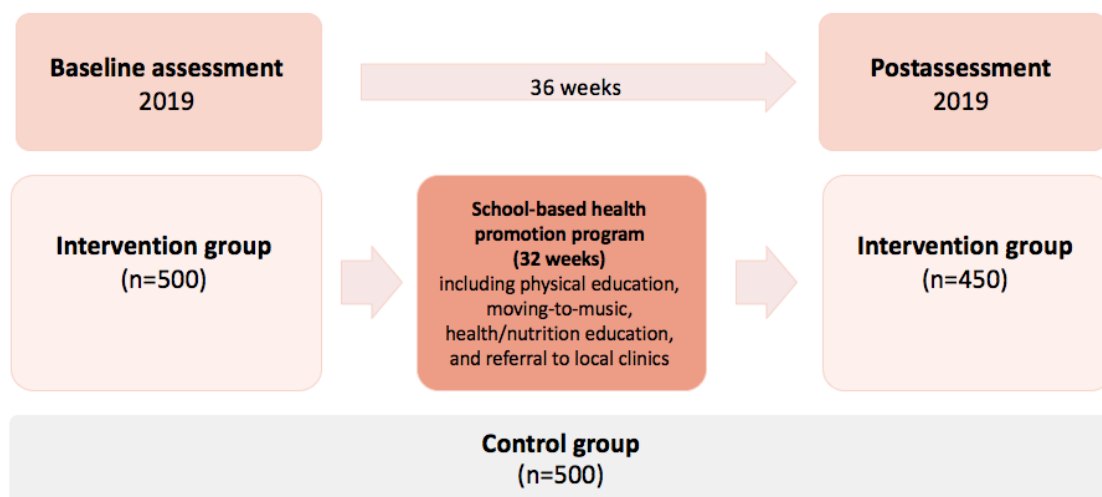
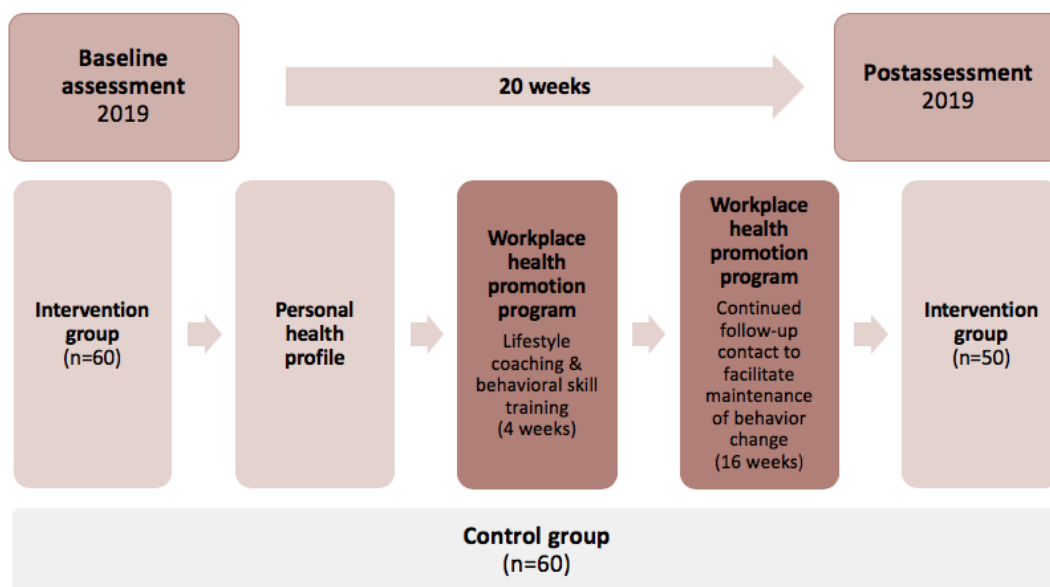


Figure 5. *KaziBantu* study design of testing the *KaziHealth* tools.



The intervention program consists of the 3 main components discussed below.

Component 1: *KaziKidz* and *KaziHealth* Teaching Material

It is a holistic education and instructional tool designed for primary school teachers. This teaching material was pilot tested at 2 elementary schools in the Port Elizabeth area in August 2018. Feedback from teachers was obtained and the material revised accordingly. Through the implementation of 3 content pillars—(1) PE, (2) moving-to-music, and (3) health and hygiene and nutrition education lessons—the toolkit aims to enhance children’s overall health in disadvantaged South African primary schools. The *KaziKidz* teaching material consists of lesson plans within each of the 3 content pillars. The lessons have been designed in line with South Africa’s Curriculum and Assessment Policy Statement. Ready-to-use assessments can be found at the end of each section, which may be integrated into formal assessments of children’s performance and can complement the school’s academic curriculum. The purpose is to lead children

through content, games, and activities, partly supported by music and conducted in a joyful manner that encourages and promotes a healthy lifestyle throughout childhood and into adolescence. *Kazi* (an animated active mascot, designed to encourage children to participate in *KaziKidz*) and lesson plans will guide teachers through the teaching material. We expect that by using the *KaziKidz* teaching material, teachers will contribute to further the health and well-being of the children they teach and educate.

- Physical activity: Regular physical activity opportunities (1 PE lesson of 40 min per week) will be incorporated into the main school curriculum in grades 1 to 7 over 32 weeks of the school year. A physical activity–friendly school environment will be created. These interventions are designed toward improving children’s physical activity levels and positively affecting their psychosocial well-being.
- The moving-to-music classes have been designed to promote physical activity through song and dance. The music utilized was developed by professional musicians from the Nelson Mandela University and is locally known

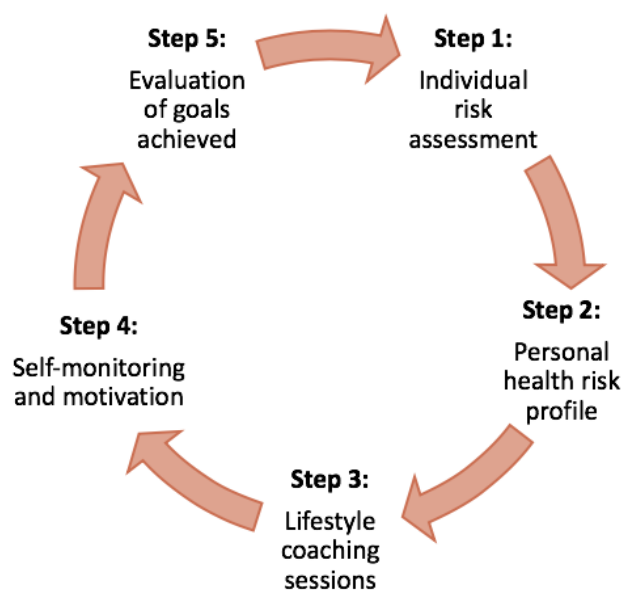
and age-appropriate. Weekly lessons of 40 min each are designed with easy-to-follow illustrations that allow teachers to instruct without participating physically in the lessons. Schools or teachers who have a sound system available can make use of movement songs that have been created with cues specifically tailored to the lessons. Options for creating music through drums or any other form of percussion or clapping hands are also provided. Within the lessons, direct speech is used to address the children for easy application [35].

- Health, hygiene, and nutrition education: A series of classroom-based lessons have been developed [36]. School children will be educated on the prevention and treatment of intestinal parasite infections, such as proper hygiene, sanitation habits, and the importance of consuming clean water and food. By addressing these factors and educating children about appropriate health and hygiene behaviors, both the teachers and the school children are at a reduced risk of infection. Another series of classroom-based lessons will help to increase awareness about the importance of healthy nutrition. The South African National School Nutrition Program attempts to address micronutrient deficiencies and alleviate short-term hunger by providing

food that supplies at least one third of the daily energy requirements of a child. To complement this, the nutrition education lessons (3x 40-min lessons per grade for grades 1-7) should bring dietetics closer to the learners in a playful way and encourage sustainable healthy eating habits throughout the learners' lives. In addition, an analysis of the schools' feeding program will be done to identify ways to improve their present diet. The food preparers in schools will also be trained in basic nutrition and hygiene during preparation of the school meals as unhygienic circumstances and poorly prepared meals can lead to infections and low nutrient intake [37].

KaziHealth is a workplace health promotion program that aims to educate and improve health behaviors among teachers. The program starts with an individualized health risk assessment followed by face-to-face lifestyle coaching sessions and self-monitoring and motivation through the *KaziHealth* mobile app. All teachers willing to participate in the program will undergo a comprehensive health risk assessment. In addition, teachers of the intervention schools will have the option to participate in a 20-week workplace health promotion program (Figure 6).

Figure 6. The 20-week workplace health promotion program for teachers.



Component 2: Workshops

Teachers of 2 schools will participate in workshops for both *KaziKidz* and *KaziHealth*. The teaching content (lessons and assessments) of *KaziKidz* will be explained to the teachers before the implementation of the teaching material (2 sessions of 90 min each, as well as practical demonstrations and instruction at schools) and for *KaziHealth*, individually tailored lifestyle coaching workshops (2 sessions of 90 min each). The workshops will be relatively small (maximum of 20 teachers per workshop) and led by health professionals specializing in physical activity promotion, diet, nutrition, and psychosocial health. Furthermore, education, motivation, and self-monitoring will be provided through the *KaziHealth* mobile app [35] to assist individuals in making healthier lifestyle choices and decrease health risks.

The *KaziHealth* mobile app [35] integrates 3 lifestyle interventions; namely, physical activity, nutrition, and stress management to guide individuals in achieving personal health goals. To test the efficacy of the workplace health promotion program over time, teachers will be assessed a second time after 20 weeks.

Component 3: Teacher Coaches

In the 2 schools where teachers will be offered coaching, trained sports students from the Department of Human Movement Science at the Nelson Mandela University will act as teacher coaches assisting the teachers in teaching and ensuring that the intervention is implemented in the schools correctly and as intensively as planned. Furthermore, they will also monitor the intervention process.

Sample Size and Randomization

Assuming that the prevalence of obesity varies across schools according to a log-normal distribution with a mean value of 3% and a SD of 2%, 125 children per school in each of the 8 schools would provide a prevalence estimate between 1.5% and 5% with a probability of 95%. Under this assumption, 95% of school-specific prevalence would range between 0.8% and 8.2%. Hence, our aim is to recruit 125 children per school.

The power calculation for the intervention study is based on the change in a quantitative outcome variable from baseline to follow-up. We denote the SD of its change across schools and children by σ . Assuming an intervention effect size of $0.5 \times \sigma$ and an intraclass correlation of .04 for the clustering of individual changes within schools (corresponding to a random effect SD of $0.2 \times \sigma$), 400 children in the 4 intervention schools (ie, 100 children per school) participating in baseline and follow-up, and 400 children in the 4 control schools would provide over 85% power to observe a statistically significant difference in the mean change of the respective outcome variable between intervention and control schools at the 5% level.

Enrollment of schools will be done by the local research team. To prevent contamination of the intervention effects, schools rather than classes were randomized in January 2019. Before randomization, schools were divided into 2 geographic groups; namely, township areas and northern areas, each containing 4 schools. Township areas are predominantly inhabited by black Africans and northern areas by colored people (after an apartheid-era classification, which refers to people from a multiracial ethnic background and can include persons of Khoi and San origin).

The randomization into intervention and control schools was done separately in each of the 2 groups so that each group was assigned 2 intervention and 2 control schools. To keep the design as balanced as possible, the 4 intervention schemes (ie, teaching materials only, teaching materials plus teacher workshops, teaching materials plus teacher coaching, and teaching materials plus teacher workshops plus teacher coaching) will be assigned in such a way that the intervention schools of 1 group will get teaching materials plus either teacher workshops or teacher coaching. Randomization will allow to determine which of the 2 groups gets which of the 2 pairs of intervention schemes. Sequentially numbered, opaque, sealed envelopes will be used for the assignment of the intervention arms to the schools.

Study Participants

The effect of the *KaziKidz* teaching material will be evaluated in 1 randomly selected class in grades 4, 5, and 6 (=intermediate phase) in each of the 8 study schools (interventions are randomly assigned to any of the 4 northern area or 4 township schools) even though *KaziKidz* teaching material will be offered to all classes in grades 1 to 7 as part of the life skills and life orientation courses in the school curriculum.

For *KaziHealth*, all teachers from the 8 schools will be invited to participate in the program. All participating teachers will undergo the full health risk assessment, and teachers at the intervention schools will have the option to participate in the 20-week intervention. The teachers from the control schools

will be offered the intervention program after the completion of the study.

School Selection, Participant Recruitment, and Written Informed Consent

South African public schools are classified into 5 groups, with quintile 5 representing the least poor and quintile 1 representing the poorest. The quintiles are determined through the national poverty table developed by the treasury [38]. Areas are being ranked on the basis of income levels, dependency ratios, and literacy rates in the area. The quintile ranking of a school determines the no-fee status of the school and the amount of money that a school receives from the government, with the poorest schools receiving the greatest per-child allocation. Approximately 200 principals and/or representatives from 349 quintile 3 primary schools (no-fee paying schools) of the Nelson Mandela Bay Municipality attended information-sharing sessions at the Eastern Cape Department of Education in October 2018. The intention was to be inclusive and invite as many interested principals as possible to inform them of the study. A total of 64 responses were received from interested schools; however, only 8 of the responses (representative of typical quintile 3 primary schools) matched the following criteria:

1. Geographical location and representation of the target communities: *township areas* inhabited predominantly by black African people and the *northern areas* inhabited by predominantly colored people; both these communities needed to be represented equally.
2. Spoken language (IsiXhosa, Afrikaans, or English).
3. Commitment by school principal to support the project activities.

The school authorities will be informed about the project and asked for their interest and consent. Interested schools will be visited, and the investigators will consult with the school administrators to find out if the school environment is conducive for conducting the study. Principals and teachers from selected schools will be informed about the objectives, procedures, and potential risks and benefits of the study. Teachers, children, and parents or guardians will be informed and teachers and children invited to participate in the study. Before enrollment, a participant information sheet will be provided in English, IsiXhosa, or Afrikaans (local languages) to all potential participants and in case of the children, their parents or guardians. For the evaluation part of the study, oral assent of each participating child will be obtained, whereas written informed consent will be obtained from parents or guardians and teachers. Participation is voluntary; hence, children and teachers can withdraw anytime without any further obligations.

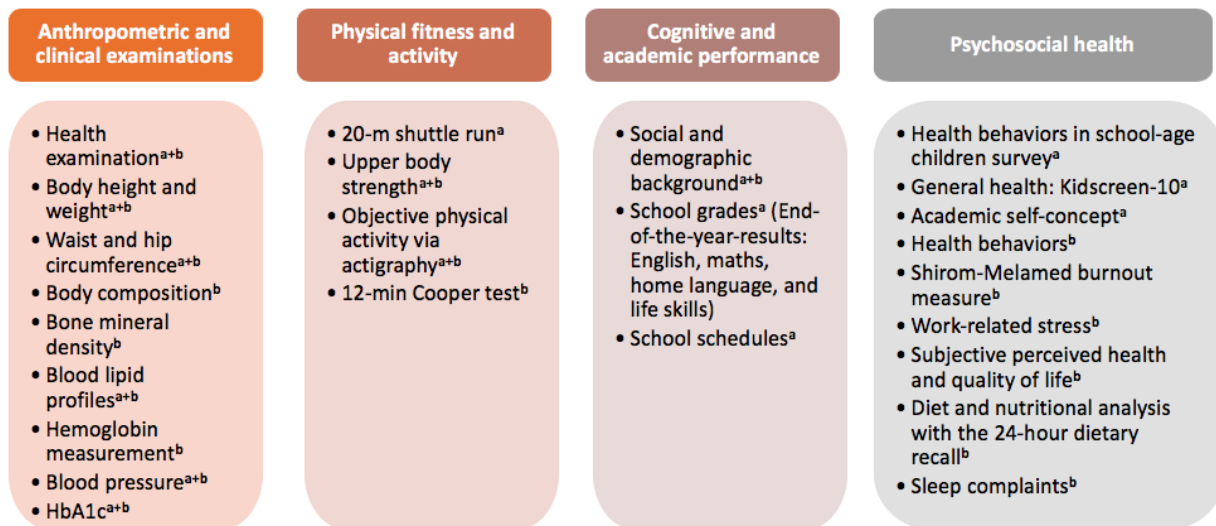
Potential participants will be enrolled in the project for evaluation purposes if they meet the following inclusion criteria: (1) are willing to participate in the study, (2) have a written informed consent (for children by a parent or guardian), (3) are not participating in other clinical trials during the study period, and (4) do not suffer from severe medical conditions, as determined by qualified medical personnel. Approximately 1000 grade 4 to 6 school children, aged 9 to 13 years, and approximately 60 teachers from 8 primary schools will be recruited during the *KaziBantu* baseline survey in early 2019.

Assessment Methods

Primary outcomes for the *KaziKidz* testing battery include (1) anthropometric and clinical examinations, (2) physical fitness and self-reported and objectively assessed activity, (3) cognitive and academic performance, and (4) questionnaire for assessment of psychosocial health. Primary outcomes for the *KaziHealth* testing battery include (1) anthropometric and body composition assessments, (2) clinical examinations, (3) self-reported and objectively assessed physical activity and physical fitness, and

(4) questionnaire results from psychosocial health assessment. Further measures include diet and nutritional analysis with the 24-hour dietary recall. Secondary outcomes for both tests are gender, ethnicity, SES, age, weight, and height. [Figure 7](#) summarizes the assessment methods to be utilized in this study. For baseline and follow-up surveys, the same scientifically recognized procedures will be selected and conducted by professional staff, adhering to standardized, quality-controlled protocols.

Figure 7. Measurements and tests performed among school children (a) and teachers (b) in the *KaziBantu* study.



KaziKidz Assessment Protocol

Anthropometric Measurements

The anthropometric measurements are as follows:

- For each participant, body weight and height will be measured by standing on a digital weighing scale and against a stadiometer with back erect and shoulders relaxed, recorded to the nearest 0.1 kg and to the nearest 0.1 cm, respectively. Age- and gender-specific height or height-for-age and weight-for-age z-scores will be calculated from the current Centers for Disease Control and Prevention (CDC)/World Health Organization (WHO) growth reference data. Body mass index (BMI) and specific z-scores will be calculated as follows: (1) $BMI = \text{weight (kg)} / \text{height (m)}^2$, (2) BMI for children older than 5 years, an indicator for weight-for-height proportion (WHO growth reference for children older than 60 months) [20], (3) height-for-age, an indicator of growth disorders (WHO growth reference for children older than 60 months), and (4) weight-for-age.
- A measuring tape will be used to determine the waist circumference of the participant, measured midway between the rib cage and the iliac crest on a gender-appropriate basis. After measuring the hip circumference, the waist-to-hip ratio will be calculated, a risk indicator for heart disease (ie, the smaller the waist in comparison with the hips, the lower the risk of heart disease) [39].

Questionnaires

To gather information on children's social and demographic background, SES, self-perceived stress, school satisfaction, academic self-concept, self-reported physical activity behavior, and general health status, the following questionnaires will be applied:

- The demographic data and SES of each participant will be determined.
- The KIDSCREEN-10 will be implemented to determine children's physical and psychological well-being, moods and emotions, self-awareness, autonomy, parenting and family life, financial resources, peers and social support, school environment, and bullying. The questionnaire comprises 10 points and has proven to be a valid tool for assessing the psychosocial health of children aged 8 to 18 years [40-42].
- A total of 3 items from the Health Behavior in School-age Children survey [43] will be used to assess individual perceived stress, school satisfaction, and academic self-concept. Learners will be asked how they perceive the pressure, including from homework, related to school [44]. To estimate school satisfaction, children will be asked to respond to the question: *How do you feel about school at present?*
- Children will also be asked questions about their physical activity behavior, including sports participation, being physically active during school hours, and type of play during school hours and in their free time. Information will be collected over a 7-day period. The questions are adjusted using the Physical Activity Questionnaire for Children, an

instrument used to gain insights into general levels of physical activity throughout the elementary school year for children attending grades 4 to 8, aged between 8 and 14 years [45].

Clinical Examinations

Clinical examinations will include:

1. The children's health review will include a detailed history and physical examination. Self-reported health status will focus on intestinal symptoms, including abdominal pain and changes in bowel movements. In addition, we will assess children's evolution of cognitive and physical development. The physical examination is directed toward evidence of anemia (eg, conjunctival pallor), abdominal conditions (eg, hepatomegaly and splenomegaly), and evidence of pulmonary hypertension (eg, jugular venous pressure and cardiac auscultation).
2. Regarding high blood pressure detection, each participant's blood pressure will be measured 3 times after the participant has been seated for 5 min with a calibrated Omron digital blood pressure monitor (Omron M6 AC model; Hoofddorp, The Netherlands). The cuff is wrapped around the left arm so that only a finger can fit between the cuff and arm. The bottom of the cuff is placed about 4 cm above the elbow with the palm facing up, while the blood pressure is taken. For children, a cuff size of 17 to 22 cm will be used (Omron CS2 Small Cuff; Hoofddorp, The Netherlands). As the first measurement often results in higher values, the average of the second and third measurements will be utilized to estimate systolic and diastolic blood pressure. To analyze the data, children will be categorized into a normotensive, prehypertensive, or hypertensive group, based on percentiles, taking into account the age, sex, and height of the children (normotensive: less than the ninetieth percentile; prehypertensive: at or above the ninetieth percentile to at or below the ninety-fifth percentile; and hypertensive: at or above the ninety-fifth percentile).
3. For determination of the full blood lipid profile (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides, non-HDL cholesterol [non-HDL], cholesterol high-density lipoprotein ratio [C-HDL ratio]), glycated hemoglobin (HbA1c) affecting diabetes, and a point-of-care (POC) instrument (Alere Afinion AS 100 Analyzer, Abbott Technologies; Abbott Park, United States of America) will be used, providing results within 8 min. The HbA1c level reflects the average plasma glucose concentration levels over the last 8 to 12 weeks. After the participant's fingertip is cleaned with an alcohol swab, a nurse will prick the fingertip with a safety lancet and gently squeeze out 2 drops of blood. The first drop will be wiped away, and the second drop will be collected for analysis. Before the assessments, all machines will be tested and calibrated with controls.

Physical Fitness Tests

For the purpose of this study, selected tests from the Eurofit fitness battery [46] will be utilized:

1. Cardiorespiratory fitness of children will be measured with the 20 m shuttle run test by Léger et al [47]. In brief, a 20 m flat course, measured by tape and marked with cones will serve for the test. A total of 10 tracks are set. The prerecorded sound signals are played to the children, and they are prompted for the test run in 2 intervals (2x 20 m). Once the children are familiar with the test procedures, they are invited to run back and forth in groups of 10, following the preset pace of the sound signals. Starting at a speed of 8.5 km/h, the frequency of the signal is gradually increased so that the speed increases by 0.5 km/h from 1 min to the next. If children cannot follow the signal and do not reach the 20 m line for 2 consecutive intervals, they will be asked to stop the test and the distance traveled (in full laps) will be recorded. To calculate cardiorespiratory fitness, the number of laps is converted to a speed value, and along with the participant's age, used in the formula provided by Léger et al [47] to estimate the maximal oxygen uptake ($\text{VO}_2 \text{ max}$; $\text{ml} \times \text{kg}^{-1} \times \text{min}^{-1}$).
2. Upper body strength will be determined using the handgrip resistance test, which measures the maximum isometric grip force. The field investigator will demonstrate how to grip the dynamometer. Each participant will have 1 preliminary trial per hand (with a 30-sec rest in between) to grip the dynamometer as hard as possible. In addition, the dominant hand will be noted. The participants will remain in a standard bipedal pose with their shoulder adducted and neutrally rotated, elbow flexed at 90 degrees, forearm in neutral position holding the Saehan hydraulic dynamometer (MSD Europe BVBA; Tisselet, Belgium) without making contact with any body part. The dynamometer will be adapted to the hand size of each participant, and the maximum readings of 6 trials (measured to the nearest 0.1 kg, 3 trials per hand) will be recorded. The highest score will be used as the final result. Higher values indicate better performance.

Objective Activity Measurements

Physical activity behavior will be assessed with an ActiGraph wGT3X-BT accelerometer [48]. Participants will be instructed to wear the device at all times (except during activities involving water contact) for 7 days around the hip. The measured period will include 5 school days and 2 weekend days. Devices will run on the most recent firmware version (version 1.9.2 at the time of writing) and will be initialized with the ActiLife version 6.13.3 (Actigraph LLC) at a sampling rate of 30 Hz. Analyses will be performed using the ActiLife software.

Cognitive Performance

In cooperation with the schools, the school exam grades for the following subjects will be obtained: English, mathematics, home language, and life skills. The sum score of these 4 subjects will be used to estimate the academic achievements. In addition, we will obtain school schedules to monitor the overall academic progress of the children. A school schedule is a quarterly summative tool used by schools to measure and track the progress of the learners, across all their subjects, in an academic year. In addition to tracking the child's progress in the grade, the school schedule is used at the end of the academic year to

determine whether the child will proceed to the next grade or be retained in the present grade.

KaziHealth Assessment Protocol

At baseline and follow-up testing, a comprehensive health risk assessment by health care personnel will be performed on the participating teachers via the *KaziChat*, a comprehensive health assessment tool, which will be used to capture and interpret all assessed health parameters. Internationally accepted cut-off and normative values will be used to rate each tested parameter based on a traffic light model. A personal health risk profile will be generated, with easy-to-understand explanations of the tested parameters as well as further referrals to a general practitioner, if needed.

Anthropometry and Body Composition

Utilizing the same protocol as for *KaziKidz*, each participant's body weight and height will be measured to calculate the BMI. Utilizing the same protocol as for *KaziKidz*, waist and hip circumferences will be measured to determine waist-to-hip ratio, a risk indicator for heart disease [39]. Bone mineral density and body fat percentage will be measured with the Discovery Hologic Dual-Energy X-ray Absorptiometry (DXA) QDR 4500A (APEX System Software Version 4.0.2) by a qualified radiographer. Pregnant individuals, individuals who underwent investigations using radioisotopes in the previous 10 days, and individuals with internal metal artifacts will be excluded from the DXA scan. Calibration will be conducted before testing, using the quality check test. Participant's height, weight, gender, birth date, and ethnicity will be entered before the participant is instructed to lay supine on an open X-ray table within specified position boundaries. The participant will be instructed to lay still and breathe normally while the scan is being conducted, a process that takes approximately 7.5 min.

Clinical Measures

The clinical measures are as follows:

1. A detailed family and medical history will be taken from each participant by a health care professional. Current and previous signs or symptoms of cardiac disease (eg, myocardial infarction, palpitations, and arrhythmias), NCDs (eg, hypertension, dyslipidemia, and diabetes) and psychological conditions (eg, headaches, sleep disorders, and depression) will be recorded. The Physical Activity Readiness Questionnaire will be used to determine whether medical clearance from a general practitioner will be required before the physical fitness assessment [49].
2. Each participant's blood pressure will be measured 3 times after the participant has been seated for 5 min with a calibrated Omron digital blood pressure monitor (Omron M6 AC model; Hoofddorp, The Netherlands) for the detection of prehypertension and hypertension. A medium or large adult cuff size, 22 to 32 cm or 32 to 42 cm, respectively (Omron Medium and Large Cuff; Hoofddorp, The Netherlands) will be used depending on the participant's arm circumference. The same protocol as indicated for *KaziKidz* will be followed to determine the final systolic and diastolic blood pressure values.

3. Dyslipidemia and glycosylated hemoglobin will be tested with a POC instrument (Alere Afinion AS 100 Analyzer, Abbott Technologies; Abbott Park, United States of America) using a full lipid profile (TC, LDL-C, HDL-C, TG, non-HDL, and C-HDL ratio) and HbA1c test, respectively. The same protocol used for *KaziKidz* in this regard will also be applied for assessing these variables.
4. For the detection of anemia, the hemoglobin concentration will be measured to the nearest 0.1 g/L, using a HemoCue Hb 301 system (HemoCue AB; Ängelholm, Sweden). The Eurotrol Hb 301 Control will be used to verify the precision and accuracy of the measuring device.

Physical Activity and Physical Fitness

Using the same protocol as for *KaziKidz*, physical activity behavior will be assessed with accelerometry. Cardiorespiratory fitness will be assessed through the Cooper 12-min run-walk test. The test is a simple, self-paced, maximal running test that is used to determine an individual's maximal oxygen uptake (VO_2 max). The aim of the test is to run or walk as far as possible within 12 min. VO_2 max is then calculated with the following formula:

$$VO_2 \text{ max (ml x kg}^{-1} \text{ x min}^{-1}) = (d_{12} + 504.9)/44.73$$

where d_{12} refers to the total distance covered in 12 min in meters [50]. Before the test starts, blood pressure and heart rate are measured and a 10-min warm-up period is offered. All participants will receive the same instructions, and no verbal encouragement is allowed throughout the test. After the test is completed, a 5-min cool-down period will be given. Although all possible measures will be taken to reduce risk, all maximum exercise tests involve some risk. The test will be supervised by trained health care professionals with the necessary knowledge to deal with any medical emergency that may arise. Furthermore, an automated external defibrillator will be available on site.

Upper body strength will be determined with the handgrip resistance test utilizing the same procedure as described in the *KaziKidz* protocol.

Psychosocial Health Questionnaires

To gather information about the demographic profile and SES, health behaviors, and psychosocial health indicators of each participant, the following assessments will be completed by each participant by means of a questionnaire survey:

1. Demographic data and SES determined through household income and assets (property and car ownership).
2. Cigarette smoking, alcohol use, and screen time per day.
3. Subjective perceived health measured with 2 items from the 12-item short form health survey, adapted from the SF-36 [51]. Participants will be asked to rate the following questions: *In general, would you say your health is?* and *How motivated are you to improve your lifestyle?*
4. Work-related stress will be assessed using the short version of the original Effort-Reward Imbalance questionnaire [52].
5. The Shirom-Melamed Burnout Measure, a validated and widely used tool, will be used to assess occupational burnout [53].
6. Diet and nutritional analysis with a 24-hour dietary recall.

7. The General Health Questionnaire will assess mental distress or minor psychiatric morbidities [54].
8. Subjective sleep complaints will be assessed utilizing the brief 7-item self-report Insomnia Severity Index [55].

Data Collection and Statistical Analysis

The following data will be collected: (1) quantitative data on blood pressure, glycated hemoglobin and blood lipids, anthropometry and levels of physical fitness, cognitive performance and psychosocial health, (2) SES and demographic data, and (3) qualitative data on the feasibility and acceptability of the intervention measures implemented through FGDs. Quantitative data will be entered twice and cross-checked using EpiData version 3.1 (EpiData Association; Odense, Denmark). Cleaned data will be transferred to STATA version 13.0 (STATA Corp, College Station, TX, United States of America). Questionnaire data will be collected using the software package EvaSys (Survey Automation Suite, version 7.1) and analyzed with STATA.

Clinical and anthropometric indicators, physical fitness, cognitive performance, and psychosocial health values will be summarized by their mean and SD at normal distribution and otherwise by their median and interquartile ranges. Questionnaire information on psychosocial health will be expressed as a percentage.

For the analysis of cross-sectional and longitudinal associations, mixed linear or mixed logistic regression models will be used, depending on the type of outcome variable. These models will be adjusted for clustering within classes and schools using random intercepts. In analyses of cross-sectional associations, the models will include personal characteristics of children, such as gender and age, SES of parents or guardians, and other potential confounders of the associations of interest. Models assessing intervention effects will additionally include 3 indicator variables, as defined at the level of schools, 1 for schools of the intervention arm, 1 for schools receiving teacher workshops, and 1 for schools receiving teacher coaching. In addition, these models may include the value of the respective outcome variable at baseline. As intervention effects may also depend on the child's initial characteristics, stratified analyses and analyses with interaction terms will be performed. Potential effect modifiers to be tested include gender, age, SES, ethnicity, health status, and physical fitness at baseline.

The primary objectives of the statistical analyses are (1) to assess the physical fitness of the participants and their associations with cognitive performance and psychosocial health at the beginning and over the course of the intervention, and (2) the effect of interventions on disease status and other health parameters. The secondary objective is to assess the feasibility and acceptability of the health interventions, as determined by FGDs.

Availability of Data and Materials

The datasets generated and/or analyzed during the present study are not publicly available due to confidentiality but are available from the corresponding author on reasonable request.

Results

Overview

The project was funded in April 2017 and enrollment of the participants was completed in January 2019. The baseline survey was conducted from January to March 2019. At the time the present paper is being written, the *KaziKidz* and *KaziHealth* intervention are underway. The follow-up survey is planned for September to October 2019. At the end of the study, the results will be communicated to the Department of Health and the Department of Education in Port Elizabeth, as well as the involved schools. All intervention materials will be made available to the control schools after completion of the study. Workshops will be offered to the control schools to prepare teachers to implement the *KaziKidz* teaching material. Furthermore, teachers of the control schools will have the possibility to take part in the workplace health promotion intervention program after the completion of the second health assessment. The key findings will be submitted for publication to the peer-reviewed literature and presented at national and international conferences.

Discussion

Principal Findings

Results from the DASH study revealed that the prevalence of soil-transmitted helminth infections among grade 4 children was above 60% (90/149) in several schools in Port Elizabeth [56]. Moreover, infected children had lower VO₂ max compared with their noninfected peers [56]; helminth infections and low physical fitness were significant predictors of low selective attention and poor academic achievement [16]; physical activity was associated with health-related quality of life [57]; almost one-third of all school children were classified as hypertensive [58]; and the physical activity intervention component contributed to the maintenance of academic performance [27] and resulted in a significantly delayed increase in children's BMI [59]. Importantly, the DASH intervention package was well received in all schools.

The *KaziBantu* project is a logical continuation and expansion of the DASH project and aims at contributing to healthy schools and healthy communities. Teachers, as leaders in communities, have an important role to play in this regard. We conjecture that teachers as healthy role models will be able to promote better health behaviors and encourage a healthy, active, and inspiring environment for learners and peers at school. Various health professionals will empower teachers with specific knowledge related to infectious and NCD risk factors, physical activity and fitness, and psychosocial health and nutrition. Improved health and well-being increase teachers' productivity, benefiting their own health and well-being and that of the children they teach and educate. We hypothesize that implementing *KaziBantu* will result in less absenteeism, a reduction in stress, and better coping with work demands.

Pursuing the present study protocol will provide specific answers to the following questions: Are *KaziKidz* teaching materials useful? What are the difficulties in using the teaching materials

from the perspective of the teachers? What are the teachers' experiences with regard to the coaching by the teacher coaches? What experiences do the coaches have in their work with the teachers? What attitudes do teachers have with regard to the lessons proposed? What are the conditions for an effective and sustainable implementation of this teaching material? Does the acceptance of the *KaziKidz* teaching material by the teachers moderate its effectiveness?

With regard to the implementation of *KaziKidz* and *KaziHealth*, 3 languages are spoken by the communities in the study area, namely, Afrikaans, IsiXhosa, and English. To ensure comprehension, questionnaires translated into the local languages have been pretested by native speakers, with an emphasis on those that focus on mental health indicators to match the educational attainment of children and help them to understand and answer the questions. The study will be conducted in impoverished and harsh environments where illiteracy, neglect, and violence are common [60,61], which might have an impact on the granting of informed consent by parents and guardians. For illiterate parents or guardians, a literate witness will be invited to sign, whereas participants will be asked to provide a thumbprint. To ensure return of the signed consent forms, we might ask potential study participants several times. Specific safety measures are in place to implement the research. Although it is difficult to predict the extent of people's mobility and movement, we anticipate a substantial loss to follow-up as people show considerable mobility in this setting.

Multiple imputations will be used to deal with missing data, as appropriate.

Conclusions

Taken together, the *KaziBantu* project presented here builds upon the previous DASH study and aims to improve physical health and well-being, cognitive performance, and psychosocial and clinical health of children and teachers. The South African Department of Education seeks to create a lifelong learner who is confident, independent, literate, numerate, multiskilled, compassionate, and has respect for the environment and the ability to participate in society as an active citizen. The Department of Education also envisions healthy teachers who are qualified, competent, dedicated, and caring and who will be able to fulfill the various roles of an educator. Hence, the project aspires to assist the Department of Education by contributing to the development of the full potential of each learner and the transformation of education in South Africa. In addition, developed and validated *KaziKidz* workshop material may be translated into short learning programs for accreditation of Teachers' Continued Professional Development. The *KaziChat* app will be made available to the Department of Education's directorate responsible for human resources for distribution to all teachers together with encouragement for implementation. This study builds on local evidence and offers the opportunity of providing new evidence on health intervention responses to NCD risk factors as a benchmark for future controlled studies that will enable comparisons among marginalized communities between South Africa and other African countries.

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Authors' Contributions

All authors were involved in the design of the study and contributed to the development of the study protocol. UP and CW are the principal investigators. IM wrote the first manuscript draft. All authors reviewed, edited, and critically commented on the draft. All authors read and provided comments on the drafts and approved the final version of the paper before submission and resubmission. UP and CW are guarantors of the paper.

Conflicts of Interest

AA, ZG, and CW are employees of the Novartis Foundation (Basel, Switzerland). All other authors declare no financial competing interests.

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Abbreviations

- BMI:** body mass index
- CDC:** Centers for Disease Control and Prevention
- DASH:** Disease, Activity and Schoolchildren's Health
- DXA:** dual-energy x-ray absorptiometry
- EKNZ:** Ethics Committee Northwest and Central Switzerland
- FGD:** focus group discussion
- HDL-C:** high-density lipoprotein cholesterol
- LDL-C:** low-density lipoprotein cholesterol
- LMIC:** low- and middle-income country
- MVPA:** moderate-to-vigorous physical activity
- NCD:** noncommunicable disease
- non-HDL:** nonhigh density lipoprotein cholesterol
- NTD:** neglected tropical disease
- PE:** physical education
- POC:** point-of-care
- RCT:** randomized controlled trial
- SES:** socioeconomic status
- VO₂max:** maximal oxygen uptake
- WHO:** World Health Organization

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Protocol

Dissemination and Effectiveness of the Peer Marketing and Messaging of a Web-Assisted Tobacco Intervention: Protocol for a Hybrid Effectiveness Trial

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Abstract

Background: Smoking continues to be the leading preventable cause of death. Digital Interventions for Smoking Cessation (DISCs) are health communication programs accessible via the internet and smartphones and allow for greater reach and effectiveness of tobacco cessation programs. DISCs have led to increased 6-month cessation rates while also reaching vulnerable populations. Despite this, the impact of DISCs has been limited and new ways to increase access and effectiveness are needed.

Objective: We are conducting a hybrid effectiveness-dissemination study. We aim to evaluate the effectiveness of a machine learning-based approach (recommender system) for computer-tailored health communication (CTHC) over a standard CTHC system based on quit rates and risk reduction. In addition, this study will assess the dissemination of providing access to a peer recruitment toolset on recruitment rate and variability of the sample.

Methods: The Smoker-to-Smoker (S2S) study is a 6-month hybrid effectiveness dissemination trial conducted nationally among English-speaking, current smokers aged ≥ 18 years. All eligible participants will register for the DISC (Decide2quit) and be randomized to the recommender system CTHC or the standard CTHC, followed by allocation to a peer recruitment toolset group or control group. Primary outcomes will be 7-day point prevalence and risk reduction at the 6-month follow-up. Secondary outcomes include recruitment rate, website engagement, and patient-reported outcomes collected via the 6-month follow-up questionnaire. All primary analyses will be conducted on an intent-to-treat basis.

Results: The project is funded from 2017 to 2020 by the Patient Centered Outcomes Research Institute. Enrollment was completed in early 2019, and 6-month follow-ups will be completed by late 2019. Preliminary data analysis is currently underway.

Conclusions: Conducting a hybrid study with both effectiveness and dissemination hypotheses raises some unique challenges in the study design and analysis. Our study addresses these challenges to test new innovations and increase the effectiveness and reach of DISCs.

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KEYWORDS

smoking cessation; peer recruitment; digital Intervention; tailored, dissemination

Introduction

Smoking continues to be a public health concern and is the leading cause of preventable death in the United States [1]. Annually, over 6 million deaths in the world are attributable to smoking, including 480,000 in the United States [1]. Although the overall rates of smoking have reduced, the rates among socioeconomically disadvantaged subgroups are considerably higher [2]. In particular, African American smokers suffer disproportionately due to smoking-related diseases including several cancers, cardiovascular disease, and cerebrovascular disease [2-4]. Although they smoke fewer cigarettes and start smoking at an older age, these smokers are more likely to die from smoking-related diseases than white smokers [1]. Identifying strategies to increase reach and effectiveness of tobacco cessation programs, especially among vulnerable populations, is an ongoing research challenge [5].

Digital Interventions for Smoking Cessation (DISCs) are health communication programs readily accessible via the internet and smartphones. DISCs can include a number of functions designed to support a smoker's cessation attempt. Previous research has shown that DISCs can be effective. In our prior trial, our DISC—Decide2Quit [6]—achieved a cessation rate of 30% at 6 months, which is much higher than the 7% rate at which smokers quit without support [7]. DISCs have the potential to reach a large and diverse group of smokers. Access to DISCs

has previously been limited for many smokers because of the disparities in internet access. However, the digital divide in internet access has decreased considerably with increased broadband availability and smartphone use [8,9]. Despite this increased access and potential for effectiveness, the impact of DISCs has been limited. New ways to increase the access and effectiveness of DISCs are needed.

In response to a Patient Centered Outcomes Research Institute (PCORI) call for communication and dissemination research, we proposed a dissemination study—Smoker-to-Smoker (S2S)—to test whether providing access to a peer recruitment toolset that facilitates recruitment of friends and family members to the intervention will increase recruitment rate and increase variability of the sample. Because of feedback from PCORI and peer review, we expanded our study to also test the effectiveness of a machine learning–based approach (recommender system) for computer-tailored health communication (CTHC). Thus, our project is a hybrid effectiveness dissemination trial including both effectiveness and dissemination hypotheses (Textbox 1). Conducting a hybrid study with both effectiveness and dissemination hypotheses raises some unique challenges in the design and analysis of our study. Our paper describes the intervention functions and the study protocol we developed to address previously mentioned challenges. We also describe the budget impact analysis we will use to assess the cost of implementing this intervention.

Textbox 1. Study hypotheses.

Hypothesis 1: Dissemination

- H1A: Peer recruitment will recruit a greater proportion of African American smokers compared to standard online recruitment.
- H1B: Peer recruitment will reduce recruitment time (time to recruit each participant) compared to standard online recruitment.

Hypothesis 2: Repeated use of Decide2Quit functions

- H2A: Repeated use among those exposed to the fully enhanced group (access to peer recruitment toolset and recommender CTHC) will be greater than repeated use among those exposed to (1) peer recruitment toolset only, (2) recommender CTHC with no peer recruitment toolset, and (3) standard group (no peer recruitment toolset and standard CTHC).
- H2B: Repeated use among those exposed to the peer recruitment toolset will be greater than repeated use among those exposed to the standard group.
- H2C: Repeated use among those exposed to the recommender CTHC will be greater than repeated use among those exposed to the standard group.

Hypothesis 3: Effectiveness

- Quit rates and risk reduction among participants exposed to the recommender CTHC (A+B) will be greater than those among participants exposed to the standard group (C+D).

Methods

Study Overview

The goal of this study (ClinicalTrials.gov: NCT03224520) is to recruit 1200 smokers to test our effectiveness and dissemination hypotheses. To participate in the study, all smokers will register online for the Decide2Quit DISC. Randomization will occur after registration using a multilevel approach, as detailed below. We will follow smokers for 6 months from their registration date. Following a description of the intervention and comparison, our protocol is described in detail below. The protocol of our study was approved by the Institutional Review Board at the University of Massachusetts Medical School.

The Smoker-to-Smoker Functions

The Computer-Tailored Health Communication System

CTHC is a frequently used tool in behavioral science and is focused on the selection of appropriate messages for an individual. CTHC increases personal relevance of health messaging by matching the messages to an individual's or group's characteristics [10]. CTHC can be effective in motivating behavior change [11-17]. Standard CTHC has traditionally been accomplished using rule-based approaches in which selected variables from patients' baseline profile are matched to specific if-then tailoring rules to send tailored messages to specific subsets of patients [10,18]. As an

alternative to rule-based approaches, companies such as Amazon use machine learning algorithms (ie, recommender systems) to tailor content. These recommender systems have several advantages over rule-based approaches, including the ability to continuously learn from user feedback (eg, liked product and products purchased) and enhance personal relevance. [Textbox 2](#) provides an example of how a standard and recommender CTHC may differ in DISCs [18]. In our prior pilot randomized controlled trial (RCT) [19], we developed a recommender CTHC and compared this system with a standard CTHC system that showed effectiveness. The recommender system significantly outperformed the rule-based system on the number of days (out of 30) in which message relevance influenced smokers to quit. In the recommender system smokers, 74% strongly agreed or agreed that the messages influenced them to quit smoking, while this was only reported by 45% in the standard group ($P<.01$) [20]. Among those who completed follow-up, 36% (20/55) of the recommender system smokers and 32% (11/34) of the rule-based system smokers stopped smoking for one day or more ($P=.70$). Our goal in the S2S study is to rigorously test the recommender system against the standard CTHC for smoking cessation over a 6-month period. The primary difference between the recommender CTHC and standard CTHC will be the way in which messages are selected for the participant. Since our goal is to test the selection method, both systems will select from the same database of messages. We will first describe the motivational message database used in the study followed by the standard CTHC selection system and the recommender CTHC system.

Textbox 2. Computer health-tailored communication (CHTC). An example of a standard CHTC versus a recommender CHTC [17].

John Smith, a 38-year-old smoker, has been smoking for 15 years. He has made multiple quit attempts in the past, but during each attempt, he gained between 10 and 20 pounds. Currently, fear of weight gain is a significant barrier to another quit attempt.

John is trying to quit again and registers on Decide2Quit. For 8 weeks, the system sends two tailored emails per week to John Smith to help him quit.

Standard CTHC

- In this approach, tailoring is based on information that John provides when he registers. For this example, we focus on one characteristic only: gender.
- Since women are typically more concerned about weight gain after quitting [21,22], experts have specified that half of the emails sent to women should contain information related to weight gain, but only one quarter of the emails sent to men should be focused on weight gain.
- After registering on Decide2Quit, John receives the first email that targets weight gain support in the second week (third message) of the intervention. John likes the message and finds the tips it offers useful. He looks forward to receiving similar messages. However, the next five messages he receives focus on other topics. The next weight gain message arrives only on week 5.
- John does not think the system helped and fails in his attempt to quit.

Recommender CTHC

- In this approach, the selection of the message is based on the collective intelligence data, not on preset rules.
- After registering on Decide2Quit, John visits the weight gain support page on the website (implicit data). The system uses these data and selects one of the messages targeting weight gain and sends it to John on week 2 (third message). John likes the messages and rates the message highly (explicit data). The system then notes both items of implicit and explicit feedback and regularly sends messages targeting weight gain to John. The system also repeats the message that John rates highly.
- Because the intervention targeted his needs more specifically, John finds these messages useful and succeeds in his attempt to quit.
- We have provided a simple example for ease of understanding. We have not included in this example how the group's feedback can help John.

The Motivational Messaging Database

The messaging database includes 500 messages that were developed in our prior RCT, consisting of both expert-written messages and peer-written messages [23]. Expert-written messages were developed through an iterative expert group review process (behaviorists, physicians, and nurses). These messages were informed by current guidelines [24] and the Social Cognitive Theory [25], which incorporates vicarious learning, verbal persuasion, and expert messages that reflect the theoretical determinants of quitting such as positive outcome expectations and self-efficacy-enhancing small goals [25]. Peer-written messages were written by current and former smokers responding to an online survey that presented four scenarios tailored by gender, age, and readiness-to-quit. These messages were then reviewed for use in our system. More details of our methodology to generate peer written messages have been previously published [23].

The Standard Computer-Tailored Health Communication System

Our comparison standard CTHC is a rule-based (if-then-else) system that tailors messages based on a smoker's readiness to quit. For example, when a smoker logs on to Decide2Quit and indicates their readiness as "not ready to quit," a message from those categorized for "not ready to quit" smokers will be picked at random and sent to the smoker. Similarly, if the smoker indicates their readiness as "set a quit date," a message categorized for "set a quit date" smokers will be sent to the smoker. This system was tested in our prior study and demonstrated to be effective in increasing the 6-month smoking cessation by 9% (odds ratio [OR] 1.69, 95% CI 1.03-2.8) over a nonmessaging control [26]. Thus, our comparison will be a robust, active, and effective standard CTHC system.

Recommender Computer-Tailored Health Communication System

The details of our development and evaluation of the recommender system were previously published [20,26,27]. Briefly, we developed a hybrid recommender system that uses three input data sources to generate the recommendations, including metadata description of the messages, implicit feedback data, and explicit feedback data (smokers in the prior and current study). The recommender system consists of multiple components.

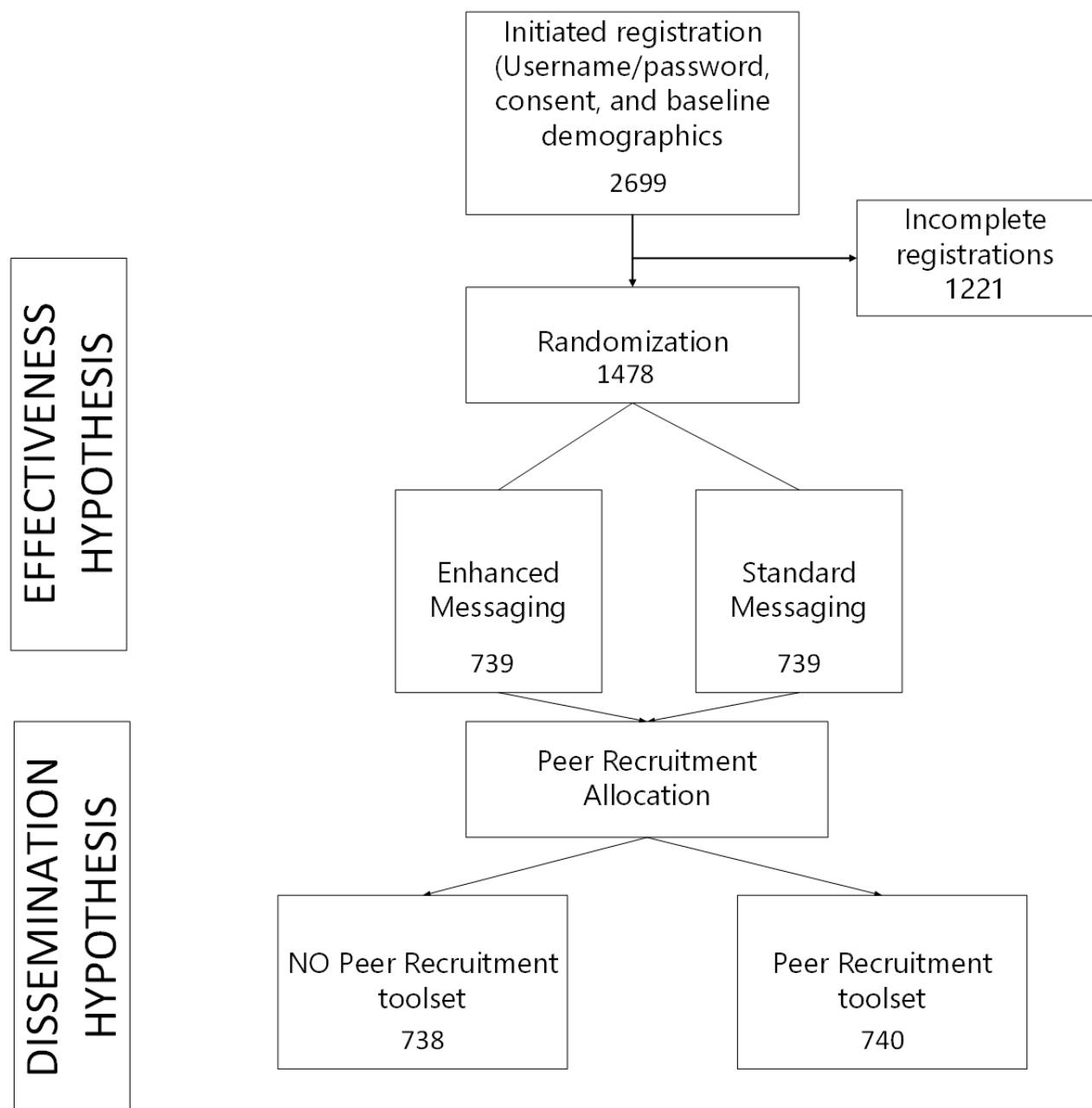
Our metadata includes a comprehensive coding of the messages. We developed these codes to facilitate further understanding of what did and did not work in these messages. These codes include constructs from multiple behavioral theories such as the Social Cognitive Theory, the Transtheoretical Model, and

the Theory of Reasoned Action [28]. We also coded the messages for content that may be pertinent to a specific user, including health and lifestyle status, health issues, and treatment options. Overall, we developed 48 codes divided into 8 categories (General Treatments, Behavioral Treatments, Over the Counter and Prescription Treatments, Motivations, Health, Sociocultural Attributes, Author Attributes, and Author Interaction). Implicit feedback data are derived from user actions. As our implicit feedback data, we used the website return data of 900 smokers that participated in our prior RCT [19]. When an email was sent to these smokers, we tracked their website usage in the days following the email. Thus, we had data on the frequency at which each message promoted the use of Decide2Quit and the characteristics of the smokers that received these messages. Explicit feedback data consist of self-reported item ratings. We recruited 846 current or former smokers from online and local sources to rate the messages on the influence scale (see Data Collection and Outcomes). Each smoker was asked to rate 20 messages, resulting in 16,920 ratings. Several classic and state-of-the-art collaborative filtering methods were evaluated for accurate prediction methods. The Bayesian Probabilistic Matrix Factorization (BPMF) was identified as the best single model in our evaluation and was used to develop the recommender CTHC. The BPMF model estimates a probability distribution over a joint embedding of users and items into complementary latent spaces. The rating a given user supplies for a given item is approximated by the expected value of the product of the latent user and item factor vectors representing the user-item pair, with the expectation taken over the uncertainty in embeddings [29]. In addition to explicit feedback ratings from smokers in prior studies, the recommender CTHC is programmed to use the explicit ratings of smokers receiving the messages (see Data Collection and Outcomes).

Access to a Peer Recruitment Toolset

The primary element of the peer recruitment toolset is our Facebook website plugin [20,26,27]. The Facebook plugin will allow smokers to browse through their Facebook friends and recruit them by sending private recruitment messages. In our pilot study [20,26,27], providing smokers access to peer recruitment quadrupled our sample (190 smokers recruited 569 more smokers to the Decide2Quit DISC). Further, the smokers recruited by their peers were more likely to be African American as compared to those who were directly recruited from an online social network (23.8% vs 10.8%; $P < .01$ for all comparisons). Thus, in our dissemination hypothesis, we are testing if providing smokers access to peer recruitment specifically increases the proportion of African Americans in our sample.

Figure 1. Flow of participant randomization. Allocation to receive the peer recruitment tools occurs in two phases or waves. Wave 1: Half of the enrolled smokers are randomized to receive peer recruitment tools, while the others do not receive the tools; and Wave 2: All subsequent smokers who are randomized to the effectiveness trial and also report they were peer-recruited are given access to the peer-recruitment tools.



The basic flow of a single hypothetical smoker through the peer-referral, registration, and subsequent initiation of new peer-recruitment is described in Figure 1. Peer recruitment will take place in waves. As is common in peer recruitment approaches, to initiate the waves, we will recruit the first wave (wave 0 or seeds) of smokers. Seeds will be recruited using online advertisements. Once a seed registers on Decide2Quit and receives the peer recruitment toolset, we expect the following to occur:

1. The seed consents to be in the study and recruit smokers from his/her network using the peer-recruitment tools (by sending a Facebook private message).
2. The successfully peer-recruited smoker (wave 1 recruit) registers on the system and consents to recruit other smokers in his/her social network.

3. The wave 1 recruit then continues the peer-recruitment chain, recruiting smokers his/her their social network.
4. The successfully peer-recruited smoker then registers (wave 2 recruit). The waves progress until the target sample size is reached.

Study Design

As noted in Figure 1, all participants registering online on the Decide2Quit DISC will first undergo an effectiveness randomization and then a peer recruitment allocation. The effectiveness randomization will randomly assign participants to either receive access to the recommender system CTHC or the standard CTHC. The peer recruitment allocation will depend on the recruitment source. As noted in the section below, we will either directly recruit participants to the study (via search engine advertisements and research match) or they will be

recruited by their peers (peer recruited). Directly recruited peers will be randomized to either receive the peer recruitment toolset or not receive the toolset. All peer recruited participants will receive access to the peer recruitment toolset. We are using this approach for the peer recruited smokers to enhance blinding. This decision was made because these recruited smokers may communicate with their peers about the intervention.

Recruitment

Process

Our primary recruitment method will be to directly recruit smokers online using search engine advertisements or ResearchMatch. Participants having access to the peer recruitment toolset will be able to recruit their friends and family smokers to the website. To recruit via search engine advertisements, we will develop and post online advertisements customized to appear to smokers searching for quit smoking-related search terms online. When smokers click on these advertisements, they are redirected to Decide2Quit, where they are provided study information and registration instructions. The functions are provided in the ad managers of the search and social media website-targeted ads for smokers. For example, the Facebook ad manager allows advertisers to target users based on their interests derived from their profile's keywords, pages they like, and groups they visit, which are then displayed on the Facebook page of the user. ResearchMatch is a free and secure online tool developed by Vanderbilt University and used by academic institutions across the country. To register, volunteers enroll on the ResearchMatch website, fill out demographic and optional health history questionnaires, and submit their profile. As noted, we will test peer recruitment for increasing access to the Decide2Quit DISC. Thus, we may also have participants who are peer recruited to the study as a consequence of our peer recruitment experiment.

Randomization

We will embed randomization within the technology. Our statistician will generate a randomization table; the randomization sequence will be conducted in random blocks of different sizes ($n=8$ and $n=12$) to ensure balance among the groups and reduce predictability of the allocation process. Thus, randomization will occur automatically at the time of initial registration. Following randomization, there will be an allocation to receive the peer recruitment toolset or not to receive the toolset. Study staff will be blinded to allocation during initial baseline assessment and follow-up.

Study Participants

Participants will be included if they are current smokers over 18 years of age and can read or speak English. Prisoners will be excluded. Pregnant women may be incidentally enrolled. In such cases, this research poses no risks to the fetus.

Data Collection and Outcomes

S2S will include multiple data collection stages (Table 1). At each time point (1 week, 1 month, and 6 months), we will send participants email reminders to complete the online follow-up surveys. We will send up to four email reminders over the course of 2 weeks from the targeted follow-up date (eg, if the participant is due for their 6-month follow-up on January 1, we will send them reminders for the 2 weeks following that date). If participants fail to respond to our email messages, we will call them to complete the survey over the phone. To calculate the success of our intervention, we will use the RE-AIM framework and evaluate results along the RE-AIM dimensions for success of health behavior interventions including reach, effectiveness, adoption, implementation, and maintenance [30-32]. Table 1 provides a list of study outcomes associated with RE-AIM dimensions. Our primary and secondary outcomes are listed below.

Table 1. Study measure by time points and associated RE-AIM dimensions.

Construct	Description	RE-AIM dimension
Baseline measures		
Demographics	<ul style="list-style-type: none"> Age, gender, race, ethnicity, education level Contact Information 	Reach
Smoking habits	Current smoking habits	Reach
Quit attempts	<ul style="list-style-type: none"> Readiness to quit Nicotine dependence Nicotine replacement therapy use E-cigarette use 	Reach
Family-based intervention and social network	<ul style="list-style-type: none"> Household status Smokers in social network Interest in family-based intervention 	Reach
Reach and registration	<ul style="list-style-type: none"> Number of users who saw and clicked on online advertisements Number of users who registered following online advertisements 	Reach, Adoption
1-month measures		
User feasibility and acceptability	<ul style="list-style-type: none"> User feedback on use of the system 	
Peer recruitment success	<ul style="list-style-type: none"> Number of peer recruiters Number of peers recruited 	Reach, Adoption, Effectiveness
Peer recruitment experience	<ul style="list-style-type: none"> Number of friend/family smokers a recruiter contacted for recruitment (network reached) Use of tools outside the Smoker-2-Smoker peer recruitment toolset Barriers/facilitators to peer recruitment Primary reasons a potential recruitee chose to be peer recruited or not 	Reach, Implementation, Maintenance
Perceived influence of peer recruitment on cessation	<ul style="list-style-type: none"> Beneficial to the participant's quit smoking efforts Motivated to get support from those around the participant to quit smoking Increased the participant's craving for cigarettes Made the participant feel like they were being helpful to their family and friends who are smokers 	Effectiveness
6-month measures		
7-day point prevalence smoking cessation	<ul style="list-style-type: none"> Do you currently smoke cigarettes (smoked even 1 puff in the last 7 days)? [33] 	Effectiveness
Biochemical verification of smoking cessation	<ul style="list-style-type: none"> NicAlert uses a dipstick to measure the level of cotinine in a sample of saliva. We will mail strips with instructions on how to take and return a picture of the results to us electronically. 	Effectiveness
Continuous measures		
Website engagement	<ul style="list-style-type: none"> Number of visits to decide2quit Number of pages used 	Adoption
Message feedback	<ul style="list-style-type: none"> Influence survey sent after each email (explicit) 	Effectiveness

Effectiveness Outcomes

Smoking Cessation: 7-Day Point Prevalence and Verification by Saliva Test NicAlert

The primary outcome measure will be 7-day point prevalence at the 6-month follow-up. The 7-day point prevalence will be assessed by asking, "Do you currently smoke cigarettes (smoked even 1 puff in the last 7 days)?" [33] The 7-day window provides an appropriate stringent measure to account for a

cross-sectional snapshot. In a cessation trial, biochemical verification is used to monitor for differential misclassification by the randomization group. The degree of misclassification is moderated by characteristics of the smoking cessation intervention [34]. Studies that are in-person and intense generally have more misclassification because of the personal connection between the smoker and the counselor and therefore require biochemical verification. Less misclassification occurs in low intensity, light-touch studies. Further, differential misclassification increases with intervention differences between

two groups. Since our intervention and control are both texting interventions, the potential for differential misclassification is reduced. Further, requiring biochemical verification can, in fact, lead to additional issues, including refusal to participate, thus biasing the sample [34,35]. However, based on peer review, we are conducting biochemical verification. To reduce the potential for biasing the sample due to the need for biochemical verification, we are using an opt-in procedure to conduct biochemical verification among those who indicated they had quit smoking at 6 months. If a participant indicates they have quit smoking at 6 months, they are contacted by the research study staff to see if they would like to opt-in to the biochemical verification. If a participant opts in, they will be mailed the NicAlert test strips (Nymox Corporation, St Laurent, Quebec, Canada) within 24 hours with clear instructions on how to take a picture and return the picture of the results to us electronically. NicAlert is a semiquantitative method that uses a dipstick to measure the level of cotinine in a sample of saliva. The test strip displays the result in seven zones. Each zone represents a range of levels of cotinine/smoking (eg, zone 0: 0-10 ng/mL, a nonsmoker, zone 6: >1000 ng/mL, a heavy smoker). The results will be read as 0-6, and as recommended, any value ≥ 1 will be considered as tobacco use [36-38]. Our staff will also be available by phone to help the smokers complete testing. Participants sending back the sample will receive an additional US \$50 incentive (as outlined in the consent form) for completing biochemical verification.

Risk Reduction (Reduction in the Number of Cigarettes Smoked)

We will calculate risk reduction by subtracting the number of cigarettes smoked at baseline from the number of cigarettes smoked at the 6-month follow-up.

Dissemination Outcomes

Secondary outcomes include recruitment rate, website engagement, and patient-reported outcomes collected via the 6-month follow-up questionnaire.

Recruitment Rate

When smokers register on Decide2Quit, they will be assigned a unique identifier and their registration date and time will be recorded. We will compute recruitment time from these data as the time taken to recruit each participant from the time that the first participant in the group was recruited.

Website Engagement and Feedback: Implicit and Explicit

We will use repeated use over other use measures (number of logins) to measure website engagement, as this has demonstrated an association with smoking cessation [39]. This is an ordinal scale of the number of Decide2Quit functions used after the first DISC visit (0: no functions used; 1: use of 1-2 functions, 2: >2 functions used). We will also continuously assess explicit (influence survey) and implicit (days to click on website) feedback after each email sent. When a smoker is sent an email, we will include a link to rate the message on the influence scale.

Sample Size

Hypothesis 1: Dissemination

Our previous work [26,27] showed that having access to peer recruitment increased the proportion of African Americans to 23%, compared to 11% in the initial seeds (those recruited by advertisements). Using 10% as the base rate in the nonpeer recruitment group (no access to peer recruitment), we estimated sample size requirements by varying the proportion in the peer recruitment from 16% to 20%. With these assumptions, for our primary aim, we will need 219 smokers in each group to detect a difference of 10% (power=80%, $\alpha=.05$). If we reduce the difference to 8% and 6%, we will need 319 and 525 participants in each group, respectively. Given that we will work with our panel to encourage recruitment of African American smokers in the peer recruitment group and may see bigger differences than those in our pilot study, we will have adequate power, particularly with the proposed sample size of 600 in each recruitment method. For recruitment time, previous trials estimated that the mean number of days to recruit a sample of 700 smokers was 244 (SD 81) days [27,40]. Assuming that peer recruitment proceeds with the same rate and SD, we can detect a difference in recruitment time as low as 14 days. Since we expect the comparison rate to be much slower, we are adequately powered to detect differences with a sample of 600 (power=80%).

Hypothesis 2: Repeated Use of Website

We used the method published by Whitehead to calculate power for this hypothesis [41]. In our previous work, we found a linear association between the 6-month cessation and repeated use by using the repeated use scale. For every increase by one in this scale, odds of smoking cessation increased (OR 2.10, 95% CI 1.03-4.30) [39]. With the current sample size of 300 per group, we can detect a difference a cumulative odds ratio of 1.7. Thus, our study is adequately powered to measure a reasonable difference in the repeated use measure.

Hypothesis 3: Effectiveness

We assumed a control cessation rate of 15% [42], and a two-sided significance level of .05. A sample size of 300 in each group will achieve 80% power to detect a difference of 9% (quit rate in intervention=24%) in quit rates between the two groups, based on a Z-test with pooled variance. We will categorize the NicAlert test results into smokers and nonsmokers and use the chi-square statistic to test for differences. We calculated the detectable difference in risk reduction with 300 smokers in each group and a mean of 3.3 cigarettes in the comparison group, using SDs of 2 and 3 with 80% and 90% power, respectively. We will have 90% power to detect a difference of 0.80 (or smaller) in the number of cigarettes smoked between the two groups. This difference is likely to be achieved based on the results of our PCORI pilot, in which we achieved a reduction of 0.85 (4.15-3.3) in 30 days compared to smokers receiving the standard CTHC messages; smokers receiving the recommender CTHC had a higher reduction in the number of cigarettes at 30 days (Standard CTHC: mean 3.3; S2S adaptive CTHC: 4.15).

Statistical Analyses

All primary analyses will be conducted on an intent-to-treat basis. Secondary analyses will explore dose-response effects among those with variable levels of adherence to the intervention. All analyses will be two-sided, and the alpha error will be set at .05. We will begin our analysis by examining univariate statistics (means, medians, SDs, and 95% CIs) and distributions. We will examine the balance of participant characteristics by study groups and account for any imbalances in our multivariable analysis. As appropriate, differences in measured characteristics (ie, demographics and prebaseline smoking behaviors) by group will be tested using Chi-square tests of independence (categorical variables), analysis of variance (continuous variables), or the equivalent nonparametric tests, depending on the distribution of the variables. Differences in baseline characteristics of the intervention and comparison groups will be assessed.

To test Hypothesis 1, we will categorize the smokers as either African Americans or not, and then use the chi-square statistic to test for differences between the peer recruitment and standard groups. We will also compare mean recruitment time between the two types of recruitment method using a *t* test. We will explore possible factors that may not be balanced between the smokers recruited from the two methods. If we find any significant differences, we will develop a linear regression model to further adjust for the influence of the confounders on the time to recruitment outcome. Within the peer recruitment groups, we will conduct a secondary analysis examining differences in demographic characteristic between peer recruited and directly recruited smokers. Using data provided by search engine advertisement managers, we will evaluate the performance of our online advertisements (number of users registered on Decide2Quit following an advertisement on the search engine).

To test Hypothesis 2, we will use a generalized linear model, which includes indicators of peer recruitment and recommender CTHC and the interaction between the two indicators as independent variables.

To test Hypothesis 3 (effectiveness), we will compare participants randomized to enhanced CTHC and those randomized to standard CTHC. We will use the 7-day point prevalence cessation of the 6-month follow-up as the dependent variable in generalized linear models. Using mediation analysis, we will examine the potential mechanisms through which we anticipate the intervention to produce a beneficial effect. We will categorize the NicAlert test into smokers and nonsmokers' categories and use the Chi-square statistic to test for differences. If risk reduction (decreased number of cigarettes smoked) is normally distributed, we will use the identity link function in the generalized linear model. We will also model risk reduction using count regression with a Poisson or negative binomial regression modeling if the variance of the distribution of risk reduction is over dispersed. For Hypotheses 2 and 3, we will compare African American smokers across the groups, and African American and white smokers for heterogeneity.

To assess the difference in smokers comparing the peer recruitment and standard recruitment, we will use a three-step strategy. First, we will collect data on covariates (minority

status, education, readiness to quit, and income) that have been shown to differ between the peer recruitment and standard recruitment [26]. We will use these variables to adjust our overall models with the outcome of smoking cessation, comparing participants from peer recruitment and those from standard recruitment. Second, peer recruitment is, in many ways, analogous to clustering. Each person who is recruited by another individual is clustered in the group of the initial peer recruiter. Thus, some component of the difference is within the relationship between recruiter and recruitee. To address this issue, we included a marker for each "recruiter" as a fixed effect in the model. Third, we will use an advanced approach, termed complier-averaged causal effect analysis (CACE), to compare those who complied (peer recruited or not) in the intervention group with those who would have complied in the comparison group if they had been exposed to the intervention (peer recruitment). Thus, after adjustment using the first and second approach, we will conduct additional models using CACE.

For the budget impact analysis, we will compare the costs of the four intervention arms from the perspective of an implementing organization. The research team will track staff time associated with each intervention arm, including time for training, recruiting, and administering the different aspects of the intervention such as incentives for recruitment. In addition, we will work with the research team to estimate development costs of each intervention component (eg, the adaptive component of the CTHC) and any equipment or supply costs. We will compare the costs of the different intervention arms in multiple scenarios in which we examine how costs change based on changes in the components of the intervention and the types and amount of staffing provided for implementation. The economic analyses for will primarily consist of descriptive statistics. Using the estimates of costs of supplies, equipment, and staff time and the potential savings that result from decreased health care costs related to smoking cessation, we will calculate the budget impact of implementing a particular treatment strategy from the perspective of an implementing or disseminating organization. We will follow the guidelines outlined for best practices in budget impact analysis [43]. We will create tables to describe the assumptions of our inputs and outputs of our budget impact analysis and perform sensitivity analyses to examine how changing the assumptions of the model impact the potential costs for an organization implementing the intervention.

Results

The project was funded in 2017, and enrollment will be completed in 2019. Preliminary data analysis is currently under way.

Discussion

The S2S study addresses a key question raised in the State-of-the-Science Conference Statement on Tobacco Use: What are the effective strategies for increasing consumer demand for and use of proven, individually oriented cessation treatments, including among diverse populations? [5]. The primary goal of the intervention is to disseminate and increase

the use of a tobacco cessation website using peer recruitment and enhanced CTHC. These methods will be compared to traditional online advertisements and standard CTHC. Although our pilot data are promising, we acknowledge that an effect size could have occurred due to chance and because the cessation results were limited to a short-term outcome (1 day). Thus, the present study is needed to detect if differences exist when fully powered while also examining a long-term (6-month) cessation outcome. We also identify the inherent challenge of measuring cessation outcomes by recruitment type for our dissemination hypothesis (testing the reach of standard versus peer recruitment). We have addressed this unavoidable challenge in our statistical analysis plan.

PCORI defines dissemination as the active and targeted approach of spreading evidence-based interventions to potential adopters and the target audience through determined channels using planned strategies, and its goals is to increase the reach of information, motivation, and patients' ability to use and apply

evidence [44-46]. Thus, both recruitment and use measures are needed to appropriately evaluate our DISC dissemination strategy. If recruitment is unsuccessful, the intervention's reach is low. If recruitment is successful, but the intervention does not motivate repeated use, there is low intervention fidelity, which may reduce the patient's motivation and ability to apply evidence. To ensure successful recruitment, we will continuously monitor these methods with our patient stakeholders to refine our advertisement strategies.

As access to the internet continues to grow, interventions like S2S will be increasingly accessible. It is important to continue to test methods to disseminate technology interventions to augment care for users. These technology interventions can serve as important augmentation for those receiving in-person and telephone counseling (to use between sessions and for longitudinal support). For those without access to other options, these technology interventions may serve as the only source of tobacco cessation support.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Patient Centered Outcomes Research Institute peer-review letter.

[[PDF File \(Adobe PDF File\), 104KB - resprot_v8i7e14814_app1.pdf](#)]

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Abbreviations

- BPMF:** Bayesian probabilistic matrix factorization
- CACE:** complier-averaged causal effect analysis
- CTHC:** computer-tailored health communication
- DISC:** digital intervention for smoking cessation
- PCORI:** Patient Centered Outcomes Research Institute
- RCT:** randomized controlled trial
- S2S:** Smoker-2-Smoker

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Protocol

Text Messaging to Improve Linkage, Retention, and Health Outcomes Among HIV-Positive Young Transgender Women: Protocol for a Randomized Controlled Trial (Text Me, Girl!)

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Abstract

Background: Transgender women in the United States experience numerous risk factors for HIV acquisition and transmission, including increased rates of homelessness, alcohol and drug use, sex work, and nonprescribed hormone and soft tissue–filler injections. In addition, transgender women face discrimination and social/economic marginalization more intense and deleterious than that experienced by lesbian, gay, or bisexual individuals, further worsening health outcomes. Although little research has been done specifically with young transgender women aged 35 years and younger, existing evidence suggests even further elevated rates of homelessness, substance use, and engagement in HIV transmission risk behaviors relative to their older transgender women and nontransgender young adult counterparts. Young transgender women living with HIV experience a range of barriers that challenge their ability to be successfully linked and retained in HIV care.

Objective: The aim of this randomized controlled trial, *Text Me, Girl!*, is to assess the impact of a 90-day, theory-based, transgender-specific, text-messaging intervention designed to improve HIV-related health outcomes along the HIV care continuum among young (aged 18-34 years) transgender women (N=130) living with HIV/AIDS.

Methods: Participants were randomized into either Group A (immediate text message intervention delivery; n=61) or Group B (delayed text message intervention delivery whereby participants were delivered the text-messaging intervention after a 90-day delay period; n=69). Over the course of the 90-day intervention, participants received 270 theory-based text messages that were targeted, tailored, and personalized specifically for young transgender women living with HIV. Participants received 3 messages per day in real time within a 10-hour gradual and automated delivery system. The text-message content was scripted along the HIV care continuum and based on social support theory, social cognitive theory, and health belief model. The desired outcome of *Text Me, Girl!* was virological suppression.

Results: Recruitment began on November 18, 2016, and the first participant was enrolled on December 16, 2016; enrollment closed on May 31, 2018. Intervention delivery ended on November 30, 2018, and follow-up evaluations will conclude on August 31, 2019. Primary outcome analyses will begin immediately following the conclusion of the follow-up evaluations.

Conclusions: Text messaging is a communication platform well suited for engaging young transgender women in HIV care because it is easily accessible and widely used, as well as private, portable, and inexpensive. *Text Me, Girl!* aimed to improve HIV care continuum outcomes among young transgender women by providing culturally responsive text messages to promote linkage, retention, and adherence, with the ultimate goal of achieving viral suppression. The *Text Me, Girl!* text message library is readily scalable and can be adapted for other hard-to-reach populations.

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KEYWORDS

HIV; AIDS; transgender persons; text messaging

Introduction

As a population, transgender women bear a disproportionate burden of HIV/AIDS and other health disparities. In the United States, transgender women experience numerous risk factors for HIV acquisition and transmission [1-3], including increased rates of homelessness [4-6], alcohol and drug use [6,7], and sex work [7,8]. In addition, many transgender women use nonprescribed hormone injections and/or medically unsupervised soft tissue–filler injections, HIV risk factors that are specific to this population [5,9,10]. Furthermore, transgender women face discrimination and social/economic marginalization more intense and deleterious than that experienced by lesbian, gay, or bisexual individuals [4], further worsening expected health outcomes [11-13].

Although HIV surveillance data are often not collected for transgender persons in the United States [14], meta-analytic and aggregated jurisdictional data suggest that HIV prevalence rates among transgender women are an order of magnitude higher than the US general population (18.4%-30.6% [7,15] vs 0.3%-0.4% [16]), with the odds of becoming HIV-positive estimated to be 34.2 times higher for transgender women than other US adult populations [15]. Within Los Angeles county (LAC), there is a stark disparity such that transgender women exhibit the second highest estimated HIV prevalence rate of any priority group (16.7%), marginally lower than the prevalence for men who have sex with men (MSM) (18.4%) [17]. A community-based convenience sample of transgender women in LAC evidenced an increase in self-reported HIV prevalence of close to 60% over a 17-year period, from 22% in 1998-1999 to 35% in 2015-2016 [18]. Although transgender women make up only 0.1% of the general population in LAC, they represent 1.3% of all people living with HIV (PLWH) and 1.4% of recent diagnoses from 2009 to 2013 [19]. A study found that more than half of the respondents reported recent homelessness, less than a third were employed, more than two-thirds reported doing sex work in the past 3 months, 85% reported HIV transmission risk behaviors, and 20% were HIV-positive [20]. As a result, transgender women have a nearly 7 times higher likelihood in delaying medical care after an HIV-positive diagnosis than cisgender women [21]. Multilayered stigma, accompanied by an inability to pay for care and misinformation about both the need for antiretroviral therapy (ART) and/or the existence of ART/hormone therapy interactions, often contributes to low linkage to and retention in care outcomes among young transgender women [22,23].

With the high HIV prevalence rate among transgender women, it is necessary to develop interventions to improve linkage to ART and address the multitude of barriers experienced by transgender women to enhance their retention in HIV care. A potential solution to improve adherence and retention among transgender women is through mobile phone text messages. Several studies have found success in improving health services

and outcomes through the use of text message interventions with PLWH [24-28]. In 2014, internet and mobile phone use among people in the United States aged 12 to 29 years was over 90% [29]. Unlike internet-based social media platforms, text messaging is easily accessible, private, portable, inexpensive, and used daily by nearly all the youth and the young adults in the United States, including the most vulnerable transgender women [30-32]. Text messaging is an appropriate modality for reaching young transgender women because this population regularly uses text messaging and social media platforms to gain positive perspectives on their gender identity, develop Web-based communities, gather health information, purchase gender-confirmation hormones, and acquire sex partners [33-36].

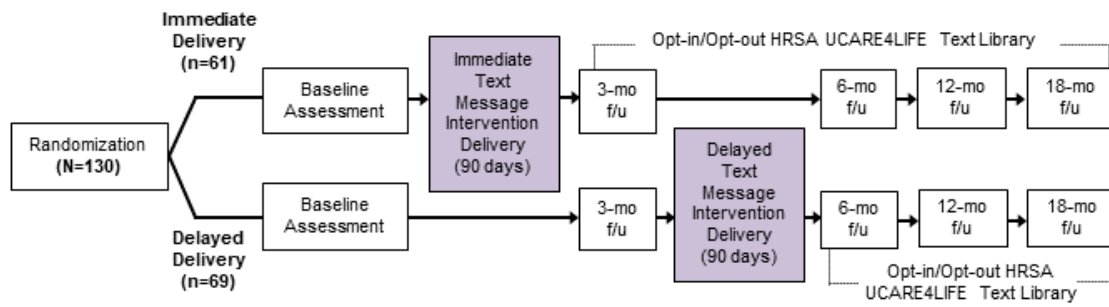
In regard to HIV care, a study with PLWH found that a personalized daily text message reminder improved participants' adherence to ART compared with those who received a beeper reminder [24]. Likewise, in another trial, youth living with HIV who had poor adherence reported better self-management of their HIV medication after 3 months when receiving culturally relevant and motivational daily text messages [27]. Given the rapid increase of mobile phone use and its accessibility to transgender women, it is important to understand the significance of text message use in facilitating HIV care among this high-risk population. Therefore, the purpose of this study was to determine whether providing culturally responsive text messages that promote healthy living and linkage, retention, and adherence may help young transgender women living with HIV in LAC be successfully linked and retained in HIV care with the ultimate goal of viral suppression.

Methods**Study Design**

Text Me, Girl! was a randomized controlled trial to assess the impact of a 90-day theory-based, transspecific, text-messaging intervention designed to improve health outcomes along the HIV care continuum, with the desired outcome of viral suppression among HIV-positive young transgender women (Figure 1). The HIV care continuum is a model used to identify gaps in HIV services and develop strategies to improve engagement in care among PLWH. The HIV care continuum outlines sequential stages as follows: diagnosis of HIV infection, linkage to care, retention to care, adherence to ART therapy, and achievement of viral suppression [37]. All study procedures were approved by the Friends Research Institute (FRI) Institutional Review Board and the Western Institutional Review Board.

During the 90-day intervention period, participants received 3 scripted, theory-based, transspecific text messages per day (270 text messages total), which were targeted, tailored, and personalized. The *Text Me, Girl!* text message library was adapted from a larger library of 616 messages originally developed for a study with methamphetamine-using MSM [38].

Figure 1. *Text Me, Girl!* study design. f/u: follow-up; HRSA: Health Resources and Services Administration; mo: month.



Only the messages related to the HIV care continuum were modified: (1) HIV positivity/physical and emotional health, (2) linkage/retention in HIV care, and (3) ART medication adherence/viral load suppression. The text message library was tailored specifically to the needs of young transgender women living with HIV in terms of verbiage and content. The text message library was personalized in that participants could customize their 10-hour delivery timeframe, that is, intervention time period, and could personalize their delivery platform to their mobile phone or an email inbox. Several iterations occurred; the first level of modifications was made with 4 young adult transgender service providers who were given the original text-message library to adapt for young adult transgender women living with HIV. Following several revisions, the library was brought before the transspecific Community Advisory Board for the second level of modifications. The Community Advisory Board is multicultural and comprised both transgender women living with HIV and HIV-negative transgender women, program consumers, gatekeepers and stakeholders, service providers from local community-based organizations that provide services to transgender women, and members of local community planning and advocacy groups (eg, LAC Commission on HIV, Transgender Service Providers Network, and Transgender Task Force). The Community Advisory Board members reviewed and discussed every message in detail. Following the adaptation into a culturally responsive text-message library for young adult transgender women living with HIV, the research team reviewed each message and, if necessary, made minor modifications to ensure that each message had a theoretical foundation.

Text messages were based on, and equally distributed across, 3 behavioral theories: social support theory [39,40], social cognitive theory [41,42], and health belief model [43]. Social support theory encompasses instrumental, emotional, and

informational supports, which have been shown to reduce stress and improve health outcomes [40,44,45]. Social cognitive theory serves to increase individuals' self-efficacy and help develop self-regulation skills [42,46]. As low self-esteem has been associated with increased HIV risk among gender/sexual minority populations [47], increased self-esteem can serve to optimize HIV care outcomes. Health belief model states that threats to health can increase one's likelihood of engaging in protective health behaviors [43]. Table 1 illustrates how the text message library was developed to have both a theoretical foundation and be transgenderculturally responsive.

Text messages were transmitted through gradual automation administration every day including weekends, in real time, within a 10-hour period. The automated text message delivery system was developed specifically for this study by Qualtrics, a digital survey development and administration company. Thus, participants received a text message every 5 hours (eg, at 12:00 pm, at 5:00 pm, and at 10:00 am). Each text message was unique, so participants did not receive the same scripted text message twice. The intervention was designed to be cost-efficient, sustainable, and easily scaled by community agencies throughout the United States.

Ethical Approval

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.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Table 1. Sample *Text Me, Girl!* theory-based and transspecific text message library.

HIV care continuum	General message	Transspecific message	Theoretical foundation
HIV positivity/physical and emotional health	Take care of yourself.	Trans pride is taking care of yourself.	Social support theory
Linkage/retention in HIV care	See your doctor.	Protect your trans beautiful body, see your doctor.	Health belief model
Antiretroviral therapy medication adherence	Take your meds.	Take your meds, girl! You can do it!	Social cognitive theory

Sample

The study inclusion criteria were as follows: gender identity as a woman, assigned a biological sex of male at birth, aged between 18 and 34 years, confirmed HIV-positive serostatus, ability to receive daily text messages on either a personal mobile phone or via an email account, tested HIV positive for the first time within the last 12 months or had not had an HIV care visit in the previous 6 months or had a viral load of ≥ 200 copies/mL on her last lab test result or not currently prescribed ART medication or was currently prescribed ART medication but did not rate her ability to take all her medications as excellent, willing and able to provide informed consent, and willing and able to comply with study requirements. Individuals were excluded if they did not meet all the eligibility criteria.

Study Procedures

Recruitment

A total of 6 recruitment strategies were utilized to ensure enrollment targets were met and a diversity of participants were enrolled to foster a diverse range of sociodemographic characteristics: (1) Web-based banner ads and digital flyers placed through geo-mapping (ie, the ads only displayed in areas where study recruitment was possible) on websites and social media sites that target transgender women, (2) ads placed in print media and via an email blast for transgender women or that transgender women read; (3) street- and venue-based outreach by 2 research assistants (RAs) utilizing a modified semistructured time-space sampling methodology (ie, no sampling frame was created for random selection and sites and times were rotated on a schedule based on known migration tendencies in the community) at locations where young transgender women congregate, such as boutiques, parks, street corners, bars, clubs, hotels, nail and hair shops, and cruising boulevards, (4) study posters placed at collaborating community-based organizations containing details about how to contact an RA for further information regarding the study, (5) in-services at collaborating community-based organizations and other programs on site, and (6) participant referrals. The RAs were trained on appropriate outreach strategies and confidential screening.

Enrollment

At the enrollment session, potential participants were screened for eligibility, completed the informed consent process, and were administered a baseline assessment that took approximately 90 min. RAs administered screeners using computer tablets and assessments via audio computer-assisted self-interview (ACASI) to maximize accurate disclosure of high-risk and sensitive behaviors. Questionnaire Development System software was used to implement the ACASI. At the completion of the visit, an RA oriented the participant on how to maintain confidentiality and privacy on mobile devices with respect to the intervention. Participants were shown how to lock their phone, establish and use a pin code to password protect their phone or email account, and were instructed to periodically delete the intervention text messages.

Random Assignment

After completing the baseline assessment, participants were assigned to a condition through an urn randomization procedure. The urn randomization procedure provided balance across age (18-24 and 25-34 years), race/ethnicity (Latino/Hispanic and all other race/ethnicities), and HIV care continuum status (linked, nonlinked to HIV care). Participants were randomized into 1 of the 2 conditions: Group A—immediate text message intervention delivery (n=61) or Group B—delayed text message intervention delivery (n=69) whereby participants were delivered the text-messaging intervention after a 90-day delay period. Both groups received the same 90-day text-messaging intervention. The randomized 2-group repeated measures design assessed participants at 3, 6, 12, and 18 months post randomization.

Postintervention Opt-In/Opt-Out Retention and Engagement Text Messages

Immediately following the 90-day text-messaging intervention, participants were offered an opportunity to opt in to receive additional weekly text messages at a reduced schedule through their final distal follow-up evaluation. Participants in both study conditions could opt to receive the postintervention messages. Postintervention retention/engagement messages comprised 2 topic areas: (1) linkage/retention support (ie, participant received a message about linking/remaining in HIV care) and (2) ART adherence reminders (ie, participant received a message about the importance of medication adherence); a participant could opt in to any one or both of the topic areas. Each of the 2 topic areas were transmitted once a week for a maximum of 2 weekly messages. Postintervention retention/engagement messages were derived directly from the text messages already available through the Health Resources and Services Administration (HRSA)–funded UCARE4LIFE library. At each follow-up visit, participants were asked if they wanted to opt in/out to receive these additional retention/engagement text messages and were informed that they could stop the additional messages at any time by texting back *stop* to the system.

Incentive Schedule

Incentives comprised the following: (1) incentives for admission procedures (US \$50 gift card), (2) incentives for completing follow-up assessments (US \$50 gift card for completing the 3-month follow-up assessment, a bonus of US \$20 for completing the 3-month follow-up assessment within an average of 5 days of the exact 3-month date, a US \$50 gift card for completing the 6- and 12-month follow-up assessments, and a US \$100 gift card for completing the 18-month follow-up assessment), and (3) a small gift (eg, make-up, earrings; valued at approximately US \$2) when an active participant brought a potential participant to the site, and a US \$20 gift card if the potential participant was eligible and enrolled (maximum of 3 eligible and enrolled participants per active participant). The total amount a participant could earn for enrolling and participating in the study was US \$380.

Evaluation Procedures

The evaluation plan for *Text Me, Girl!* was 2-fold, with both a cross-site and a local evaluation. Under the sponsorship of the

HRSA Special Projects of National Significance (SPNS) Social Media Initiative, the Evaluation and Technical Assistance Center (ETAC) at University of California, Los Angeles, was responsible for providing technical assistance and capacity building to the local demonstration sites on clinical and program activities and leading the cross-site evaluation. The cross-site evaluation included both a behavioral and clinical assessment. The clinical assessments were carried out by a medical care provider at one of the collaborating HIV medical care clinics. Once data were collected and abstracted by the HIV medical care provider, FRI submitted the data to ETAC via a Web-based system called the ETAC Social Media Project Portal.

For the local evaluation component, the outcomes were selected based on HRSA priorities and the Los Angeles Enhanced Comprehensive HIV Prevention Plan [17]. *Text Me, Girl!* collected and reported on the required performance measures, including program-specific and required ETAC data at baseline and at follow-up data visits administered at 3 months post enrollment, and approximately 6, 12, and 18 months post enrollment. The project director, research coordinator/evaluator, and RAs were trained in administration of the assessments and on the procedures to be used for data submission to HRSA.

In addition to the local and cross-site assessments, process evaluation and study monitoring were also carried out as part of the overall evaluation of *Text Me, Girl!*. Process evaluation procedures included the following: (1) formative evaluation of the study to update and refine study components that were responsive to the needs of young HIV-positive transgender women, (2) process monitoring of the delivery of the study, and, (3) process evaluation of successful linkage, engagement, and retention among participants. An intervention exposure (IE) question was administered as part of the reporting protocol. Using the study mobile phone, an RA sent a monthly IE text message to each participant on a Wednesday afternoon between 3:00 pm and 7:00 pm. The IE text message was as follows: "In the past month, how many of the text messages did you read? Please text back one of the following: 1) none, 2) some but less than half, 3) about half, 4) a lot but not all, or 5) all."

Outcome data were generated through 2 mechanisms: (1) assessments performed onsite at baseline and at 3, 6, 12, and 18 months post baseline and (2) electronic medical record (EMR)/electronic health record (EHR) data abstraction. In each case, data were imported from delimited text format (ie, .csv, the native format for the cloud-based data storage, scanned paper assessments, and extracted EMR/EHR data) into Stata v13SE (StataCorp).

Measures

All primary outcomes came directly from the US Health and Human Services (HHS) Common HIV Indicators for the HRSA/SPNS project (FOA HRSA-15-029). Utilization of these collection procedures provided data that could be compared with other clinical services and programs serving high-risk populations and populations that are underrepresented in HIV care. As the ETAC cross-site evaluation procedures and measures are described in detail elsewhere [48], only the local evaluation measures are described below.

Local Evaluation for Text Me, Girl! Only

The Local Evaluation was a behavioral assessment that included questions in the following domains: gender identity and presentation including hormone use, sexually transmitted infections, sexual behaviors, and HIV self-efficacy. The assessment measures that were used as part of the local (not cross-site) evaluation component of *Text Me, Girl!* are described below.

HIV Health Assessment

Originally developed by the principal investigator (PI) CJR, for an intensive prevention case management intervention, this instrument records demographics (eg, sexual identity, age, and racial/ethnic identities), educational attainment, housing status, access to insurance, HIV treatment status (including position in the HIV care continuum), HIV medication status (including medication type and dose) and self-reported ART adherence, and barriers to receiving HIV care [49]. Only the domains specific to the outcome measurements of this study that did not duplicate the ETAC cross-site evaluation were used.

The Los Angeles Transgender Health Survey

This instrument was developed by CJR and colleagues in 1997 in consultation with members of the LAC transgender women communities and appropriately updated in the interim years. The instrument comprises 7 modules: screening, sociodemographic characteristics, health care access and medical history, sexual behaviors (at all stages of gender transition and gender confirmation surgery), drug and alcohol use, legal and psychosocial issues, and HIV prevention [50]. Only the domains specific to the outcome measurements of this study and those that did not duplicate the HIV health assessment or the ETAC cross-site evaluation were used.

HIV Treatment Adherence Self-Efficacy Scale

The HIV treatment adherence self-efficacy scale (HIV-ASES) comprises 12 items assessing participants' self-efficacy to adhere to their ART medication regimen (0=cannot do it at all to 10=completely certain can do). Cronbach alpha for the measure is robust (routinely >.90). The HIV-ASES is lightly adapted to the target populations' lower average literacy level and refers specifically to participants' level of confidence that they can maintain adherence. The scale assessed how confident participants were to integrate treatment into daily routines, stick to a treatment plan even if it was disruptive or they felt unwell, continue treatment plan even if the level of T cells drops significantly, and get something positive out of participation in treatment even if the medication did not seem to improve their health [51].

Statistical Analyses

Table 2 provides all evaluation outcomes and their chosen measurement models. Power calculations are based on assumptions of alpha=.05 (2-tailed tests), a sample size of 130 HIV-positive young transgender women, and a power standard of 0.80. It was calculated that logistic regression analyses of primary outcomes would be able to find a minimum detectable odds ratio of 2.98 for linkage/uptake of ART and achievement of an undetectable viral load (the primary outcomes of interest).

Table 2. Study outcomes and measurement models.

Primary outcome	Measurement model
Linkage to HIV primary care (self-report and EMR ^a /EHR ^b abstraction)	0= Participant did not attend HIV medical visit within 3 months of enrollment; 1= Participant attended within the first 3 months
Prescribed ART ^c medication (self-report and EMR/EHR abstraction)	0=Participant is not prescribed HIV medication; 1=Participant is prescribed HIV medication
Retention in HIV primary care (self-report and EMR/EHR abstraction)	0=Participant did not attend a second HIV care appointment after the initial 3 months; 1=Participant attended an additional HIV primary care visit after the initial 3 months
ART adherence (self-report)	Ordinal scale (Likert)
Viral load monitoring (self-report and EMR/EHR abstraction)	Binary (0=>200 copies/mL, 1=<200 copies/mL)

^aEMR: electronic medical report.

^bEHR: electronic health report.

^cART: antiretroviral therapy.

All regression analyses assess assumptions of normality and model fit. In addition to the primary outcomes listed in Table 2, participants were assessed for changes in their HIV-related self-efficacy from baseline to follow-up evaluations. The HIV-ASES scale was used to assess HIV self-efficacy, producing continuous values suitable for ordinary least squares (OLS) regression. In addition, if during implementation, a sufficient number of participants opted in to receive one or more of the postintervention retention/engagement text messages available through final distal follow-up evaluation, additional analyses were carried out to estimate the observed effect(s) of receiving these postintervention text messages.

All calculations of detectable effects for primary outcomes were based on expected cultural/demographic subgroup analyses premised on known social determinants of risk (eg, racial/ethnic identity, language and health insurance) and are displayed in Table 2. Secondary analyses related to HIV self-efficacy were analyzed using OLS regression and should produce detectable effects at $f^2=0.067$. Given these values, detectable effects of all analyses should, if benchmarked, fall in the *small to moderate* ranges. Given an expected follow-up rate of at least 85% (111/130) at each time point, associations between primary outcomes and optional postintervention retention/engagement messages should produce minimum detectable effects exhibiting a 3% (repeated measures survival analysis testing time-based dichotomous outcomes, eg, linkage) to 18% (OLS regression for secondary analyses, eg, HIV-related self-efficacy scores) increase in detectable effect size (ie, outcomes will be more difficult to detect), resultant from participant attrition.

Primary outcome analyses comprised bivariate contrasts of outcomes over time (ie, HIV care continuum outcomes at baseline and each follow-up, with differences tested via *t* test and chi-square analyses) and multivariate analyses of these same

outcomes regressed on random study arm assignment, self-reported exposure to theory-based text messages, and time. Observations were nested within participants, and sociodemographic controls were tested for inclusion during sensitivity testing of the models. Secondary outcomes included sexual risk behaviors, substance use, self-efficacy, and changes in gender identity over time.

Results

Recruitment began on November 18, 2016, and the first participant was enrolled on December 16, 2016; enrollment closed on May 31, 2018. Intervention delivery ended on November 30, 2018, and follow-up evaluations will conclude on August 31, 2019. Primary outcome analyses will begin immediately following the conclusion of the follow-up evaluations.

Discussion

Text Me, Girl! was designed to meet the needs of underserved young transgender women living with HIV/AIDS. Young transgender women living with HIV experience a range of barriers that challenge their ability to be successfully linked and retained in HIV care. Text messaging is a communication platform well suited for engaging young transgender women in HIV care because it is easily accessible, widely used, private, portable, and inexpensive. *Text Me, Girl!* aimed to improve HIV care continuum outcomes among young transgender women by providing culturally responsive text messages to promote linkage, retention, and adherence, with the ultimate goal of achieving viral suppression. The *Text Me, Girl!* text message library is readily scalable and, if successful, can be adapted for application with other hard-to-reach populations.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report from the Health Resources and Services Administration.

[[PDF File \(Adobe PDF File\), 87KB - researchprotocols_v8i7e12837_fig.pdf](#)]

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Abbreviations

- ACASI:** audio computer-assisted self-interview
- ART:** antiretroviral therapy
- EHR:** electronic health record
- EMR:** electronic medical record
- ETAC:** Evaluation and Technical Assistance Center
- FRI:** Friends Research Institute
- HHS:** Health and Human Services
- HIV-ASES:** HIV Treatment Adherence Self-Efficacy Scale
- HRSA:** Health Resources and Services Administration
- IE:** intervention exposure
- LAC:** Los Angeles county
- OLS:** ordinary least squares
- PI:** principal investigator
- PLWH:** people living with HIV
- RA:** research assistant
- SPNS:** Special Projects of National Significance

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Protocol

Text Message Reminders and Unconditional Monetary Incentives to Improve Measles Vaccination in Western Kenya: Study Protocol for the Mobile and Scalable Innovations for Measles Immunization Randomized Controlled Trial

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Abstract

Background: Globally, 21 million children do not receive the measles vaccine each year. With high levels of mobile phone access and ownership, opportunities exist to leverage mobile health technologies to generate demand for immunization.

Objective: The aim of the Mobile and Scalable Innovations for Measles Immunization trial is to determine if text message (short message service, SMS) reminders, either with or without mobile phone-based incentives, can improve measles immunization coverage and timeliness in rural western Kenya.

Methods: This is a 3-arm, parallel, randomized controlled trial (RCT). Using simple randomization, caregivers in Siaya County, Kenya, will be randomized and evenly allocated to 1 of 3 study arms: (1) control, (2) SMS reminders only, and (3) SMS reminders plus a 150 Kenyan Shilling (KES) incentive. Participants assigned to the SMS group will be sent SMS reminders 3 days before and on the day before the measles immunization visit scheduled for when the child is 9 months of age. Participants in the incentive arm will, in addition to SMS reminders as above, be sent an unconditional 150 KES mobile-money incentive to their mobile phone 3 days before the child becomes 9 months of age. Children will be followed up to the age of 12 months to assess the primary outcome, a measles vaccination by 10 months of age. Log-binomial regressions will be used to calculate relative risks.

Results: Enrollment was completed in March 2017. We enrolled 537 caregivers and their infants into the following groups: control (n=179), SMS reminders only (n=179), and SMS reminders plus 150 KES (n=179). Results will be made publicly available in 2020.

Conclusions: Few RCTs have examined the effect of text message reminders to improve measles immunization coverage. This is the first study to assess the effect of SMS reminders with and without unconditionally provided mobile-money incentives to improve measles immunization coverage.

Trial Registration: ClinicalTrials.gov NCT02904642; <https://clinicaltrials.gov/ct2/show/NCT02904642> (Archived by WebCite® at <http://www.webcitation.org/78r7AzD2X>).

International Registered Report Identifier (IRRID): RR1-10.2196/13221

(*JMIR Res Protoc* 2019;8(7):e13221) doi:[10.2196/13221](https://doi.org/10.2196/13221)

KEYWORDS

measles vaccine; text messaging; Kenya; vaccination coverage

Introduction

Background

In 2017, 20.8 million age-eligible children worldwide did not receive measles-containing vaccine [1]. Measles is a highly contagious virus, which is evident from measles outbreaks occurring in populations comprising as little as 10% susceptible, or immunologically unprotected, individuals [2]. Given that every year immunization programs are estimated to save over 3 million lives globally [3], innovative interventions that are easily scaled and that target hard-to-reach and underimmunized populations are needed.

Mobile phone technologies and tools, broadly referred to as mobile health, have been used successfully for a variety of public health problems [4,5] and to strengthen and improve health systems [6,7]. The Classification of Digital Health Interventions, released by the World Health Organization in 2018, categorizes digital health interventions by the health systems challenges they address [8]. As mobile phone ownership and access levels continue to rise in lower income countries [9], digital health solutions that address demand-side deficiencies in immunization services become more realistic.

Short message service (SMS), or *text message*, reminders and incentives are 2 of the more common interventions that have been used to generate demand for immunization services [10,11]. Text message reminders have been shown to modestly improve immunization uptake in studies in the United States and other high-income countries [12]; although their evidence to improve uptake in low- and middle-income countries (LMICs) is limited. [13].

With regard to incentives, at least 4 studies have evaluated the impact of small monetary and nonmonetary incentives, such as coupons and food, on vaccination in LMICs. Studies in India [14], Kenya [15-17], and Pakistan [18] found that monetary and nonmonetary incentives have the potential to improve vaccination coverage and also suggest that incentive-based interventions have the potential to affect hard-to-reach populations. Moreover, all of the identified studies provided a conditional incentive, where the caregiver was only given the incentive if the child was vaccinated. To our knowledge, no studies have provided unconditional incentives for vaccination.

This study builds on the success of the recently completed Mobile Solutions for Immunization (M-SIMU) cluster randomized controlled trial (RCT). The M-SIMU trial found that providing a 200 Kenyan Shilling (KES) mobile-money incentive, or approximately US \$2.50 at the time of the study, conditionally to caregivers who vaccinated their child within 2 weeks of the Expanded Program on Immunizations (EPI) due date significantly improved the proportion of fully immunized children and measles vaccination coverage measured at 12 months [15,19]. A conditional incentive approach may be difficult to scale because it requires staff at the clinic to document immunization and to calculate whether the

immunization was received in time. Additionally, unconditional incentives may be more effective at increasing the intended health outcome if the transferred money is used to offset incurred travel costs, rather than receiving the money after visiting the health facility, as in a conditional approach.

Objective

To counter these logistical and implementation challenges and to facilitate their scalability, the Mobile and Scalable Innovations for Measles Immunizations (M-SIMI) RCT seeks to evaluate the impact of providing rural Kenyan caregivers SMS reminders and unconditional monetary incentives on measles immunization coverage at 10 months of age.

Methods

Study Design

The M-SIMI study is an individually randomized, parallel, controlled trial (Figure 1). Caregivers will be randomized into 1 of 3 study arms using a 1:1:1 allocation ratio. The study arms include (1) control, (2) text message reminders only (SMS only), and (3) text message reminders plus a 150 KES incentive (SMS plus 150 KES); where 100 KES=US \$1 as of June 2016. Participants randomized to the intervention arms will be sent 2 SMS reminders—3 days and 1 day before measles immunization visits scheduled at 9 months of age. Incentives will be unconditionally sent to the participant's mobile phone 3 days before the measles vaccination due date at 9 months of age. The trial is registered with ClinicalTrials.gov (NCT02904642; September 2016).

Setting and Participants

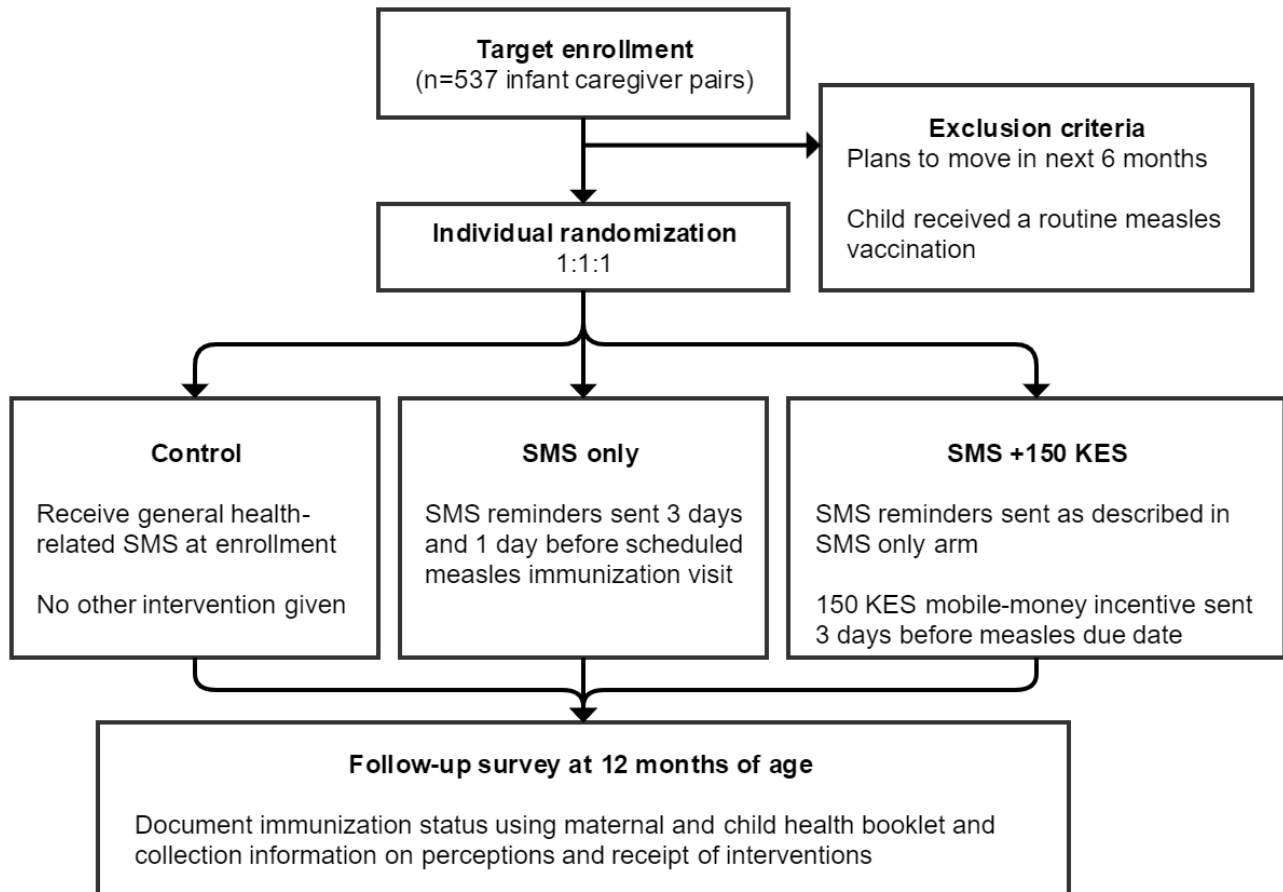
The M-SIMI study will take place within the boundaries of the Kenya Medical Research Institute (KEMRI) and the Centers for Disease Control and Prevention (CDC) Health and Demographic Surveillance System (HDSS) in Siaya County, Kenya. The rural study site has high levels of malaria, tuberculosis, and HIV transmission [20]; the majority of residents are subsistence farmers; and approximately 50% of caregivers own a mobile phone [21]. Data from the control arm of our previously conducted RCT found that 98% and 51% of children received pentavalent and measles vaccination by the age of 12 months, respectively [15].

The HDSS has served as a platform for numerous studies, including the M-SIMU trial, which provided text message reminders and conditional mobile-money incentives for pentavalent and measles vaccinations [15]. Potential caregivers and their children will be identified by community health workers (CHWs). CHWs are a component of Kenya's national community health strategy and typically have a catchment area of 1 village, where the CHW visits each household at least once a month to provide minimal health services and education. Community interviewers (CIs) hired by the project will approach CHW-identified caregivers to describe the study and screen caregivers for their eligibility on the following criteria (see Textbox 1).

Caregivers will be enrolled into the study independent of mobile phone ownership. Caregivers only need to have access to a mobile phone, where access will be defined by the participant. If a caregiver cannot identify an accessible mobile phone, CIs

will relay text message reminders and incentives to the participant. Caregivers will neither be provided a mobile phone nor airtime.

Figure 1. Consolidated Standards of Reporting Trials diagram of study design. SMS: short message service; KES: Kenyan Shilling.



Textbox 1. The Mobile and Scalable Innovations for Measles Immunizations screening criteria.

Inclusion criteria:

- Caregiver of infant aged 6 to 8 months at the time of enrollment
- Self-reported resident of one of the study villages
- Willing to sign informed consent for the study

Exclusion criteria:

- Child of enrolled caregiver has already received 1 dose of measles vaccine, not including any supplemental measles vaccines
- Caregiver plans to move away in the next 6 months

Procedures

Enrollment

During their monthly visit, CHWs will identify households with children aged 6 to 8 months. CHWs will approach caregivers of age-eligible children, provide a brief explanation of the study, and answer any questions the caregiver might have. The CHWs will call the field supervisor to notify the study team that they have identified a child aged 6 to 8 months. The field supervisor will then assign a CI to visit the child's compound to explain

the trial and screen the caregiver for the eligibility criteria as described above.

Eligible caregivers will be required to provide written informed consent to the CI. Upon obtaining written informed consent, the CI will send an enrollment SMS to the RapidSMS server, a free and open-source platform. The enrollment SMS is structured and requires the CI to enter the study identification number, the phone number that can be used to receive text message reminders, the child's date of birth, the preferred language to receive reminders, the child's first and last name, and the study arm. If the CI sends an incorrectly formatted SMS,

he or she will receive an error SMS, which asks the CI to correct the SMS. The RapidSMS server will then send a personalized text message to the newly enrolled caregiver that welcomes him or her to the study (Table 1). The CI will confirm receipt of the enrollment SMS.

Control Arm

Aside from the welcome text message received at the enrollment visit, no additional text messages or incentives will be sent to caregivers randomized to the control arm.

Intervention Arms

The interventions, text message reminders, and unconditional incentives are designed to motivate caregivers and increase demand for measles vaccination. At enrollment, participants who were randomized to an intervention arm will be told to expect 2 text message reminders for measles vaccine; first, at 3 days before and, second, on the day before the scheduled visit for measles vaccination at 9 months of age. At most, enrolled caregivers will receive 3 text messages (2 for the measles vaccine and 1 for welcoming the caregiver to the study). Text messages will be sent in English, Kiswahili, or Dholuo language, according to the caregiver's preference.

Caregivers randomized to the incentive study arm will, in addition to being told about SMS reminders as described above, be informed of the measles vaccine due date and that the project will send a 150 KES incentive 3 days before the child turns 9 months (ie, sent on the same day as the first SMS reminder). Caregivers will receive this one-time mobile-money incentive unconditionally. The incentive is intended to subsidize the cost of transportation to the health facility. The transaction costs

associated with mobile-money transactions will be borne by the study such that caregivers will receive the full 150 KES. The incentive amount was informed by results of the M-SIMU trial [15].

Randomization

Caregivers will be evenly randomized (1:1:1) to 1 of 3 study arms. A computer will randomly allocate the study arm to 537 unique study identification numbers. The study identification numbers will be divided into 5 groups (for each of the 5 CIs who will enroll caregivers) and labeled A to E. Each group will contain 109 study identification numbers, labeled 1 to 109. For example, group A will have study IDs labeled 001A through 109A, group B will have study IDs labeled 001B through 109B, etc. The allocation code will be saved on the data manager's computer. The allocation will be printed on a small card and placed in an opaque envelope by the data analyst. The envelopes will be sealed and stamped to ensure that they cannot be tampered with. Biweekly, the study coordinator will deliver the sealed envelopes to the field supervisor who will then distribute them to the CIs.

CHWs will identify eligible caregiver-infant pairs and place a phone call to the field supervisor to provide information on the location of the child. The field supervisor will notify CIs who will then approach caregivers of age-eligible children to conduct a screening for further eligibility requirements and to obtain informed consent. If the caregiver is eligible for the study and decides to participate, the CI will open the envelope containing the study arm and read the appropriate informed consent form to the caregiver.

Table 1. Content of text messages sent to caregivers' mobile phones.

Message type	Message timing	Arm 1: control	Arm 2: SMS ^a only	Arm 3: SMS+150 Kenyan Shilling
Enrollment message	Enrollment	Thank you for enrolling Baby <BABY'S FIRST NAME> in M-SIMI ^b study. The greatest wealth is health. This study is sponsored by KEMRI ^c .	Thank you for enrolling your child in the KEMRI M-SIMI study. You will get SMS reminders for Baby <BABY'S FIRST NAME>'s measles vaccination. The greatest wealth is health.	Thank you for enrolling your child in the KEMRI M-SIMI study. You will get SMS reminders for Baby <BABY'S FIRST NAME>'s measles vaccination. The greatest wealth is health.
3 day reminder message	Date of birth + 9 months – 3 days	No message	Tell Mama <BABY'S FIRST NAME> that Measles vaccine is due this week. Most Gem babies get vaccinated, be one of them!	Tell Mama <BABY'S FIRST NAME> that Measles vaccine is due this week. We are sending 150ksh to assist with travel. Most Gem babies get vaccinated, be one of them!
1 day reminder message	Date of birth + 9 months – 1 day	No message	Tell Mama <Baby Fname> that Measles vaccine is due this week. Go to the clinic if you haven't already. Vaccines save Kenyan babies lives.	Tell Mama <Baby Fname> that Measles vaccine is due this week. Go to the clinic if you haven't already. Vaccines save Kenyan babies lives.

^aSMS: short message service.

^bM-SIMI: Mobile and Scalable Innovations for Measles Immunizations.

^cKEMRI: Kenya Medical Research Institute.

Due to the nature of the intervention, participants will not be blinded to the study arm. Additionally, because this trial is conducted to mimic circumstances of what a scaled reminder or travel subsidy program would look like, participants will be told which study arm they have been assigned to at enrollment. As an example, in a scaled program, caregivers would know that they would receive an incentive when their child reached the age of 9 months. Trained interviewers will not be blinded to study arm allocation because of the nature of the trial.

Data Collection

The enrollment survey, which will collect baseline health and sociodemographic data about the child, caregiver, and household, will be administered by CIs using a mobile phone equipped with Open Data Kit software. Specifically, we will collect information on the caregiver's phone ownership and usage and the caregiver's demographics including age, education, marital status, and literacy level, household assets, number and type of livestock owned, water source, type of cooking fuel used, and current occupation. When children reach 12 months of age, a CI will conduct a household visit to document measles immunization status. Caregivers will be asked to present their maternal and child health (MCH) booklet so that CIs can record a written immunization history of Bacillus Calmette–Guérin, pentavalent, polio, and measles vaccines. If the MCH booklet is unavailable, CIs will collect a verbal report of the child's immunizations. If the child is found to not be up to date with all vaccinations, the CI will refer the caregiver and infant to the nearest clinic, but the study will not pay for transport or health care costs. In addition to the immunization history, the follow-up survey will ask questions surrounding text message reminders and incentives, as applicable. Costs of the interventions (eg, SMS, mobile-money incentive and staff time) will be collected throughout the study for future cost-effective analyses.

Data will be stored in a secure database at KEMRI Center for Global Health Research (KEMRI/CGHR) in Kisian, Kenya. Photo identification and key cards are required to enter the data storage area. Only a limited number of authorized staff will have access to the data. Data will be deidentified for analysis and will only be shared with investigators of the study protocol. Caregivers will be assigned a study ID number in line with current HDSS operating procedures. Linkages with HDSS data will be made so that the CHW enrollment approach can be compared with existing HDSS population estimates.

Outcomes

The primary outcome is the proportion of children who received measles vaccination by 10 months of age. Measles vaccination at 12 months is a secondary outcome. Data for primary and secondary immunization outcomes will come from written immunization records found on the child's MCH booklet at household follow-up visits. If dates in MCH booklet are illegible, missing, or vaccination history was provided verbally, the health facility immunization registries will be searched to identify vaccines given. Data from our previous study conducted in the same setting indicated that over 95% of caregivers had an MCH booklet at 12 months of age [15].

Data Analysis

The analysis and reporting of results will be conducted in accordance with the Consolidated Standards of Reporting Trials [22]. A blinded statistician will conduct analyses for primary and secondary outcomes. The primary analyses will be conducted with intention-to-treat principles. The primary outcome, measles immunization at 10 months of age, will be defined as a binary variable. Log-binomial regressions to calculate risk ratios for achieving the primary outcome will be calculated for the intervention arms as compared with the control arm. As a secondary analysis of the primary outcome, time-to-immunization curves will be constructed using the Kaplan-Meier method, and study arms will be compared using the Cox model. The 25th, 50th, and 75th percentiles for time to measles immunization will also be calculated by the study arm. Effect estimates will be presented in whole and stratified on mobile phone ownership and clinic proximity. Mobile phone ownership will be defined as a binary variable (*owns a mobile phone* or *doesn't own a mobile phone*). Additional stratified estimates will be presented based on calculated risk factors for not receiving measles vaccine in control arm infants. Adjusted analyses will be conducted if our randomization produced imbalanced sociodemographic characteristics by the study arm. A per-protocol analysis of primary and secondary outcomes will also be conducted. Per-protocol delivery of the interventions will be defined as caregivers who were sent 2 text message reminders for measles vaccination in the 2 intervention arms and as caregivers who were sent an incentive in the third study arm.

Socioeconomic quintile scores will be calculated using a multiple correspondence analysis of household assets, livestock owned, water source, type of cooking fuel used, and occupation [23]. In villages where HDSS and CHWs are active, we will conduct a sensitivity and specificity analysis of our CHW approach to identify age-eligible children. The HDSS database, which relies on village reporters to enumerate the population, will be used as the gold standard. We will compare the costs of a CHW versus HDSS approach of identifying eligible children. An alpha of .05 will be assumed for all statistical tests of significance.

Sample Size

The primary objective is to assess the effect of the interventions on their ability to improve measles vaccination coverage by an absolute difference of 15 percentage points at 10 months of age as compared with the control arm (eg, 70% measles coverage in the control arm and 85% coverage in an intervention arm). This effect size was selected because it represents a meaningful public health impact and could motivate decision makers to adopt this intervention. Data for the sample size calculation come from the M-SIMU trial; where we found a measles vaccination coverage of 70% at 10 months of age in control arm children [15]. Assuming a 70% outcome in the control group, an absolute 15% difference in the primary outcome between control and intervention arms, a type 1 error (alpha) of .05 and a power (1-beta) of 0.80, we calculated that 134 caregivers are needed in each study arm. Adjusting our sample size for a 25% loss to follow-up (death, outmigration, verbal report of measles

vaccination at 10 months of age, and other reasons), our adjusted sample size is 179 participants per study arm, yielding a total sample size of 537 caregivers across the 3 study arms.

Ethical Considerations

This study protocol received ethical clearance from the Scientific Steering Committee, the KEMRI Scientific and Ethics Review Unit (SERU; KEMRI/SERU/CGHR/003/3311; [Multimedia Appendix 1](#)), and the Johns Hopkins University Bloomberg School of Public Health (deferred ethical clearance to KEMRI-ERC). All participants will provide written informed consent. If a participant is illiterate, consent forms will be administered and signed in front of an impartial witness. At the 12-month household visit, study staff will refer the caregivers of unvaccinated children to the nearest health facility that provides measles vaccination.

Results

M-SIMI completed enrollment in March of 2017. We met our sample size requirement and enrolled 537 caregivers and their infants into the following groups: control (n=179), SMS reminders only (n=179), and SMS reminders plus 150 KES (n=179). Results will be made publicly available in 2020.

Discussion

Differences Between Previous Studies

This proposed study differs from our previous cluster RCT, the M-SIMU study, in several ways [15,19]. First, M-SIMU enrolled infants younger than 5 weeks and provided reminders and incentives for the pentavalent vaccine series at 6, 10, and 14 weeks of age and for measles vaccine at 9 months of age. The significant effect of incentives on measles coverage may be due to caregivers previously receiving travel subsidies and reminders for the 3 pentavalent doses. Contrastingly, the M-SIMI study seeks to enroll caregivers of children aged 6 to 8 months and to provide reminders and unconditional travel subsidies only for measles vaccination.

A second difference, and perhaps a more important one, is that M-SIMU provided conditional incentives for vaccination, where the incentive was only given if the caregiver brought their child for vaccination within 2 weeks of the EPI due date. M-SIMU-employed health facility recorders were stationed at each clinic to confirm a timely vaccination. With busy clinic

workers, this conditional approach is difficult to scale because it requires staff at the clinic to document immunization and to calculate whether the immunization was received in time. To counter these logistical and implementation challenges, the M-SIMI trial will provide an incentive unconditionally, that is, the caregiver receives an incentive 3 days before the child's 9-month birthday and independent of whether the child has been vaccinated for measles.

A third difference between M-SIMU and M-SIMI is in the enrollment strategy. Where the M-SIMU trial employed KEMRI HDSS village reporters to identify births and deaths, this proposed study seeks to leverage CHWs, a component of Kenya's national community health strategy, to identify and enroll children into a travel subsidy scheme. Village reporters are a unique component of the HDSS, making the external generalizability of our results somewhat limited, whereas numerous countries have national CHWs.

Limitations

This study has several potential limitations. First, not all caregivers will provide written immunization records at the 12-month follow-up visit. Evidence from other settings implies that they may under or overestimate actual vaccination coverage [24-26]. It is likely that social desirability bias may lead those who received an incentive in this study to verbally report vaccination. At the same time, this bias may be minimal as the M-SIMU trial found that over 95% of caregivers had an MCH booklet at 12 months of age [15]. An additional limitation of this study is that the CIs who will collect measles vaccination status at the follow-up visit will also be responsible for assigning the study arm at enrollment (ie, not blinded to study arm allocation). To minimize the risk of outcome ascertainment bias, the follow-up questionnaire will be structured to collect vaccination data before any questions that identified the study arm allocation. For CIs to be biased when ascertaining vaccination status, they would have had to rely on their memory of the participant's study arm allocation during the enrollment visit, which was conducted 4 to 6 months before the follow-up visit.

We hypothesize that the interventions will improve measles vaccination coverage and that they will be effective in many of the traditionally hard-to-reach populations. By designing this study with scalability in mind, the results of this trial will hopefully approximate the effects of national or subnational programs.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Center Scientific Committee review comments.

[[PDF File \(Adobe PDF File\), 92KB - resprot_v8i7e13221_app1.pdf](#)]

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Abbreviations

CDC: Centers for Disease Control and Prevention

CHW: community health worker

CI: community interviewer

EPI: Expanded Program on Immunization

HDSS: Health and Demographic Surveillance System

KEMRI: Kenya Medical Research Institute

KES: Kenyan Shilling

LMICs: low- and middle-income countries

MCH: maternal and child health

M-SIMI: Mobile and Scalable Innovations for Measles Immunization

M-SIMU: Mobile Solutions for Immunization

RCT: randomized controlled trial

SMS: short message service

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Protocol

Acupuncture to Improve Symptoms for Stable Angina: Protocol for a Randomized Controlled Trial

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Abstract

Background: Acupuncture has demonstrated physiologic analgesic effects in Chinese patients with stable angina. One proposed mechanism of action for these analgesic effects is the downregulation of M1 macrophages, interleukin 1 beta, interleukin-6, interleukin-18, and tumor necrosis factor alpha.

Objective: This study aims to test a 10-session, 5-week acupuncture treatment protocol as a complementary therapy for symptoms of stable angina for American patients, who vary from Chinese patients in health care systems and other salient variables.

Methods: We are conducting a randomized controlled trial (RCT) of 69 adults (35 assigned to initial acupuncture and 34 to an attention control condition) with a medically confirmed diagnosis of stable angina, whose pain and associated symptoms have not been controlled to their satisfaction with guideline-directed medical management. Participants in the experimental group will receive a standardized traditional Chinese medicine point prescription. The attention control group will view non-pain-related health education videos over 5 weeks equal to the 10 hours of treatment for the acupuncture group. Participants will complete the McGill Pain Questionnaire and the Seattle Angina Questionnaire-7, as well as have inflammatory cytokines measured at baseline and study completion. The primary outcomes are anginal pain and quality of life.

Results: This study has been funded over 2 years by the National Institutes of Health, National Institute for Nursing Research. We are currently recruiting and expect to have initial results by December 2020.

Conclusions: We will generate data on feasibility, acceptability, effect sizes, and protocol revisions for a future fully powered RCT of the protocol. Findings will help determine if patients with persistent ischemic symptoms experience a proinflammatory state and hyperalgesia caused by multiple neural and immune processes not always relieved with medication.

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KEYWORDS

acupuncture; stable angina; ischemic heart disease; complementary medicine

Introduction

Background

The significance of managing the symptoms of stable angina is critical, given that stable angina increases the risk of acute coronary syndrome for women and mortality for men [1,2]. Camm et al [3] found that one-third of patients with stable angina have suboptimal management of their pain. Guideline-directed therapy for stable angina includes nitrates, beta-blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors [4]. These drugs can have side effects such as headache, flushing, fatigue, and cough, which can lead to nonadherence and reduced symptom control [5]. Acupuncture, if effective, may help control angina pain for patients nonadherent to medications because of debilitating side effects.

Acupuncture has demonstrated physiologic analgesic effects. It regulates the autonomic nervous system and reduces sympathetic stimulation to the heart and vasculature by modulating the midbrain, releasing endorphins and dynorphins, with a resultant decrease in production of norepinephrine and epinephrine [6-12]. These processes impact the cardiovascular system by reducing blood pressure, heart rate, and arrhythmias [13] centrally mediated in the brainstem [12]. Acupuncture may help relieve pain by activating mu opioid receptors, which decreases pain [6], increasing serum beta endorphins [7] and downregulating M1 macrophages, interleukin (IL) 1 beta, IL-6, IL-18, and tumor necrosis factor (TNF) alpha [14], which reduces inflammation [15]. The mechanism of action is stimulation of a neuronal circuit that detects inflammatory mediators and releases dopamine, inhibiting release of inflammatory cytokines [15]. No studies have directly examined the physiologic effects of acupuncture on the cardiovascular system for the treatment of angina.

In traditional Chinese medicine (TCM), *qi* is the vital energy flowing within and surrounding the body [16]. Disorders of *qi* or blood can result in pain, and *qi* can be deficient or in excess (stagnant or obstructed). The channels through which *qi* and blood flow in the body are called meridians [17]. Acupuncture needles are inserted into acupuncture points, which access the meridians and promote the circulation of *qi* and blood [18]. Deficient *qi* and/or blood is strengthened (tonified); excess *qi* and/or blood is moved to reduce stagnation or obstruction [19,20]. Thus, the body becomes balanced, and pain and other symptoms are reduced [18,19]. In the TCM model, it is theorized that the pain, shortness of breath, and fatigue of stable angina result when there is an excess or a deficiency in *qi* and/or blood in the meridians that flow through and around the heart [20-22].

Objectives

The scientific premise of our study is that patients with persistent ischemic symptoms experience a proinflammatory state and hyperalgesia caused by multiple neural and immune processes not always relieved with medication [15]. The aims of our study are to test the feasibility of a 10-session, 5-week acupuncture treatment protocol as a *complementary* therapy for symptoms of stable angina in *American* patients and to estimate effect sizes for change from pre- to postintervention scores for pain/symptoms, inflammatory cytokines, functional status, and health-related quality of life (HRQoL) between the acupuncture and control groups. We hypothesize that participants with stable angina will see a reduction in pain following acupuncture [8].

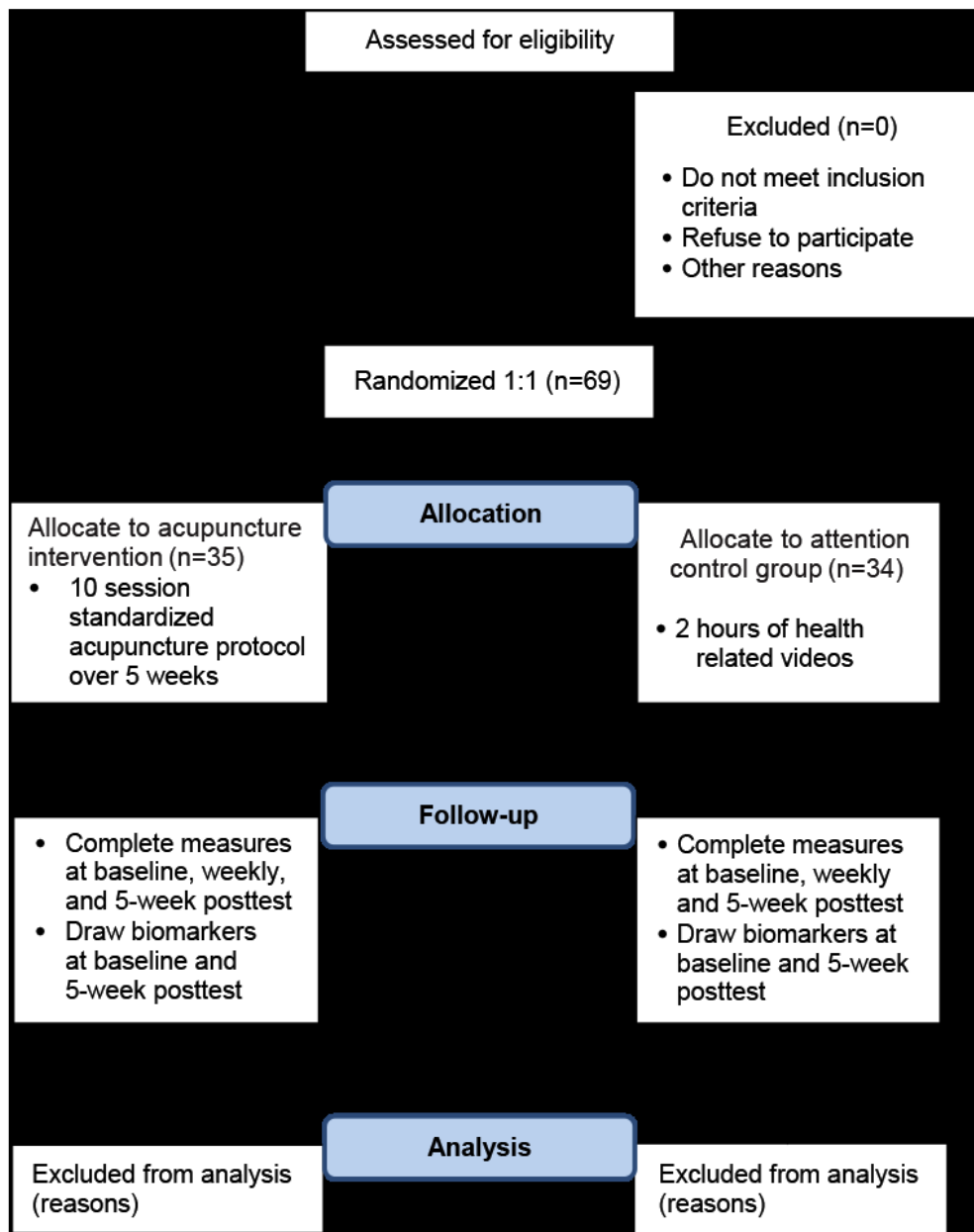
Methods

Study Design

This randomized attention-control feasibility study will be conducted at an academic medical center in the Midwest. This design will facilitate the calculation of effect sizes for within- and between-group differences in pain and symptoms. The design is more appropriate than either *placebo* or *sham* acupuncture interventions at this stage of investigation because the protocol has not been tested in an American population of patients with stable angina. A placebo control design is not possible because neither the clinician nor participant can be blinded to the acupuncture treatment without the use of double-blind acupuncture needles. Currently, double-blind needles are being produced by hand, tested in small studies, and are not yet commercially available [23,24]. Sham acupuncture, whereby needles are inserted into nonacupuncture points on the body, is inferior to randomized control trial (RCT) with attention control design because needle punctures anywhere on the skin may be considered an *ashi* point (ie, an active acupuncture point that may have therapeutic effects) [25,26]. Following consent and upon enrollment in the study, participants will be randomized 1:1 to the acupuncture or attention control group using a permuted block approach, stratified by biological sex. This study was approved by the University of Illinois at Chicago Institutional Review Board (UIC IRB).

Sample and Setting

A total of 69 patients with a confirmed diagnosis of stable angina will be included. Only those patients with Canadian Cardiovascular Society (CCS) class I to III will be included. By definition, CCS Grade IV (angina at rest for >20 min) is unstable angina [27], and these patients will not be recruited. We are recruiting participants from the University of Illinois Hospital in Chicago, Illinois. Participants are being recruited from the hospital, clinic, and through campus flyers (Figure 1).

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow chart.

The inclusion and exclusion criteria have been presented in [Textboxes 1-3](#). Participants will continue to take their prescribed medications as directed. The study will be conducted in clinical research exam rooms. Licensed acupuncturists will administer 10 acupuncture treatments to 35 participants in the experimental group (and up to 34 participants in the control group upon study

completion). We are using 7 acupuncturists to improve the likelihood that the protocol, and not the acupuncturist, is responsible for the therapeutic effects. All other therapeutic elements will be controlled through our standardized protocol. Acupuncturists will not discuss protocols with the participants.

Textbox 1. Screening tool—inclusion criteria.

1. Confirmed diagnosis of stable angina for at least 6 months (pain, pressure, or discomfort in the chest or other areas of the upper body)
2. Experiencing symptoms at least once per week
3. Canadian Cardiovascular Society angina class I, II, III
4. Age 21 years or older
5. Speak and read English

Textbox 2. Screening tool—exclusion criteria.

1. Physical or cognitive limitations that will prevent completion of study tasks (Mini-Cog score 0-2 with abnormal clock face);
2. Exacerbation of heart failure (B-type natriuretic peptide >500 or escalating dose of diuretic or admission to hospital for heart failure in past 3 months).
3. Autoimmune dysfunction (use of steroid or prescription anti-inflammatory medications)
4. Moderate to severe chronic obstructive pulmonary disease
 - Moderate (treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids)
 - Severe (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure
5. Pregnant
6. Use of prescription analgesic medications
7. Currently undergoing treatment with biofeedback, massage, or other acupuncture

Textbox 3. Screening tool—additional questions.

1. Study explained (purpose, rights of participants, informed consent, compensation for time)
2. Has clear understanding of study purpose and requirements
3. Agrees to participate?
4. Reason for declining?
5. If declined: age, sex, race

Measures**Demographic**

Personal demographic characteristics (age, race/ethnicity, marital status, education, income, employment, and insurance) will be measured.

McGill Pain Questionnaire

The McGill Pain Questionnaire (MPQ) measures the multidimensionality of pain in 4 domains: sensory (location, intensity, quality, and pattern), affective (anxiety, depression, and fear), evaluative (a comprehensive assessment of the pain), and behavioral (behaviors that worsen or lessen pain) [28]. Current, least, and worst pain in the past 24 hours are scored on a Likert-type scale with 0=no pain to 10=excruciating pain. The MPQ has been well validated in cardiac populations [29-32].

Upper Body Diagram

Everts et al's [33] upper body diagram consists of a drawing of the human chest with 9 distinct regions plus the neck, left and right arms, and abdomen. Participants are asked to mark the location of their pain on the diagram. The total pain sites are a location measure and will be used to calculate the multidimensionality of the participant's pain.

Seattle Angina Questionnaire-7

The Seattle Angina Questionnaire-7 (SAQ-7) consists of 7 items in 4 domains (physical limitation, angina stability, angina frequency, and quality of life) measuring the impact of angina on participants' health status. Item responses are coded sequentially from worst to best status and range from 1 to 6,

except quality of life (range 1-5). Scores are generated for each domain and are scaled 0 to 100, with 0 denoting the worst and 100, the best possible status [34]. The SAQ-7 has been validated among patients with stable ischemic heart disease, those undergoing coronary interventions, and after acute myocardial infarction [35].

American Heart Association Angina Log

My Angina Log is a simple 1-page diary used to measure each episode of angina. Participants record the date and times they experienced angina, as well as triggers and treatments [36]. Severity of symptoms are measured on a 1 to 4 scale, with 1 representing mild symptoms and 4 very severe symptoms.

Protocol Acceptability Scale for Treating Angina With Acupuncture

This satisfaction instrument is a 10-item instrument used to measure acceptability of the study processes and protocols. Items are measured on a 0 (negative response; ie, did not like acupuncture) to 2 (positive response) scale. The protocol will be deemed to have high acceptability if 80% of participants score ≥ 16 .

All data except for the American Heart Association (AHA) Angina log and the chest outline to draw angina pain will be collected via the Research and Electronic Data Capture (REDCap) application, which is a Web-based application for securely building and managing surveys and databases.

Biomarkers of Inflammation

Proinflammatory cytokines IL-1 beta, IL-2, IL-8, and IL-18; C-reactive protein (CRP) [37,38]; and TNF alpha, the anti-inflammatory cytokines IL-4 and IL-10 [37], and the dual

pro/anti-inflammatory IL-6 [39] will be measured to determine if there is a significant change from baseline to post study (5 week). Venous blood (4.5 mL) will be collected in a blue-top collection tube containing 3.2% sodium citrate. Samples will be processed in our clinical lab. Samples will be centrifuged at room temperature for 15 min; plasma is then removed into 2

cryovials in 1 mL aliquots and stored in a -80°C freezer immediately. A label with study identification number, date, and time of blood draw will be placed on the cryovials before freezing. Samples will be batch analyzed using high-sensitivity multiplex technologies [40]. Table 1 lists all variables, measures, and data collection time points.

Table 1. Data collection variables, measures, and time points (both groups).

Variable	Measure/analyses	Data collection points		
		Baseline	x10	End
Primary aim 1				
Recruitment	Number of enrolled/number invited to participate; Mini-Cog instrument (screening)	✓ ^a	— ^b	—
Retention	Number retained at study completion/number recruited	✓	—	✓
Completion	Number of time points completed (11 total)	—	—	✓
Acceptability	Protocol Acceptability Scale for Treating Angina with Acupuncture	—	—	✓
Primary aim 2				
Demographic data	Demographic data form	✓	—	—
Effect size	Intraindividual effect: mean prescores minus mean postscores/pooled SD. Group effect: mean differences in scores between acupuncture and attention control group	✓	—	✓
Exploratory aim				
Biomarkers	Interleukin 1 beta, 2, 6, 8, 10, and 18; C-reactive protein, tumor necrosis factor alpha- α	✓	—	✓
Outcome measures				
Pain and symptoms	McGill Pain Questionnaire, Seattle Angina Questionnaire-7, American Heart Association Angina Log	✓	✓	✓
Functional status and HRQoL ^c	Seattle Angina Questionnaire-7, Physical Functioning and HRQoL sub-scales	✓	✓	✓

^aData were collected.

^bData were not collected.

^cHRQoL: health-related quality of life.

Randomization and Concealment

The research specialist will screen and consent eligible individuals (Textbox 1). Potential participants will be informed that they will be randomized to either the acupuncture group (10-acupuncture session protocol, 2 treatments per week for 5 weeks) or the attention control group (2-hour video session once a week for 5 weeks). After informed consent is obtained, participants will be randomized to the acupuncture or attention control group using the randomization module on REDCap [41] based on the stratified, permuted block schedule prepared by the biostatistician. We are concealing the order of treatment arm assignment from the research associate responsible for recruiting and randomizing through the use of REDCap's restricted user rights. Our block sizes are concealed and our stratified approach also help to prevent research staff from guessing the sequence.

Blinding

For this feasibility study, because of the unique nature of acupuncture and the difficulty in blinding participant and acupuncturist (see Study Design), acupuncturists and participants

will not be blinded to the group assignment. Although it would be optimal to have the research associate who collects outcome data blinded, this is not possible for the current feasibility protocol. Instead, we are using all self-administered outcome measures collected on a tablet computer. The co-principal investigators (co-PIs) and the biostatistician will remain blinded to group membership for data analyses.

Research Protocol

The research specialist will explain the nature of the study, risks, benefits, the voluntary nature of participation, and the right to discontinue participation at any time without consequences. After informed consent is obtained, participants will be randomized to the acupuncture or attention control group. All participants complete 4 measures at baseline: the Demographic Questionnaire, the MPQ [42], the Upper Body Outline [33], and the SAQ-7 [34]. Members of the acupuncture and control groups repeat the measures at the beginning of each session, either all 10 acupuncture sessions or following the 5 video sessions. All participants complete the AHA Angina Log (diary of symptoms) throughout the study, whenever they have angina symptoms. We will make copies of their paper log each time

they come to the clinic in case they misplace their logs. Venipuncture will be performed at baseline and study completion.

Acupuncture Intervention Protocol

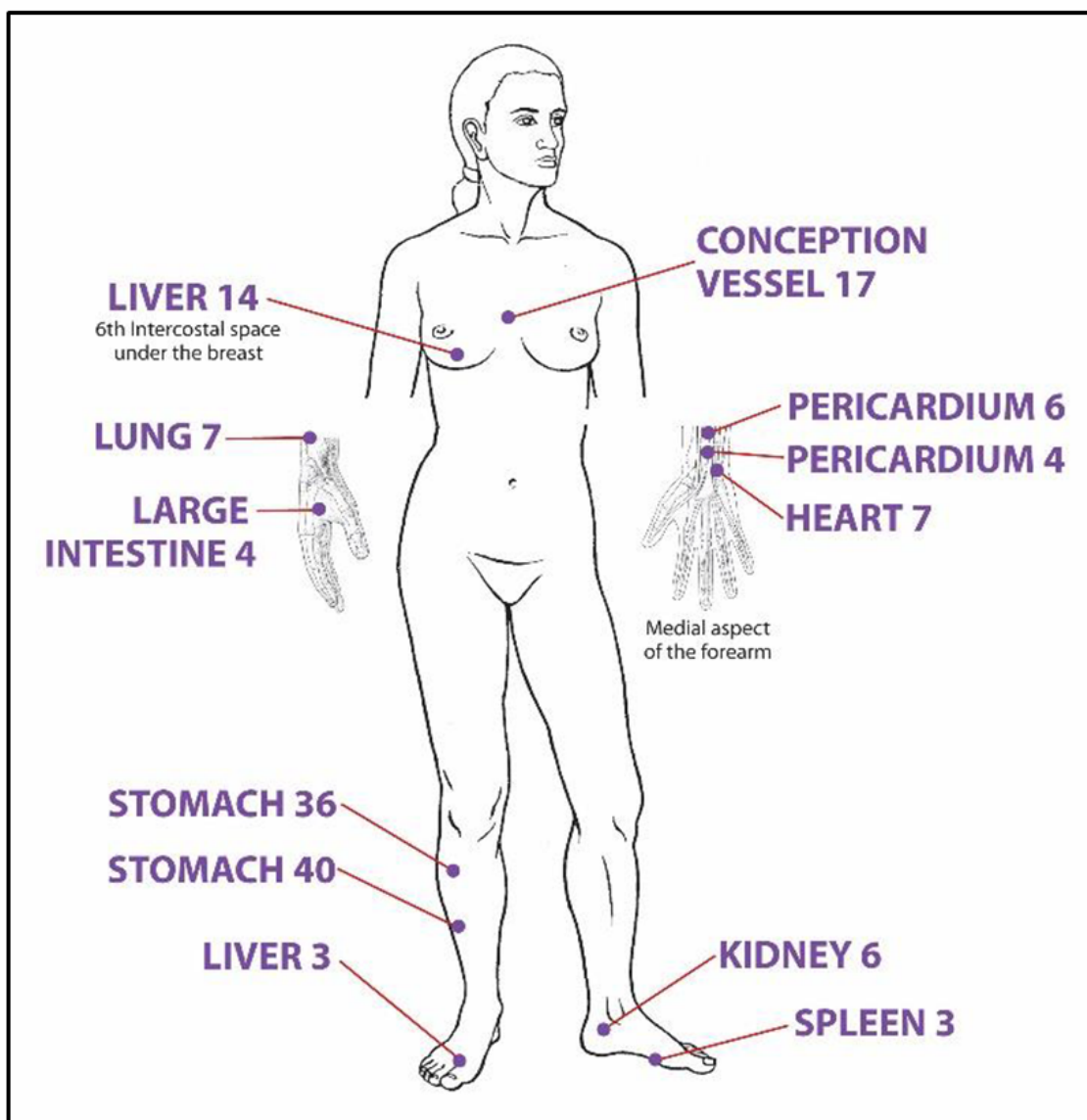
The acupuncturist will swab each point with alcohol. Needles will be inserted using a standardized TCM point prescription and retained for 30 min. Each needle will be rotated 3 times to stimulate the *qi* in the meridian; 10 min after insertion, 20 min after insertion, and just before removal at 30 min. Needles will be inserted using the standards of clean needle technique established by the Council of Colleges of Acupuncture and Oriental Medicine [43]. One size acupuncture needle, 0.25

diameter × 40 mm length, will be used for all participants receiving acupuncture. All acupuncture needles are sterile, disposable, and made of surgical stainless steel with stainless steel wound heads. Sessions will be repeated twice weekly (with at least 2 off days in between) for 5 weeks (10 sessions).

Acupuncture Point Prescription for Angina

The standardized point prescription (Figure 2) uses acupuncture points on the front of the body to enable participants, many of whom are acupuncture-naïve, to remain supine. This is aimed at reducing anxiety by enabling the participant to anticipate needle insertions.

Figure 2. Acupuncture point prescription for angina. Used with permission from the Journal of Chinese Medicine Publications [17].



Attention Control Health Videos Protocol

The attention control group will watch health videos from the NOVA Science NOW series on Public Broadcasting System television. Topics do not contain content that could potentially improve pain. Videos are viewed from weeks 1 to 5 (5 time points) and equate to the time the experimental group receives acupuncture (10 hours) [44]. Titles include: “Can we live forever?,” “Cracking your genetic code,” “Vaccines: Calling the shots,” “How does the brain work?,” “What are dreams?,” “How smart can we get?,” “Memory hackers, Cracking the code of life,” and “Can Alzheimer’s be stopped?.” The videos are shown in our private clinical research rooms. Standardized content assures complete fidelity to the control protocol.

Retention Strategies

We anticipate an attrition rate of no more than 25%. These numbers are based on accruals and withdrawals in our previous studies and our detailed retention plan. Participants will be engaged as active partners in the research by addressing possible benefits of acupuncture (experimental group) and non-pain-related health education (control group), as well as the importance of their contribution to science. To minimize participant attrition and avoid missing data, we are (1) offering the control group the acupuncture protocol, free of charge, at the conclusion of the study; (2) scheduling data collection at convenient times for participants, including weekend and evening appointments; (3) contacting patients using their preferred mode of communication (phone, text, and email) before each appointment; (4) providing patients with study team contact information; and (5) providing patient honoraria (US \$10 at each of 10 contact points for a total up to US \$100).

Data Safety Monitoring

The following data will be examined annually to evaluate safety issues every 6 months during the study: adverse events, attrition rate, reasons for attrition, and rate of adherence during the intervention. All adverse events will be monitored quarterly, but special attention will be given to serious adverse events that result in or require medical or surgical intervention to prevent death, a life-threatening situation, hospitalization, and a persistent or significant disability or incapacity. A Data and Safety Monitoring Committee (DMSC) has been appointed to provide oversight and monitoring of our data on an annual basis by individuals not directly associated with the study. The DMSC will consist of 2 scientists with expertise in RCT designs and a physician with expertise in the sample population. The co-PIs will meet with the DMSC annually and will present a written report as well as a verbal report. A report of the meeting will be submitted to the IRB. Additional meetings of the DMSC will be scheduled if the data are concerning or adverse events warrant more frequent review. If temporary or permanent suspension of the study occurs, the sponsoring institution IRBs and the National Institutes of Health will be notified.

Adverse Events

No serious adverse events are anticipated in this low risk study; however, all adverse events (eg, hospitalization or injury) and/or unanticipated problems (eg, exacerbation of angina or other acute illnesses) will be reported in writing to the IRB at UIC

within 5 days of discovery of the incident. Serious or unexpected adverse events will be verbally reported within 24 to 48 hours.

Quality Assurance

Regular team meetings will be held for the duration of the research project, every 1 to 2 weeks. One principal investigator will chair these meetings. At the first several meetings, all recruitment and data collection procedures were reviewed with the research associate collecting data, and this process was and will be documented. To minimize potential for bias and to prevent contamination of the groups, 1 staff member will administer all instruments following acupuncture, and another staff member will administer all instruments following viewing of videos (for controls).

Sample Size Calculation

We are powered to detect recruitment, retention, completion, and acceptability rates for a future efficacy study, with a 95% 2-sided CI. With our planned sample size of 69 patients, the margin of error will be 9.5% if feasibility rates are in the desired range of 80% or greater; however, will be a maximum of 11.8% if these rates are as low as 50% [45-47]. Similarly, we will compute a 2-sided 95% CI for our effect size estimates, with a half-width of 0.557 standard deviation for posttest differences between groups assuming completion by 75% of participants [48]. With a sample size of 52, we have 80% power to detect a large difference in mean change (0.7 standard deviation or greater) as statistically significant, assuming a repeated-measure correlation of 0.6 and a 2-sided *t* test with 0.05 significance level. We identified 1 similar study reporting continuous outcomes that found a large effect size of 0.85 for a pain reduction outcome and a 0.51 effect size for reduction in number of angina attacks per week [49].

Statistical Analyses

Our biostatistician will supervise data management and data analysis procedures. All data will be exported from REDCap and imported into SAS version 9.4 for cleaning and analysis. Descriptive statistics (frequencies, means, and standard deviations) and bivariate statistics by treatment group will be used to describe the sample and assess baseline differences. Nonnormal distributions may be optimally transformed using the Box-Cox method and/or analyzed using a comparable nonparametric test. Specific plans for analysis are as follows:

- Aim 1: *To determine the feasibility (recruitment, completion, and acceptability rates of 80%; retention rate of 75%) of an RCT of acupuncture for stable angina.* We will calculate the proportion of participants who are recruited, retained in the study, and complete the protocol. We will also calculate a 95% CI for these estimates. Acceptability will be examined by proportion of participants ($\geq 80\%$) scoring ≥ 16 on the acceptability instrument. These statistics will be used to determine if protocol changes are needed to conduct a larger multisite trial.
- Aim 2: *To estimate effect sizes for change from pre- to postintervention scores for pain/symptoms, inflammatory cytokines, functional status, and HRQoL between acupuncture and control groups.* Effect size estimates from the literature were not of high quality or sufficiently

comparable with power for an efficacy trial; thus, we are estimating effect sizes. However, if effects are large, our well-designed study may provide preliminary efficacy for the acupuncture intervention. We will analyze the trial's primary outcomes with a rigorous mixed-effect model for repeated measures recommended for primary analysis of clinical trials with continuous endpoints [50]. Biological sex will be included as a covariate. We will use intention-to-treat analyses, retaining all participants randomized to groups. Missing data will be addressed by using the full information maximum likelihood approach, which produces unbiased parameter estimates and SEs when data are missing at random [51,52]. Effect sizes and 95% CIs will be calculated for pain, and symptoms will be reported via survey and diary, functional status, and HRQoL. We will use the model parameter estimate for treatment group-by-time (baseline to end point), divided by the control group's baseline standard deviation for a Glass delta effect size estimate using a bootstrap method for obtaining 95% CIs [53].

- Exploratory aim: *Explore between-group differences in levels of inflammatory biomarkers (IL-1 beta, IL-2, IL-6, IL-8, IL-10, and IL-18; CRP; TNF alpha) from baseline to study completion (5 weeks).* We will calculate effect size estimates and CIs using mixed models for repeated measures models as stated in Aim 2. We will also explore how changes in biomarkers relate to change in self-reported pain. These exploratory analyses will inform mechanism hypotheses in a future trial.

Ethical Considerations

The proposed protocol has only minimal potential physical or psychological risks to participants. The risks of this study are primarily those from acupuncture needle insertions including: soreness, minor bleeding, bruising after acupuncture needle removal, and fatigue after an acupuncture session. On the basis of findings from previous studies, the likelihood of these risks is very small [54]. There is also minor risk associated with venipuncture (for biomarkers). Collection of blood samples carry a small risk of pain or infection. Collection of data from questionnaires poses minimal time and emotional burden on participants. Finally, there may be some stress associated with keeping appointments for either the acupuncture intervention or the attention control video viewing session; this stress can be mitigated by emphasizing the voluntary nature of the visits, the expertise of the acupuncturist, and the comfortable and private surroundings.

Participants can refuse to participate in any or all of the study procedures or to withdraw from the study at any time. There are 3 categories of potential risk associated with this study: (1) Stress or emotional burden. Any psychological risks are likely to be related to items on the questionnaires that focus attention on symptoms and psychosocial variables. Participants may become uncomfortable thinking about their illness, treatment, or recovery. The major risk for this part of the study is the maintenance of confidentiality. Response burden for the participants is relatively low and will consist of time spent completing instruments, undergoing acupuncture, or watching health-related videos. If participants are tired or anxious, the

sessions can be rescheduled for a later time; (2) Pain, discomfort, or physical harm. The risks from acupuncture needle insertions include soreness, minor bleeding, bruising after acupuncture needle removal, and fatigue after acupuncture. Blood will be obtained by venipuncture. Blood draws can cause syncope, temporary discomfort from the needle stick, bruising, and rarely infection. Patients will be encouraged to rest if necessary, and water and energy bars will be available for patients during each visit to the clinical research lab (for both groups); and (3) Loss of confidentiality. Every effort will be made to maintain patient privacy during data collection. In addition, a number of strategies to protect the privacy and confidentiality of each participant are in place including: proper and current Health Insurance Portability and Accountability Act (HIPAA) training and certification of all staff, compliance with HIPAA guidelines, storage of study data on a secure REDCap server and/or on a limited-access research drive, and placing angina logs and signed consent forms in a locked cabinet in the PIs office. All patients will participate only after written informed consent is obtained. The participants will retain a copy of the signed consent form. Guidelines for consent will be strictly followed according to the approval criteria of the IRB. All study data will be de-identified and stored in a private network drive at UIC that are accessible only to the co-PIs, biostatistician, and project director. Data will be collected on tablet computers, used solely for the study, and will be stored in a locked research office when not in use. Database access is limited to the co-PIs and the project director.

Results

This study has been funded over 2 years by the National Institutes of Health, National Institute for Nursing Research. We are currently recruiting and expect to have initial results by December 2020.

Discussion

Overview

The incidence of stable angina is projected to rise up to 18%, with concomitant increases in comorbid conditions [55]. It is well known that angina patients complain of side effects from antianginal drugs, including nitroglycerin-related headaches, isosorbide-related dizziness and nausea/vomiting, and beta-blocker-related fatigue, nightmares, and depression which may lead to nonadherence and increased risk for future cardiac events [5,56]. A reduction in pain and associated symptoms of stable angina has the potential to improve functional status and HRQoL [3]. After beginning efficacy of this acupuncture protocol is established, future studies will include determining acupuncture from placebo effect, duration of effect, and optimal dosage effect [24,57]. These findings will then provide insight into the need for maintenance acupuncture treatments to reduce the chronic pain of stable angina.

Conclusions

This protocol represents the first step in examining acupuncture as a nonpharmacologic approach to the treatment of symptoms associated with stable angina. Acupuncture has been shown to

have no major side effects [54,57]. Demonstrating the beginning efficacy of acupuncture for the reduction of symptoms of stable angina may shift its treatment from a purely Western model to a complementary model of care.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report from the National Institutes of Health, National Institute of Nursing Research.

[\[PDF File \(Adobe PDF File\), 162KB - resprot_v8i7e14705_app1.pdf\]](#)

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Abbreviations

- AHA:** American Heart Association
- CCS:** Canadian Cardiovascular Society
- Co-PI:** co-principal investigator
- CRP:** C-reactive protein

DMSC: Data and Safety Monitoring Committee
HIPAA: Health Insurance Portability and Accountability Act
HRQoL: health-related quality of life
IL: interleukin
IRB: Institutional Review Board
MPQ: McGill Pain Questionnaire
RCT: randomized controlled trial
SAQ-7: Seattle Angina Questionnaire-7
TCM: traditional Chinese medicine
TNF: tumor necrosis factor
UIC: University of Illinois at Chicago

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Protocol

Assessing Physical Activities Occurring on Sidewalks and Streets: Protocol for a Cross-Sectional Study

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Abstract

Background: A considerable proportion of outdoor physical activity (PA) is done on sidewalks and streets, necessitating the development of a reliable measure of PA performed in these settings. The Block Walk Method (BWM) is one of the more common approaches for this purpose. Although it utilizes reliable observation techniques and displays criterion validity, it remains relatively unchanged since its introduction in 2006. It is a nontechnical, labor-intensive, first generation method. Advancing the BWM would contribute significantly to our understanding of PA behavior.

Objective: This study will develop and test a new BWM that utilizes a wearable video device (WVD) and computer video analysis to assess PAs performed on sidewalks and streets. The specific aims are to improve the BWM by incorporating a WVD (eyeglasses with a high-definition video camera in the frame) into the methodology and advance this WVD-enhanced BWM by applying machine learning and recognition software to automatically extract information on PAs occurring on the sidewalks and streets from the videos.

Methods: Trained observers (1 wearing and 1 not wearing the WVD) will walk together at a set pace along predetermined 1000 ft sidewalk and street observation routes representing low, medium, and high walkable areas. During the walks, the non-WVD observer will use the traditional BWM to record the numbers of individuals standing, sitting, walking, biking, and running in observation fields along the routes. The WVD observer will continuously video the observation fields. Later, 2 investigators will view the videos to determine the number of individuals performing PAs in the observation fields. The video data will then be analyzed automatically using multiple deep convolutional neural networks (CNNs) to determine the number of humans in the observation fields and the type of PAs performed. Bland Altman methods and intraclass correlation coefficients (ICCs) will be used to assess agreement. Potential sources of error such as occlusions (eg, trees) will be assessed using moderator analyses.

Results: Outcomes from this study are pending; however, preliminary studies supporting the research protocol indicate that the BWM is reliable for determining the PA mode (Cramer V=.89; $P<.001$), the address where the PA occurred (Cohen kappa=.85; $P<.001$), and the number engaged in an observed PA (ICC=.85; $P<.001$). The number of individuals seen walking along routes was correlated with several environmental characteristics such as sidewalk quality ($r=.39$; $P=.02$) and neighborhood aesthetics ($r=.49$; $P<.001$). Furthermore, we have used CNNs to detect cars, bikes, and pedestrians as well as individuals using park facilities.

Conclusions: We expect the new approach will enhance measurement accuracy while reducing the burden of data collection. In the future, the capabilities of the WVD-CNN system will be expanded to allow for the determination of other characteristics captured in videos such as caloric expenditure and environmental conditions.

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KEYWORDS

observation; machine learning; behavior; environment; public health

Introduction

Background

Physical inactivity facilitates the development of chronic diseases including obesity, cardiovascular disease, type 2 diabetes, and some cancers and independently contributes to nearly 11% of total annual US health care expenditures [1-4]. Despite national and local efforts to increase physical activity (PA), approximately 51% of US adults are not sufficiently active to achieve health benefits and less than 55% of children younger than 19 years engage in an hour of PA or more per day [3,4]. Whereas psychosocial factors associated with PA are traditionally targeted within behavioral interventions, such approaches have had limited impact on population-level behavior change unless integrated into more comprehensive, multilevel (eg, individual and community) efforts [5]. Indeed, the evidence has grown exponentially regarding the key role contextual influences of the social and physical environments existing within communities play in shaping health behaviors such as PA [6-9]. As such, community-level interventions targeting environmental factors and policies affecting these factors are highly recommended and are becoming the *approach of choice* for promoting PA [6,10].

Neighborhood built environment characteristics have been studied extensively over the past 10 years and are some of the strongest correlates of PA [9,11]. For instance, higher levels of pedestrian PA have been linked to mixed-land use, access to destinations, and street/sidewalk connectivity [12-14]. Moreover, some built environment characteristics are shown to influence the degree to which individuals engage in PA [15-17]. In particular, access to neighborhood sidewalks and streets is associated with greater participation in moderate-to-vigorous PA [18-20]. Sidewalks and streets are among the most common aspects of the built environment where a considerable proportion of outdoor, PAs (eg, walking, running, and cycling) are performed largely within neighborhoods that are proximal to a person's home [19,21,22]. For example, approximately 70% of adults who engage in recreational walking report using the sidewalks and streets in their neighborhood, and adults who are physically active near their homes gain about 17% more time in daily moderate-to-vigorous PA [21,22].

Studies and evaluations of PAs performed on sidewalks and streets, whether to detect changes in usage or determine how associated environmental conditions impact their usage, necessitate a reliable, accurate, and easily administered approach for assessing PA. Self-report questionnaires are hampered by recall bias, plus they have not been adequately validated for geo-locating PAs [22-24]. This is particularly true when asking respondents if they were physical active on the sidewalks and streets in their neighborhood [22,25,26]. Objective measures including accelerometers and pedometers, combined with global positioning systems (GPSs) have been used to geo-locate PAs [27,28]. Although an improvement over self-report questionnaires, drawbacks exist. First, the logistics and cost

to use these in community-level evaluations is prohibitive. Second, accelerometers and pedometers provide no information on the location of the activity and even when coupled with GPSs, only the sample of individuals (cohort) wearing the monitor/GPS are counted, and their PA data are restricted to the geographical locations they visited. As with recall questionnaires, monitor/GPS are not useful for determining utilization rates of specific geographical areas such as sidewalks and streets.

In contrast, the observation method is a reliable approach to counting the number of individuals engaged in various PAs in different environmental settings [29-34]. It is especially useful for determining human usage of sidewalks and streets and widely employed by transportation departments to count pedestrians. In this context, it is referred to as a pedestrian count and involves a stationary observer who records the volume and direction of pedestrian traffic along various routes [35]. Our research team has converted the pedestrian count method to a mobile observation method called the Block Walk Method (BWM) [32,33]. It is reliable, and PAs assessed with the BWM are significantly associated with microlevel environmental characteristics (eg, sidewalk defects and crosswalks) [32-34,36].

The BWM uses time sampling techniques in which observers actually walk predefined segments of sidewalks and streets at a set pace while systematically chronicling the number of individuals performing activities of interest (eg, walking and cycling). The BWM is better than pedestrian counts because it captures a substantially greater proportion of the sidewalks and streets, and thus, a wider spectrum of environmental exposures and a richer context in which to explore PA behavior. Mobile observers, as used in the BWM, provide a very objective, precise, scientifically rigorous, and replicable way to assess PAs performed in diverse environmental conditions. Despite the BWM's many benefits, it has not been updated since its introduction in 2006, and limitations inherent in its original design are still present. In its current form, the BWM is time consuming, requires extensive training, and has questionable accuracy when observing larger groups.

The extension of video technology within mobile and wearable video devices (WVDs) provides extraordinary opportunities for objectively measuring georeferenced imagery including sidewalk and street users in real time. It is now feasible to leverage these technologies to supplement or replace the traditional observational methods used by the BWM. Until recently, video recording devices were bulky, and the video resolutions were crude. Video recorders can now be embedded into the frame of a pair of sunglasses or attached to an unmanned aerial vehicle to provide a completely new, more robust vantage point. Although video capture has not been used to study PAs on sidewalks and streets, it has been used along with computer vision techniques to identify and classify people in different PA intensities (eg, light, moderate, and vigorous) [37,38]. However, findings are based on small study samples in which videos were recorded from stationary cameras within controlled settings. As

such, the algorithms developed to predict PA intensity are not generalizable to free-living PA that occurs within open public spaces. Researchers have noted that the use of videos for research purposes is safer, less costly, more efficient, and more precise than traditional approaches [39]. The adaptation of current video technology to the study of PA behavior on sidewalks and streets is a logical next step in the evolution of PA measurement. Therefore, we propose a highly innovative study using a WVD to acquire information on sidewalk and street users. Further, we will analyze the videos automatically using a machine learning technique known as deep convolutional neural networks (CNNs). Deep CNNs have the ability to detect and classify objects in a scene. State-of-the-art CNNs such as You Only Look Once have been trained on millions of images from typical large datasets such as ImageNet and COCO to be able to recognize thousands of object types in real time [40-42]. Other CNNs have been trained on a narrower group of object types such as pedestrians only [43,44]. Typically, CNN approaches are more robust than traditional computer vision approaches and work with “in the wild” data. This robustness is because of the data-driven nature, which learns to ignore image artifacts and noise implicitly.

Objectives

As described above, the BWM (and PA observation methods in general) has limitations. Whether today’s technology can be used to alleviate these limitations in human populations is virtually unknown. The proposed study seeks to develop and test a new BWM that utilizes a WVD and computer video analysis to assess PAs performed on sidewalks and streets. The following aims will be completed to accomplish this objective: *Aim 1:* Improve the BWM by incorporating a WVD into the methodology. The WVD is a pair of eyeglasses with a high definition video camera embedded into the frames. We expect the WVD to be a viable option for improving the acquisition and accuracy of data collected using the BWM. *Aim 2:* Advance the WVD-enhanced BWM by applying machine learning and recognition software to automatically extract information on PAs occurring on the sidewalks and streets from the videos.

Methods

Aim 1

Overview

For this cross-sectional study, we will first identify low, medium, and high walkability areas of different size cities. Afterwards, we will randomly select a sample of observation routes (1000 foot long street segments) from each walkability and city strata. The BWM will then be conducted along each observation route on 2 different days and at 6 different times. A total of 2 observers will perform the BWM simultaneously. A total of 1 observer will follow the traditional BWM procedures, whereas the other walks side-by-side with this observer and records video using the WVD. Later, 2 investigators will review the videos and, based on the BWM criteria for counting individuals, derive independent counts of individuals being physically active on sidewalks and streets.

Comparative analyses will be conducted to determine the equivalence of the 2 approaches.

Observation Areas: Cities and Walkability

We are stratifying our sample to observe PAs occurring along sidewalks and streets given a wide range of conditions related to city size and walkability. We selected 3 cities: West Chester, Pennsylvania; Wilmington, Delaware; and Philadelphia, Pennsylvania that are small, medium, and large in terms of population, respectively (Multimedia Appendix 1) [45]. City size was considered a strata because it is associated with factors (eg, local norms, population density, and types of destinations) that could influence how humans use sidewalks and streets. In essence, our goal is to increase the generalizability of this study’s outcomes.

Drawing from our familiarity with the study cities and examinations of aerial maps, we will identify 3 neighborhoods per city we estimate as being low, medium, and high walkability. This is being done to streamline the process because there are 44, 92, and 160 defined neighborhoods in West Chester, Wilmington, and Philadelphia, respectively. Afterwards, we will actually measure walkability for each selected neighborhood using WalkScore. As WalkScores can vary across neighborhoods, we will base a neighborhood’s WalkScore on the average of WalkScores for 10 randomly selected addresses drawn from a list of all addresses in the neighborhood. This process will be repeated until 1 low (WalkScore ≤ 33), 1 medium (WalkScore 33 to ≤ 66), and 1 high (WalkScore > 66) walkable neighborhood is located in each city giving us a total of 9 neighborhoods. We are using WalkScore because it is a valid measure for estimating walkability [46-49]. It is significantly correlated with geographical information system-derived indicators of neighborhood walkability such as the availability of retail destinations, intersection density, amenities, street connectivity, residential density, and access to public transit provisions [46-48]. In addition, a higher Walk Score is significantly associated with minutes/week of transport and leisure walking independent of sociodemographic and health variables [49]. WalkScore uses publicly available data from various sources (Google, Open Street Map, and Localeze) and an algorithm to assign a score to a location based on the straight-line distance to various categories of amenities (eg, schools, stores, parks, and libraries) weighted by facility type priority and a distance decay function [50]. The result is a walkability score between 0 and 100, with 0 being the least walkable and 100 being the most walkable. The location can be entered as geographic coordinates or as an address which is then geolocated using Google Geolocation [50].

Observation Routes

The total linear length of sidewalks and streets in the 9 neighborhoods will be estimated using the ruler tool in Google Earth (a geobrowser that accesses satellite, aerial imagery, and other geographic data to represent the Earth as a 3-dimensional globe). The ruler tool is a geographical information systems-based application with submeter resolution. We have found the ruler tool to be accurate to within $\pm 1.5\%$ for measuring street segment lengths. Based on our previous work, we expect an average of 180,000 total linear ft. of sidewalks and streets

per neighborhood [32-34]. The total linear ft./neighborhood will be divided into 1000 ft. routes, and a sample of these routes representing 20% of the total number of routes in a neighborhood will be randomly selected for study, which is an adequate percentage to obtain a representative sample [51]. Given our expectations, this would equate to an average of 36 observation routes per neighborhood or a total of 324 observation routes.

Observation Schedule

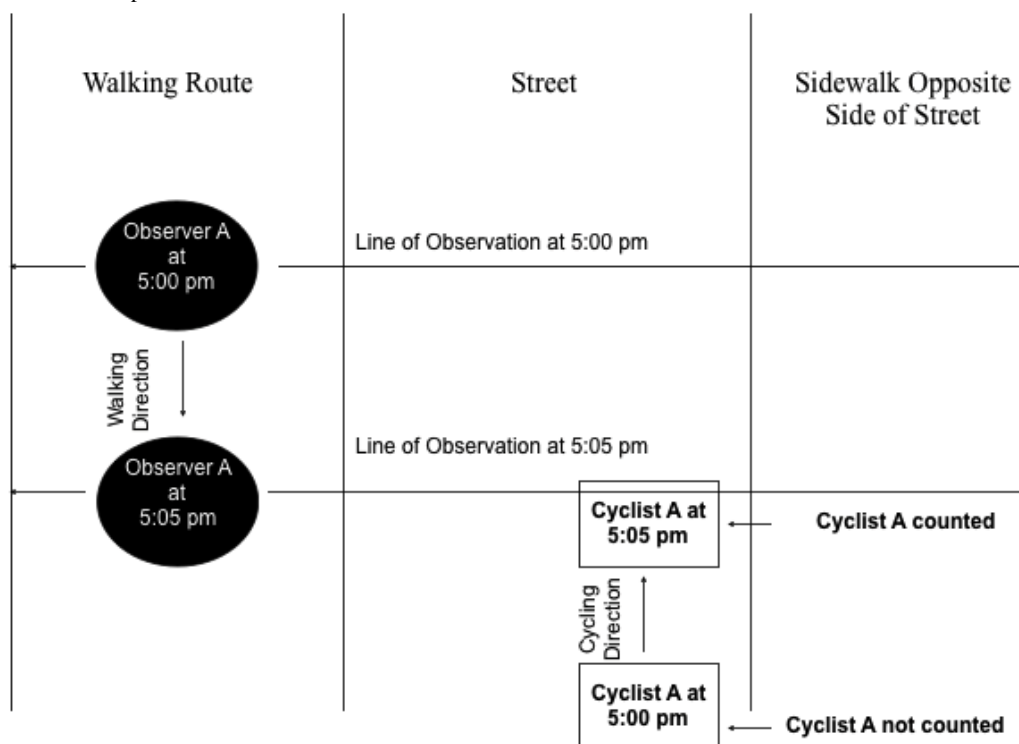
Each observation route in a neighborhood will be observed 3 times on a weekday and 3 times on a weekend day, which will give us a stable estimate of the outcome variable [52]. Each observation period will last 10 min and occur during each of the following time periods: 8 to 9 am, 12 to 1 pm, and 5 to 6 pm (note: all observations will occur during daylight hours). We will be able to complete observations of approximately 6 to 8 observation routes per week meaning a total of 5 to 6 weeks will be needed to assess all observation routes in a given neighborhood. To reduce ordering and seasonal effects, observations will be conducted in only 1 neighborhood per day with each day randomly selected from the pool of days available for the 12-month period when the BWM will be conducted. To reduce the effects of ordering within a time period, observation routes will be numbered consecutively and then placed in a random order for the observation schedule. Observations will not be conducted on days having an event that would affect counts (eg, parade and marathon) or during times when it is raining or snowing.

Block Walk Method Procedures

During an observation period, 2 trained observers (1 wearing a WVD and the other not wearing a WVD) will traverse an

observation route at a pace of 100 ft/min (50 steps/min [largo]; stride width 2 ft; pace set by a battery-powered metronome). The observer without the WVD will record the number of individuals engaging in the targeted activities within an observation field. The observation field will be defined as a line extending to the left and right of the observer’s shoulders, linear and perpendicular from the observer’s plane of motion. The observation fields are expected to range in width from 30 to 70 ft. and include both sidewalks (if present) and the streets associated with an observation route. Individuals will be counted only if they cross a parallel plane of motion with the observer (Figure 1). For example, individuals walking down the sidewalk toward the observer (from ahead or from behind the observer) are counted if they continue to walk past the observer. An individual will be counted only once in an observation route on a given day of observation. When an observer encounters a street intersecting an observation route being observed, they will cease observing, cross the street, and then resume observations. An observation recording instrument was previously developed specifically for the procedure [32]. The instrument was designed so that an observer could record the PA observed, the street name where the PA occurred, and the number of individuals engaged in the PA. The instruments will contain information specific to each neighborhood including detailed walking directions and a map (note: We decided not to use a single observer to conduct the BWM while wearing the WVD because the BWM requires an observer to look away from the observation field while entering data on the BWM instrument, and we have found this to be a source of error especially with larger groups. This is a deficit we expect the WVD to rectify).

Figure 1. Block Walk Method procedure.



Outcome Variable

The primary outcome variable for aim 1 is the number of individuals observed walking, cycling, running, and standing/sitting along each observation route/50 min of observation.

Manual Video Analysis

The 2 study's principal investigators will conduct independent evaluations of the videos obtained during the BWM. This will be done over a 1-year period beginning after the first week of BWMs are completed. They will use the BWM criteria to count individuals walking, cycling, running, and sitting/standing on sidewalks and streets along the observation routes.

Observer Training

All observers will participate in 2 training sessions before beginning data collection. During the first training session, they will be given detailed instructions on the BWM and procedures to be used. The second training session will involve mock field observations.

Meteorological Conditions

Data on meteorological conditions (rainfall, relative humidity, temperature, wind speed, and barometric pressure) for the exact

time of day observations are conducted will be obtained from an automated weather sensor system located at the local airport.

Wearable Video Device—Pivothead Smart

The Pivothead Smart (Pivothead, Denver, CO) is a state-of-the-art, noninvasive WVD indistinguishable from a pair of normal sunglasses (Figures 2 and 3). The camera is discretely centered in the bridge of the glasses for the truest first-person perspective possible, and it features an 8 MP Sony complementary metal-oxide-semiconductor sensor for capturing full 1080 p high definition 4 mega-pixel video at 30 frames per second as well as 8 mega-pixel stills (Figure 4). The glasses accept a 32 GB memory card allowing up to 8 hours of video recording per card at 1080 p. They have a self-contained battery providing 6 to 8 hours of recording time; a 77 degree field of vision, which approximates the human 90 degree field of vision; and they can be fitted with polarized prescription lenses. The Pivothead also allows for audio recordings (helpful for obtaining auxiliary information), time and date stamp, and geolocation capabilities, which can be used to create and retain precise maps of the observation routes.

Figure 2. The Pivothead sunglasses used in this study.



Figure 3. Example of Pivothead sunglasses being worn.



Figure 4. High resolution image taken with Pivothead glasses.



Aim 2

Observation Routes

We will use the videos of observation routes assessed in aim 1.

Procedures (Video Analysis)

The WVD video data, along with annotated ground truth for each human and feature of interest, will be analyzed automatically using multiple deep CNNs. The first deep CNN will be used in collaboration with the Simple, Online, and Real-time Tracking algorithms to determine the number of humans in BWM videos who cross the path of the observer (criteria for being counted) and the distance they traveled per unit time before crossing paths with the observer. For each human in the video, a bounding box will be drawn around their pixels, with identifying information such as faces blurred automatically. Once the humans in the scene are identified, activity recognition will be the next step. Activities will include standing/sitting, walking, cycling, and running. For bicycle riders, the answer is already given by the detection algorithm. For other activities, a new, separate deep network can be applied

to classify the target behavior. An activity is a temporal event that is defined across many frames, so a recurrent neural network will need to be designed to handle this. These networks must be tested and fine-tuned for ground-level views. There are several state-of-the-art networks to choose from, but because of the dynamic nature and heterogeneous viewpoints, a new network architecture may be necessary. The output of the automatic methods can be compared against ground truth to give an accuracy score for how reliable the automatic methods are.

Outcome Variable

The primary outcome variable for aim 2 is the number of individuals observed walking, cycling, running, and sitting/standing along each observation route/50 mins of observation.

Statistical Analysis

Before developing statistical models, an examination of the univariate distribution of variables will be conducted (eg, scatter plots). Statistics such as means or proportions, SEs, ranges, and

estimates of skewness and kurtosis will be derived. Data transformation procedures (eg, logarithmic) may be applied to quantitative variables whose distribution shows considerable departure from normality. Bland-Altman plots will be used to assess agreement on quantitative measures between the traditional BWM and WVD manual video analysis, the WVD manual video analysis, and the automated video analysis [53,54]. The difference between 2 methods for a variable of interest will be plotted against the average of the 2 methods for that variable. Horizontal lines representing the bias between 2 methods will be drawn at the mean difference. Additional horizontal lines will be drawn at the 95% limits of agreement (mean difference ± 1.96 [SD of the difference]). Two-way random effects intraclass correlation coefficients (ICCs) will also be calculated to examine agreement on quantitative measures between methods [55]. To test whether environmental variables (eg, obstructions such as trees) moderated outcome measure associations between methods, unadjusted and adjusted (for covariates) regression models that include a methods variable (eg, traditional BWM vs WVD-BWM), potential moderators, and interaction terms will be created to predict the outcome variable of interest (eg, number observed). In addition, we also will stratify the data by the levels of the moderator and re-examine effects. Simple effects analyses will be used to deconstruct significant interactions by examining associations between method and outcomes in separate subsamples stratified by levels of the moderator variables [56]. All statistical analyses will be performed using the SPSS statistical software package (IBM Corp Released 2015. IBM SPSS Statistics for Windows, version 23.0. IBM Corp).

Results

Our research team has published 3 peer-reviewed journal articles examining the use of the BWM. In the first study, the BWM was used in 12 urban US census block groups to record the number of individuals walking, cycling, and running on sidewalks and streets and the geographical location (address) where they were observed [32]. The level of agreement between independent observers was >98% (530/538) for the PA type recorded. The number of individuals observed was correlated with US census block group characteristics (eg, percent walking/cycling to work) and weather (eg, temperature).

As the first study was limited to urban areas, we conducted a second study of the BWM in suburban settings [33]. Following the exact same procedures as in the first study, trained observers simultaneously walked along suburban sidewalks and streets while making independent recordings of the number of individuals walking/cycling/running and the address where the activity occurred. Analyses indicated that levels of agreement were 97.7% (347/355) for the address where an activity was observed, 94.6% (336/355) for PA type, and 89.3% (317/355) for the number performing an observed PA. Cohen kappa was .85 for address ($P<.001$), Cramer V was .89 for PA type ($P<.001$), and the ICC value was .85 ($F_{1,354}=6.64$; $P<.001$) for the number performing an observed PA.

The third study was designed to determine if PAs observed using the BWM were associated with environmental

characteristics [34]. A total of 14 environmental characteristics of 60, 1000 ft. long sidewalk and street observation routes, located in an urban, residential setting, were directly measured using standardized procedures, and the number of individuals walking, running, and cycling along the routes were assessed with the BWM. A total of 473 individuals were observed during 3600 total min of observation with 315 walking, 116 cycling, and 42 running. A greater number of individuals were seen walking along routes having more traffic, sidewalk defects, graffiti, and litter and poor property aesthetics. Only 1 environmental characteristic was associated with cycling, and none were significantly related with running.

We have previously deployed CNNs to detect cars, bikes, and pedestrians at busy intersections in collaboration with the Delaware Department of Transportation. Using a GoPro Hero Silver 3 with 720 p resolution at 30 fps, videos of pedestrians and cars were recorded over the course of a few hours. Using a modification of You Only Look Once with additional postprocessing, pedestrians, bicycle riders, and cars were automatically and accurately detected from the video (97% agreement with human detection). Tracking was performed with the Simple, Online, and Real-time Tracking algorithm, which uses a deep network for feature extraction and matching and a Kalman filter to improve the reliability [57,58].

Discussion

General

Efforts to increase PA are needed to reach a large portion of the population, and community-level interventions are highly recommended for this purpose. To accurately assess their effectiveness, the proposed study is being conducted to develop a new BWM that uses current technology to capture and analyze video data for the purpose of measuring PAs performed on sidewalks and streets. At this study's completion, we will have demonstrated that a WVD can be used to improve the acquisition and accuracy of data collected using the BWM and that machine learning and recognition software can be used to automatically extract information on PAs occurring on the sidewalks and streets from the videos.

The outcomes from this study have the potential to establish new levels of accuracy for measuring PA on sidewalks and streets and advance the study of PA by using machine learning (deep CNNs) to automatically extract relevant data from the videos. In addition, the proposed study will lead to further developments in this area that will allow for other important characteristics captured by the WVD to be determined with deep CNNs including geographical-level (eg, street segment and park) caloric expenditure, demographics (eg, sex and age), health status (eg, body mass index) as well as current environmental conditions that could affect PA (eg, acts of incivility and weather). Therefore, the potential exists for this study to not only create a novel and valuable tool for researchers but develop an approach that could be easily used by public health officials, government agencies, and numerous other community groups.

Potential Problems and Solutions

Mechanical Failure

We expect the WVD to experience technical difficulties at times. In recent months, we have been working with the Pivothead Smart, and on a few occasions there were issues with the recording device stopping during use and uploading videos from the device to a computer, which was because of a faulty cable. To correct or minimize these issues, we will provide observers with a reserve pair of glasses and keep additional cables on hand.

Safety Concerns

It is probable that some observations will be conducted in high-crime areas, making it unsafe for data collectors. We have encountered this in previous studies and addressed this by having

a law enforcement officer accompany data collectors when necessary.

Hawthorne Effect

The Hawthorne effect is the alteration of behavior by the subjects of a study because of their awareness of being observed. Although this is a valid concern, in our past studies using the BWM we have not found any noticeable reaction to the observers. This is likely because of a couple of reasons such as the observers not standing out and appearing simply as individuals walking down the sidewalk. If people do react to the observers, it would most likely be because the observers walk at a slow pace and periodically write in a notebook while walking. We expect this concern to be eliminated with the use of the video glasses that are indistinguishable from regular glasses.

Conflicts of Interest

None declared.

Multimedia Appendix 1

City characteristics.

[PNG File, 32KB - [resprot_v8i7e12976_app1.png](#)]

Multimedia Appendix 2

NIH Summary Statement.

[DOCX File, 36KB - [resprot_v8i7e12976_app2.docx](#)]

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Abbreviations

BWM: Block Walk Method
CNN: convolutional neural network
GPS: global positioning system
ICC: intraclass correlation coefficient
PA: physical activity
WVD: wearable video device

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Protocol

Frameworks, Models, and Theories Used in Electronic Health Research and Development to Support Self-Management of Cardiovascular Diseases Through Remote Monitoring Technologies: Protocol for a Metaethnography Review

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Abstract

Background: Electronic health (eHealth) is a multidisciplinary and rapidly evolving field, and thus requires research focused on knowledge accumulation, curation, and translation. Cardiovascular diseases constitute a global health care crisis in which eHealth can provide novel solutions to improve the efficiency and reach of self-management support for patients where they most need it: their homes and communities. A holistic understanding of eHealth projects focused on such case is required to bridge the multidisciplinary gap formed by the wide range of aims and approaches taken by the various disciplines involved.

Objective: The primary objective of this review is to facilitate a holistic interpretation of eHealth projects aimed at providing self-management support of cardiovascular diseases in the natural setting of patients, thus priming the use of remote monitoring technologies. The review aims to synthesize the operationalization of frameworks, models, and theories applied to the research and development process of eHealth.

Methods: We will use Noblit and Hare's metaethnography approach to review and synthesize researchers' and practitioners' reports on how they applied frameworks, models, and theories in their projects. We will systematically search the literature in 7 databases: Scopus, Web of Science, EMBASE, CINAHL, PsycINFO, ACM Digital Library, and the Cochrane Library. We will thoroughly read and code selected studies to extract both raw and contextual data for the synthesis. The relation of the studies will be determined according to the elements of the frameworks, models, or theories the studies applied. We will translate these elements between each other and intend to synthesize holistic principles for eHealth development for the case at hand.

Results: The search strategy has been completed, data extraction is almost finalized, and the first synthesis approaches are underway. The search yielded 1224 citations and, after we applied the selection criteria, 17 articles remained. We expect to submit the final results for publication in 2019.

Conclusions: This review is important because it aims to create a holistic understanding of a multidisciplinary topic at the crossroads of eHealth, cardiovascular diseases, and self-management. The value of metaethnography in contrast to other systematic review methods is that its synthesis approach seeks to generate a new understanding of a topic, while preserving the social and theoretical contexts in which findings emerge. Our results will show how useful this method can be in bridging the multidisciplinary gap of eHealth research and development, to inform and advance the importance of holistic approaches, while showcasing this approach for the case of self-management in cardiovascular diseases.

Trial Registration: PROSPERO CRD42018104397; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=104397 (Archived by WebCite at <http://www.webcitation.org/75H1kP1Mm>)

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KEYWORDS

eHealth; telemedicine; research and development; implementation; evaluation; multidisciplinary approach; meta-ethnography; systematic review; remote monitoring; self-management; cardiovascular diseases

Introduction

Holistic Electronic Health Research and Development

Electronic health (eHealth) can be defined as the use of technology to support health, well-being, and health care [1]. As a field of science and innovation, eHealth is characterized by its multidisciplinary and rapidly evolving nature. In eHealth development, various disciplines such as computer, health, and behavioral sciences and design are involved. Ideally, researchers and practitioners are frequently engaged in iterative phases of eHealth development, implementation, or evaluation. The knowledge and technology generated by such processes is often grounded in a wide and overwhelming variety of frameworks, models, theories, methods, or guidelines. Because of this, accumulation, curation, and translation of the output of research and development has become a challenge and thus an important target for research itself [2].

Research has also made it clear that development of eHealth entails several challenges, such as maintaining the pace and efficiency of development cycles, promoting engagement, and applying a theoretical foundation [2]. In practical terms, multidisciplinary teams (health care providers, software developers, etc) are confronted with the need to determine the best approach for a project very early in the process. They are required to define the aims, the methods, and the overarching process that will guide development. Thus, frameworks, models, or theories not only facilitate the task, but also can increase the success of eHealth. Success in research and development can be determined by how much an intervention improves health and well-being (effectiveness), but also by providing explanations and advancing scientific knowledge on “what works for whom in what settings to change what behaviors, and how?” [2].

A holistic approach that combines multidisciplinary knowledge with novel methods and techniques is recommended to tackle the various development challenges and to ensure the effectiveness and efficacy of eHealth [3]. The term holistic refers to the importance of the whole and the interdependence of its parts [3]. In other words, when developing, implementing, or evaluating eHealth, fragmented analysis should be avoided, and each part, with its reciprocal influence on other parts, should

be emphasized (eg, across contextual, technological, and human levels) [4]. The usefulness of taking a holistic approach was recently noted during the development of a framework to understand the nonadoption, abandonment, scale-up, spread, and sustainability of eHealth [5]. In the development process, a holistic view was a helpful starting point to analyze and understand data and theory, and to integrate other frameworks [5]. Therefore, we propose that both researchers and practitioners should recognize the value of making a conscious decision to strive for optimal holism, or at least to combine the most suitable, validated, and useful guidelines that reflect on their decision. Health care is a complex and adaptive system, and this makes eHealth a potential source for innovative solutions to some of society’s most alarming health care problems [6]. The Center for eHealth Research (CeHRes) roadmap is an example of a holistic approach built on reviews of previous frameworks and on empirical research that has been extensively employed for cases such as chronic diseases, antimicrobial stewardship programs [7], and others [3,4]. Thus, such a guideline offers researchers and developers several tools and methods to integrate into a project, in order to monitor the many different stakes and processes that are at play when tackling a certain health issue.

Case Study: Self-Management of Cardiovascular Diseases Through Electronic Health Monitoring Technology

Cardiovascular diseases (CVDs) constitute a global health care crisis due to their high prevalence, long duration, and slow progression [8,9]. A key factor to lessen the burden of CVDs is to support the patients’ abilities to self-manage their own condition [10]. Self-management refers to an individual’s ability to manage the symptoms, treatment, and physical and psychosocial consequences, as well as the lifestyle changes inherent in living with a chronic condition [11]. For instance, individuals living with CVD are recommended to manage their blood pressure, control their cholesterol, reduce their blood sugar levels, become physically active, eat better, lose weight, and stop smoking [10]. An important aspect of these recommendations is that self-management has to be done outside the clinical setting, as patients have to integrate these intensive and timely activities into their daily lives. In fact, one estimate is that of the 8760 hours in a year, patients are spending only

around 10 hours (0.1%) with their health care providers [10]. To ensure that patients are seen by or under the supervision of their health care providers when they do not have face-to-face contact, remote self-monitoring is crucial. Remote self-monitoring can be defined as the process of observing changes in signs and symptoms [12], a behavior that is primarily conducted by the patient but made visible to the health care providers via technology. It supports safety because the health care team can check and be alerted in a timely manner in case of potentially dangerous changes in the patient's health status. Also, patients often feel more comfortable being able to return to their daily lives with the knowledge that important measurements are being monitored by their health care providers [13]. Because of this, remote self-monitoring technologies have become a vital part, almost a prerequisite, of home- and community-based care. In this light, recent metareviews have shown that technology-supported interventions can be at least as effective as usual care in supporting self-management of chronic conditions [14,15].

Despite promising results, the accumulation, curation, and translation of knowledge is also challenging when research in eHealth technology (computer science, design), CVDs (health sciences), and self-management (behavioral sciences) intersects. This leaves a gap that has been observed by previous reviews. The multidisciplinary gap is formed by the usage of different terms and concepts to explain the same phenomena [16], and by a lack of clarity or standardization in reporting the key ingredients of an intervention [17]. To exemplify from the behavioral science perspective, a review of eHealth physical activity interventions for adults with CVDs found that most studies did not sufficiently detail the operationalization of behavior change techniques as key components of their intervention [18]. Likewise, another review of similar interventions showed that only half of the studies had named a theory or model as the foundation [19].

The literature often provides lessons learned on a case-by-case basis in eHealth research and development to support self-management [14,15,20,21]. For example, the most common recommendations reflect the importance of applying technology integration models and a theoretical foundation. Even though this is valuable knowledge, testing should also include process evaluation for intermediate outcomes (mechanisms, mediators), derived ideally from the aforementioned theoretical background. Developers should also provide a sufficiently detailed description of the evidence-based components of the intervention (eg, behavior change techniques). Nevertheless, from these detached recommendations it is still unclear which overall development approaches have been applied in eHealth research to support self-management of CVD, and what their unique contributions have been. Even more so, the extent to which holistic principles have been considered is unknown. The uncertainty is highlighted because these interventions are

coupled with rapidly evolving technologies such as body sensors, personalization algorithms, and automatic feedback systems [21] that mark a significant shift from the traditional telephone or face-to-face delivery. In sum, much is known about development processes in eHealth, based on the many examples that exist. What is lacking at this point is an overarching understanding that relates the findings of such studies across the phases of development and across disciplines.










Aim and Focus

The aim of this review is to facilitate a holistic interpretation of eHealth projects aimed at self-management support of CVDs in a natural setting of the patients. We intend to identify the frameworks, models, and theories applied in these projects and synthesize how their elements were applied to research and development. This seeks to fill in the gap of knowledge translation and dissemination resulting from the multidisciplinary of eHealth. Figure 1 illustrates an initial framework of proposed interdependent elements for a holistic interpretation in terms of the context, the technology, and the human level.

As Figure 1 shows, the context of the review is broad. It includes patients with any particular CVD who are faced with lifestyle changes inherent to their disease and who have to cope with them predominantly at home or in their communities (not in a clinical setting). In terms of technology, we have narrowed the review aim down to the use of remote monitoring technologies such as blood pressure monitors, weigh scales, or wearables, which collect real-time data and provide feedback to the patient as a key component. This scope allows for the collection of specific knowledge on self-management support in the context of remote care. Although excluding interventions that did not use monitoring technology could be seen as a limitation, we hold that any of these applications could, and more importantly should, still be adapted to remote care; therefore, we expect our findings to showcase the missing potential. Finally, in terms of the human element, the aim is specific but also difficult to identify in published studies. The human element is represented by theory-based ingredients such as profiling or tailoring mechanisms and parameters of effectiveness to target patients' behavior change with the intention to improve health.

The review is focused on the following research questions. First, what frameworks, models, or theories have been used to develop, implement, or evaluate eHealth interventions to support self-management of patients with CVDs outside the clinical setting? Second, how do these models address the 5 principles of a holistic eHealth research and development approach (as depicted by the CeHRes roadmap [3,4])? Third, what parameters of effectiveness, profiling mechanisms, and target outcomes are used in these models to address heterogeneity between patients with CVD?

Figure 1. Holistic interpretation of electronic health monitoring technology to support self-management of cardiovascular disease (CVD).

<p>CONTEXT</p>	 <p>CVD</p>	 <p>Lifestyle changes</p>	 <p>Home or community</p>
<p>TECHNOLOGY</p>	 <p>Monitoring technologies</p>	 <p>Real-time data</p>	 <p>Feedback to patient</p>
<p>HUMAN</p>	 <p>Mechanisms or parameters</p>	 <p>Self-management</p>	 <p>Health outcomes</p>

Selecting Metaethnography (Phase 1)

Study reports of how researchers and practitioners applied frameworks, models, and theories are the qualitative data of interest for this review, which is thus based on metaethnography, a qualitative synthesis approach developed by Noblit and Hare [22]. Metaethnography is an interpretive approach to qualitative evidence synthesis that seeks to generate a new understanding of a topic, while preserving the social and theoretical contexts in which findings emerge [23]. Noblit and Hare outlined metaethnography as a 7-stage process that compares and analyzes texts, creates new interpretations in the process, and by doing this strives to build a holistic interpretation [22]. In practice, it mainly involves open coding to identify emergent categories and then constant comparison of key metaphors across studies. Key metaphors can be phrases, ideas, concepts, perspectives, organizers, or themes revealed by a study [22].

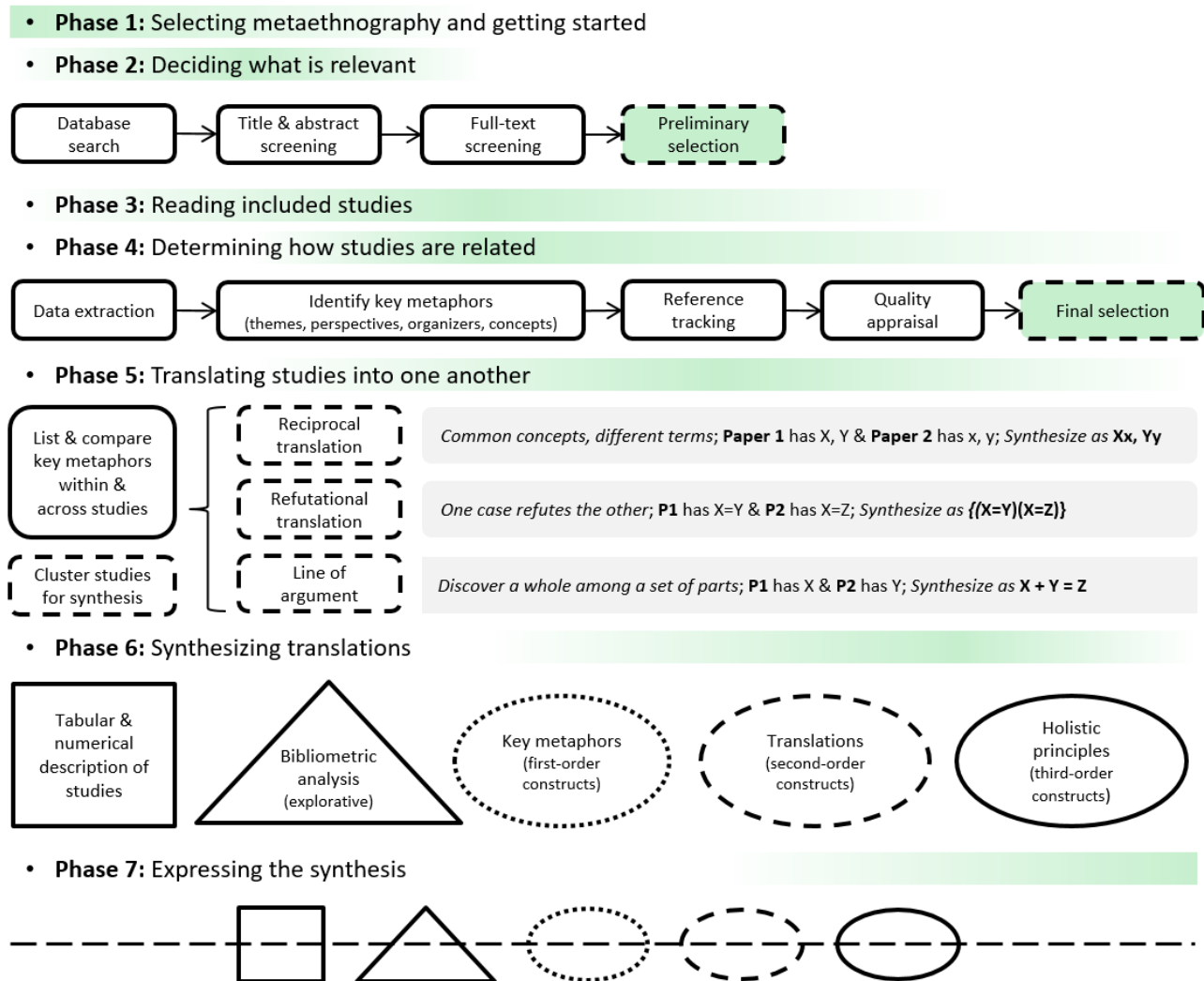
Both the guidelines on choosing qualitative evidence synthesis methods by Booth et al [24] and the support of an information specialist for social sciences (PDN) led us to choose

metaethnography over other approaches (eg. grounded theory or critical interpretive synthesis). We preferred metaethnography because it includes a synthesis approach matching the interest of the review to “move beyond description to a more interpretive examination of [themes,] their relationships and indeed any inherent contradictions” (pg 48) [23]. More importantly, metaethnography is by its very essence a technique used to translate concepts across individual studies [23], which is a perfect fit for our aim to synthesize the elements of frameworks, model, or theories. Our review is also informed by metaethnographies in related topics or with similar aims [25-29].

Methods

This protocol is in accordance with the recently developed Meta-ethnography Reporting Guidance (eMERGe) for metaethnographic studies [30]. Phase 1 (selecting metaethnography and getting started) is embodied in the Introduction; we describe the rest of the reporting criteria below. Figure 2 overviews the practical steps of the methodology.

Figure 2. Metaethnography review of frameworks, models, and theories in electronic health research and development.



Search Strategy (Phase 2)

In phase 2, we will conduct an exhaustive search to find published studies of interest. The search will consist of (1) a systematic database literature search, followed by (2) backward and forward reference tracking from selected articles. The databases that we will search are Scopus, Web of Science, EMBASE, the CINAHL, PsycINFO, the ACM Digital Library, and the Cochrane Library. We chose Web of Science and Scopus based on their coverage of multidisciplinary fields of science, including technology, medicine, and social sciences. Both of these also cover MEDLINE, which is a database of interest due to its focus on the life sciences and biomedical literature. We selected EMBASE and CINAHL because of their discipline-specific literature on biomedicine and nursing, respectively. We included PsycINFO to ensure we would miss no studies from the behavioral field. Likewise, we included ACM Digital Library due to its focus on computer science. The Cochrane Library covers medicine and other health care specialties, including systematic reviews. We will adapt the search to the features of each database. In general, the main search limiters will be the time span (2008-2018) and the language (English, Dutch, or Spanish) of publication. We determined the time span of 10 years by taking into

consideration the growth of the research field and the technological developments of interest. When possible, we will limit the search to articles that include an abstract and that are peer reviewed. The search will consist of multiple key terms. We chose terms based on the existing literature, as well as valuable synonyms of interest, and we will refine them through pilot searches. We will identify related terms and synonyms by using the Medical Subject Headings and EMBASE subject headings databases. The result is to be a very structured query consisting of 4 sets, aiming for results about frameworks, models, and theories (set 1), eHealth interventions (set 2), self-management (set 3), and CVDs (set 4).

We deem the probability of missing relevant articles after the systematic search, followed by the reference tracking and the screening procedure, to be negligible. We intend this strategy to identify articles and studies that add information about overarching eHealth projects within the scope of our review. We define a project as the overarching research project, usually identified by the name of the eHealth technology and integrating several research goals or development aims. The project can consist of 1 or more studies with specific aims (eg, usability or effectiveness). Finally, a study can be published in 1 or more articles (eg, protocol and results).

Search Processes (Phase 2)

RRCM will search the databases and track the references. We will upload the database search results to EndNote X8 (Clarivate Analytics) and use the software features to eliminate duplicates.

Selecting Studies (Phase 2)

We will select studies by uploading the citations to the Covidence Web-based software platform (Veritas Health Innovation Ltd). Articles will be screened by 2 reviewers, first by title and abstract, and then by full text. RRCM as the main reviewer will conduct the title and abstract screening stage throughout all the citations. RAA as the co-reviewer will screen 15% of the citations by default order of appearance in Covidence (alphabetically by first author's name) and will discuss any discrepancies with RRCM to fine-tune the selection criteria. The selection criteria will ensure that the selected article fit within the interest of the review in terms of the population and context (eg, CVDs as a target group), the intervention (eg, self-management support through eHealth), the content of interest for the synthesis (eg, a framework, model, or theory applied and sufficiently described), and the study characteristics (eg, date and language of publication). [Multimedia Appendix 1](#) lists the full inclusion and exclusion criteria. Covidence software allows for selecting articles on a “yes,” “no,” or “maybe” basis. Therefore, to validate the 85% of citations that will be screened by only the main reviewer, those tagged as “maybe” from the single review will also be screened by the co-reviewer. The full text of articles will be screened using the same approach. Discrepancies in article selection at all stages will be resolved in consultation with RS and LGP. We will present the outcome of the systematic search and selection process in the final report following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [31] (eg, flowchart), giving reasons for exclusion at full-text screening, especially for articles on which the reviewers did not reach agreement at once.

Reading Studies and Extracting Data (Phases 3 and 4)

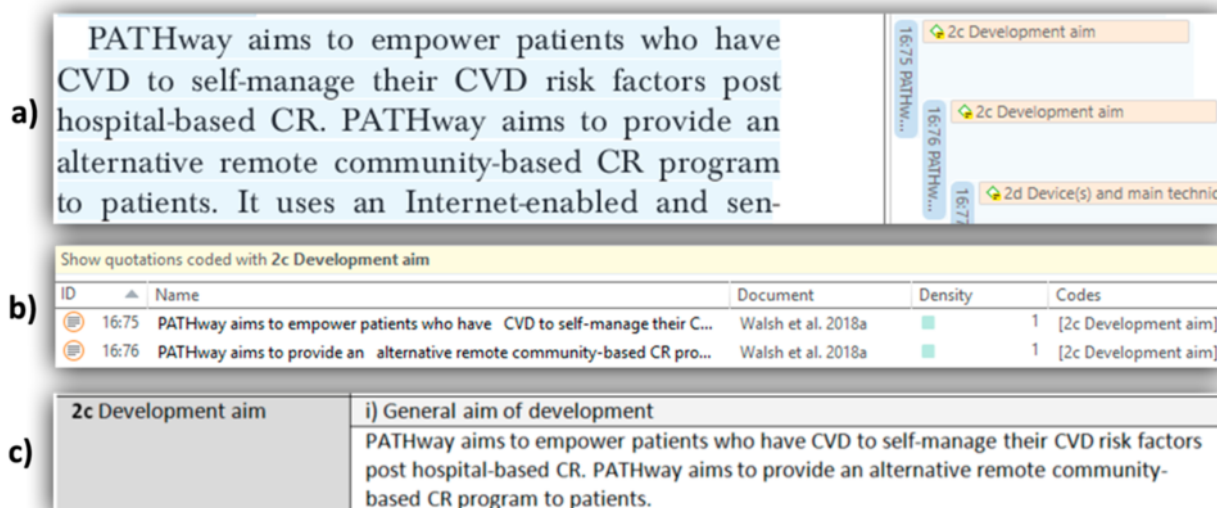
RRCM will conduct phases 3 and 4, and RAA, JW, RS, and LGP will provide feedback on the growing output at intervals. We will use a data extraction form based mainly on elements of the Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth (CONSORT-EHEALTH) checklist v.1.6 [32,33] and adapted to fit the aims of the review. We chose the CONSORT-EHEALTH checklist as the base because it is an accepted standard for reporting on eHealth studies. Because this standard was created for describing trials, we adapted it to reflect the aims of this review. [Multimedia Appendix 2](#) shows the resultant data extraction form. To increase its validity, we will pilot test this form on a first sample of selected articles and iteratively adjust it as necessary during the data extraction process. We will record all changes and report them together with the results, in order to reflect on the usefulness of the extraction form. The form is designed to collect information about (1) the study description, (2) eHealth intervention, and (3) underlying framework, model, or theory, and (4) their principles and key elements according to a holistic perspective.

The broadness of the data extraction form is intended to preserve the context of the research and development process as described in the selected article.

We will extract data using the qualitative software package ATLAS.ti version 8 (ATLAS.ti Scientific Software Development GmbH) and Microsoft Word 2016 (Microsoft Corporation). To begin, we will import PDF versions of the selected articles to ATLAS.ti and set up codes to reflect each element of the data extraction form. [Figure 3](#) shows an example of how the data will flow through the data extraction approach. To facilitate a close and critical reading, this stage will consist of the following steps. First, the reviewer will read the article and code it at the same time according to the elements of the data extraction form ([Figure 3](#), part a). We will also use open coding at this point for potential key concepts or ideas (metaphors). Second, after the article has been read and coded, we will use the quotation manager tool of ATLAS.ti to review the coding results per category ([Figure 3](#), part b). For example, if nothing is coded for “General aim of development,” the reviewer will screen the article again to ascertain whether this element was skipped while reading or if it was not reported by the authors. This process will be repeated for every element of the data extraction form. In the third and final step, the reviewer will translate the coded data into a data extraction form in Microsoft Word ([Figure 3](#), part c). This means that, for each selected article, there will be a data extraction form filled in with all the data of interest. The process will be iterative, as RRCM will continually cross-reference and refine the coding of the article and the data extraction form. RAA will independently revise the accuracy of this process by contrasting the first set of articles with each of their corresponding data extraction forms.

RRCM will also assess the quality of all selected articles using the Critical Appraisal Skills Programme's checklists. We selected these checklists because they are a suggested and frequently used tool for metaethnographies [25,29,34-39]. Although many qualitative evidence synthesis studies do not appraise qualitative research [40], and while existing checklists often don't match the goal of an individual qualitative evidence synthesis, it is considered good practice to apply it, even if in an adapted form. In addition, in the range of qualitative evidence synthesis methods, metaethnography is considered to have an objective idealism grounding (the acknowledgement that a world of collectively shared understandings exists) [38], which makes subjectivity more acceptable and puts relevance as the main inclusion criterion. Therefore, this step will not exclude any articles based on (methodological) quality, but we will keep it to encourage the reviewers to read the articles carefully and systematically [25]. In other words, articles at this stage will be considered a preselection, as they could still be excluded on the grounds of lack of relevance for the synthesis, which will be determined during the following phases (see [Figure 2](#)). We will present the characteristics of the selected articles for phase 3 in tabular and narrative format by year of publication; author(s); author's affiliation(s) (institutions and countries); journal of publication; target condition; aim; and methodological design.

Figure 3. Example of the data extraction flow using ATLAS.ti and Microsoft Word. CR: cardiac rehabilitation; CVD: cardiovascular disease.



Determining How Studies are Related (Phase 4)

Phase 4 will begin with the data extraction and thus overlaps with the reading of the studies. The main aspect of the studies to be compared will be the underlying framework, model, or theory applied, as well as the identified holistic principles and other key elements that influenced the eHealth development, implementation, or evaluation process. To make this process possible, the data extraction form is designed to identify such elements. In the data extraction form for each article, the reviewer will add notes when necessary to clarify annotations, for example, if the reviewer has to identify and screen the original source of a framework cited in the article to contrast how it is reported in the article (eg, to determine whether all elements of the framework are considered or only some of them).

To facilitate the characterization of frameworks, models, and theories according to a holistic view, we will apply the principles of the CeHRes roadmap [3,4] as an initial interpretive framework. The roadmap is itself based on a review of multiple frameworks and was defined as the integration of persuasive technology design, human-centered design, and business modeling. It proposes 5 principles for eHealth development: (1) eHealth development is a participatory development process; (2) eHealth development creates new infrastructures for improving health care, health, and well-being; (3) eHealth development is intertwined with implementation; (4) eHealth development is coupled with persuasive design [41]; and (5) eHealth development requires continuous evaluation cycles. The principles of the roadmap underpin several stages and recommended activities for development (Figure 4).

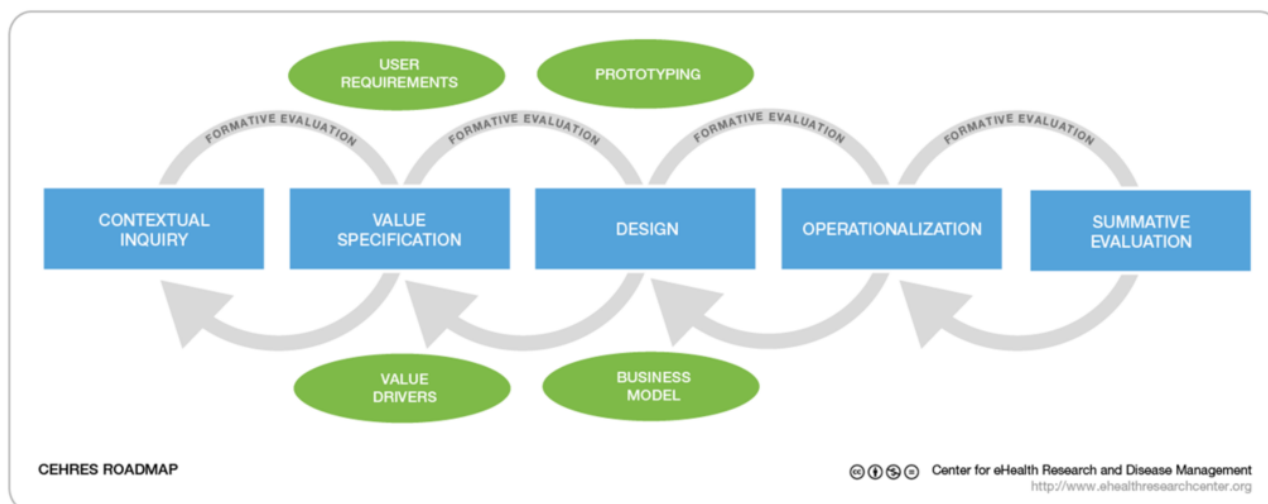
For the purpose of the review, we are using the CeHRes roadmap as an initial lens that the reviewers will apply to relate the studies and to identify new, more case-specific principles, or even gaps in the literature. We will use a list of data extraction key terms and definitions to facilitate the characterization of the frameworks, models, and theories applied in the selected

articles (Multimedia Appendix 3). The terms are grounded in the conceptualizations of the CeHRes roadmap [3,4] but are also informed by the multidisciplinary literature related to eHealth and intervention development [16,42,43].

To visualize and compare the data extracted per article and per project, we will use a matrix in Microsoft Excel 2016 (Multimedia Appendix 4). The matrix comparison will illustrate the reviewer’s characterization of the frameworks, models, and theories reported in the articles. Therefore, the matrix will allow for a first analysis of the clarity and extent of the data that can be synthesized. Multimedia Appendix 4 also shows a worked example of this. This visualization and the key metaphors that are open coded will be the basis to transition from the preselected pool of studies to the final selection of articles included in the synthesis.

The relation assessed between studies via the matrix will be complemented by 2 more tables. The first table will provide an overview of the eHealth projects by name of project; developers, sponsors, or owners; development aim; device(s) and main technical functionalities; main content feature(s) (eg, behavior change techniques); mode of delivery and implementation (eg, use parameters); and type of feedback (eg, blended care vs automated). The second table will present the frameworks, models, and theories identified by name; categorization (framework, theory, or model); studies and projects that applied it; approach to eHealth (development, implementation, or evaluation); coverage of CeHRes’s 5 holistic principles; and coverage of key elements to ensure effectiveness (behavior change, technology adoption, and outcomes). To complete this phase, JMN will conduct an explorative bibliometric analysis of the preselected pool of studies to accompany the study descriptions. This will be intended to identify the convergent points of the literature (eg, through a topic analysis or co-citation of journals) and identify potential biases or missing articles. This will also contribute to visualization of the context of the selected articles, especially the fields of science from which they draw knowledge and the common terms they share.

Figure 4. Center for eHealth Research (CeHRes) roadmap. Reproduced from van Gemert-Pijnen et al [4].



Translating Studies (Phase 5)

RRCM will conduct phases 5 and 6, supported by RAA, JW, RS, and LGP in assessing and refining the output. We will attempt the translation process through various techniques known from the metaethnography literature [22,25-29,34-37,39,44-46], for instance, by the constant comparative method, making a list of key metaphors and comparing this across all studies. Alternatively, the translation process can be by choosing an index article and translating this to another study, then translating this first translation to a third study. If necessary, we will cluster articles to facilitate translation. For example, if several frameworks recommend a step of contextualization or a needs assessment with the target group, these elements could be translated to the principle of participatory development.

We will use concept maps or other forms of visual diagrams to describe the context and the meaning of the relationships between concepts within and across studies. We will consider potential alternative interpretations or explanations in the translation and present them in the final results.

Synthesizing Translations (Phase 6)

During phase 6, we will compose the synthesis, as much as possible, in the language of holistic principles as depicted in the CeHRes roadmap. Therefore, we expect to conduct a line-of-argument synthesis (assuming that studies contribute to a shared line of thought) given the aim to provide a holistic view of the scope of the study. In any case, we will also apply a reciprocal and refutational analysis and add this to our general synthesis. For example, the synthesis could be structured according to the 5 principles of CeHRes and the content derived from the specific approaches of the selected projects. Similar to the previous step, potential alternative interpretations or explanations will be considered and presented.

We will present the new interpretation not as a newly developed metaframework, model, or theory, but rather as a set of principles synthesized from the literature about how to select, operationalize, and execute a holistic eHealth research and development process for the case of self-management of CVD

in a natural setting. For example, the synthesis can provide information about commonly used methods through which business modeling can be integrated into a holistic development of an eHealth intervention to support patients with CVD at their home.

Expressing the Synthesis (Phase 7)

We will submit our results to a peer-reviewed scientific journal that can potentially reach the multidisciplinary fields of science involved in eHealth (computer, health, and behavioral sciences, design, and others). We will contrast findings with the background literature to assess whether we have achieved a new interpretation or new knowledge. We will report the strengths and limitations of our review, and a general reflection on the metaethnography approach, focused on discussing its feasibility and usefulness for the field of eHealth. We will provide recommendations and conclusions based on the findings of the synthesis. These will include an overview of our future projects and how the metaethnographic synthesis might contribute to them.

Results

We conceived the review early in 2018 and conducted the search in July (Multimedia Appendix 5 shows a complete and detailed list of the search terms we used, as well as the search strings for each database). By December 2018, we had completed phases 1 to 3; phase 4 is in its final stage. The database search yielded 1224 citations after we removed duplicates. After we applied the selection criteria, 17 articles remained. We have read and coded these articles, and are in the process of mapping them onto the data extraction matrix. We expect to submit the final results for publication in 2019.

Discussion

This protocol describes a methodological adaptation of the metaethnography approach that serves the purpose of the review: a holistic interpretation of a multidisciplinary and rapidly evolving topic. This is why we conducted an exhaustive systematic search to find published studies within the scope.

The main variation from other systematic reviews lies in the synthesis approach of metaethnography, which seeks to preserve the context in which findings have emerged from the various research disciplines at the crossroads of eHealth, CVDs, and self-management. In other words, the conceptual richness of the literature is needed to identify and understand the role of frameworks, models, and theories in the development of eHealth interventions. This wouldn't be possible by aggregative methodologies or purely descriptive approaches. Furthermore, this review will show how several types of software (Covidence, ATLAS.ti, and Microsoft Office) can be employed to conduct

as thorough a systematic qualitative evidence synthesis as metaethnography demands. Several steps not unique to metaethnography are also applied (quality appraisal, data extraction matrix, and bibliometric analysis) to provide clarity and depth to the analysis and synthesis. Finally, of added value is that the review adheres to the recently developed eMERGE [30] for metaethnographies. Our results will show how this method can contribute to overcoming the challenges derived from the multidisciplinary and rapidly evolving nature of eHealth research and development.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Inclusion and exclusion criteria.

[\[DOCX File, 24KB - resprot_v8i7e13334_app1.docx \]](#)

Multimedia Appendix 2

Data extraction form.

[\[DOCX File, 37KB - resprot_v8i7e13334_app2.docx \]](#)

Multimedia Appendix 3

Key terms and definitions for data extraction.

[\[DOCX File, 26KB - resprot_v8i7e13334_app3.docx \]](#)

Multimedia Appendix 4

Template and worked example of the data extraction matrix.

[\[DOCX File, 43KB - resprot_v8i7e13334_app4.docx \]](#)

Multimedia Appendix 5

Key and related terms, and full search strings per database.

[\[DOCX File, 27KB - resprot_v8i7e13334_app5.docx \]](#)

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Abbreviations

CeHRes: Center for eHealth Research

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth

CVD: cardiovascular disease

eHealth: electronic health

eMERGe: Meta-ethnography Reporting Guidance

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Protocol

The Role of Cognitive Behavioral Therapy in Opioid Use Reduction in Pediatric Sickle Cell Disease: Protocol for a Systematic Review

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Abstract

Background: Sickle cell disease (SCD) is a genetic disorder of red blood cells that results in acute and chronic health problems, including painful syndromes. Opioid analgesia is the mainstay of moderate to severe pain management in SCD, although adjunctive psychosocial approaches such as cognitive behavioral therapy (CBT) are increasingly incorporated. CBT has been used in populations of various ages to address a wide range of issues, such as mood disorders and chronic pain. It is unclear if effective CBT reduces the use of opioids to manage pain in pediatric SCD.

Objective: The aim of this study is to evaluate the association between CBT and decreased opioid use in children with SCD.

Methods: In this systematic review protocol, we describe our approach to applying predetermined eligibility criteria to searches of PubMed (including Medline), Embase, Cochrane, Web of Science, and PsycINFO databases, as well as Google Scholar and grey literature. In particular, we will use keywords to search for English-language studies of individuals with SCD aged 21 years old and younger published before November 2018. Keywords will allow us to assess for the primary outcome—total use of opioid medications—and the secondary outcomes—pain intensity and emotional functioning—during pain management using a combined opioid and CBT approach, opioids alone, or CBT alone. The review team will use standardized abstraction forms to review articles at the title, abstract, and full-text levels. Finally, reviewers will assess the risk for bias, quality of evidence, and adequacy of data for quantitative versus qualitative synthesis. If meta-analysis is deemed inappropriate, a narrative review will be conducted.

Results: We will report a summary of findings across studies that meet eligibility criteria to compare the extent to which adjunctive CBT is associated with decreased opioid use among children with SCD.

Conclusions: This systematic review will present the current state of the evidence on CBT and opioid use in pediatric SCD, which may inform clinical practice and health policy to support optimized pain management.

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KEYWORDS

sickle cell disease; sickle cell anemia; pain; opioids; cognitive behavioral therapy; CBT; children; adolescents; youth

Introduction

Sickle cell disease (SCD) is an inherited form of severe anemia that affects nearly 100,000 individuals in the United States [1], including 1 in 400 African Americans and 1 in 19,000 Latinos [2]. The clinical hallmark of SCD is the acute painful episode, although the severity and chronicity of pain, end-organ complications, and requirement for frequent contacts with the health care system place children at risk for several psychosocial problems. In particular, children with SCD are at risk for psychological complications, including depression, anxiety, reduced quality of life, and neurocognitive impairment [3,4]. However, current clinical guidelines rely on sparse literature to address the psychological well-being of children with SCD.

Frequent acute painful episodes and attendant restrictions on daily activities of life require the combination of judicious opioid administration along with socioemotional supports [5]. Such painful events may be acute or chronic, treated on an inpatient or outpatient basis, or managed with opioid or nonopioid medications [6]. However, poorly treated acute pain may evolve into psychological problems, reduced quality of life, chronic opioid use, frequent health care usage, and chronic pain syndromes [7,8]. Studies have shown that up to 30% of adolescents with SCD will ultimately develop chronic pain [9]. The most effective pain management regimens are those that address biological and psychosocial antecedents and consequences of disease manifestations [5,7].

Opioids are addictive, particularly in the adolescent population, which encompasses many children with SCD [5,10]. Although concerns surrounding the opioid epidemic have risen, adjunctive psychosocial interventions, such as cognitive behavioral therapy (CBT), are increasingly considered alongside traditional pharmacologic treatments [11,12]. CBT is a commonly employed form of psychotherapy that helps individuals manage negative thoughts to overcome a wide range of problems, including stress and depression [13]. As this evidence base suggests, children with SCD are at an increased risk for depression and poor coping strategies [14-17], and CBT is a promising adjunct to manage disease-related pain [4,18,19]. Despite this encouraging nascent evidence base, the extent to which CBT decreases the use of opioid analgesia is uncertain. If CBT successfully manages pain related to SCD with decreased reliance on opioids, more financial and clinical support for this psychotherapeutic approach would be warranted.

This systematic review will determine if CBT decreases opioid use in children with SCD. Two reviews have described psychosocial interventions for SCD [19,20], but these included a range of approaches for adults and children with very few targeting the outcome of pain medications [19]. Intervention studies that focus on CBT including children with SCD [18,21,22] and CBT as an adjunct therapy in youth with chronic pain syndromes [23] are foundational to this ongoing work. Our work updates the prior reviews with the presentation of data pertinent to CBT and opioid use for painful episodes in pediatric SCD. A systematic review of the literature will guide clinical and health policy decisions pivotal to effective pain management for children with SCD.

The objective of this study is to evaluate the association between CBT and decreased opioid use in children with SCD.

Methods

Eligibility Criteria

The population will include children and youth aged 21 years and younger with SCD, the intervention will be CBT and opioid use, the comparator will be opioid use alone, and the outcome will be decreased pain.

Information Sources

We will search PubMed (including Medline), Embase, Cochrane, Web of Science, and PsycINFO for English-language articles published before November 2018. In addition, we will search the grey literature and Google Scholar. We will also review the reference list of each chosen article for additional relevant articles. The language will be restricted to English, but there will be no geographical restrictions.

Search Strategy

The search strategy will include the study population using keywords derived from the team's expertise. Search terms will include a combination of the following: sickle cell disease, cognitive behavioral therapy, cognitive coping strategies, pain coping skills training, opioids and pain, as well as related terms. We will consult with a psychologist to expand the list of search terms for CBT. We will also work with a librarian from the Keck School of Medicine of the University of Southern California's Norris Medical Library to ensure the integrity and thoroughness of our literature search.

Study Records

Data Management

After the initial search, all articles will be imported into Covidence reference manager software, and all duplicates will be removed.

Article Selection Process

The review team will independently screen the titles and abstracts for relevance to our topic. The team will then review full-text articles for inclusion or exclusion based on our research question. The reference lists of all included articles, systematic reviews, and meta-analyses that look at CBT, opioid use in children, and SCD will be manually reviewed to identify any additional articles, which will then be retrieved and reviewed. We plan to exclude studies that have used other treatment modalities (eg, physical therapy or integrated treatments) in conjunction with CBT or opioids. Articles selected for inclusion will not be limited to randomized controlled trials to increase the number of relevant reports for review.

Data Collection Process

Using a standardized data abstraction form, reviewers will independently abstract relevant data related to our research question from all articles that meet the inclusion criteria. The form will include the following data elements: author, publication year, sample size (N), age, study setting, study design, pain management intervention, outcome measures, and

results, specifically opioid use, pain intensity, and emotional functioning.

Data Items

The population to be evaluated includes children aged 21 years and younger with a diagnosis of SCD. Children with SCD who undergo CBT will be compared to children who undergo routine care and pain management. The interventions of interest include CBT alone versus opioids alone versus a combination of CBT and opioid use to manage pain. Funding sources, particularly drug-sponsored trials, will be reported.

Outcomes and Prioritization

The primary outcome of interest will be the total amount of opioids used during inpatient hospitalization or outpatient care. Of note, there can be significant variation in how quantities of opioids are measured across various studies. When actual dosing is available, a standard measurement of total morphine equivalents will be calculated and compared between studies [24].

The secondary outcomes of interest will expand our review to encompass two patient-centered outcomes meaningful to children with SCD: pain intensity and emotional functioning [25]. First, we will capture reports of pain intensity consistent with the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (PedIMPACT) recommendations for core outcome domains and measures for pediatric chronic or recurrent pain. Specifically, we will evaluate papers that include pain intensity assessments using the following measures: (1) The Poker Chip Tool for children aged 3 to 4 years [26], (2) the Faces Pain Scale-revised for children aged 4 to 12 years [27], and (3) the Visual Analog Scale for children aged 8 years and older [28]. Comparisons will be performed between subgroups of children with SCD who underwent CBT compared to children who did not receive CBT. These measures have been previously validated in pediatric sickle cell populations [29]. PedIMPACT also underscores the need to assess emotional functioning in children with chronic pain; therefore, our review will also evaluate studies of emotional functioning in children with SCD as another secondary outcome, comparing levels of emotional functioning based on receipt of CBT. Studies that include the following emotional functioning assessments will be included: (1) Children's Depression Inventory for children aged 7 to 17 years [30] or (2) the Revised Child Anxiety and Depression Scale (RCADS) [31]. Of note, previous literature highlights an association between depressive symptoms and opioid use in youth [32]. Therefore, assessment of emotional functioning in children with SCD may be particularly relevant to our primary outcome of opioid use.

Risk of Bias in Individual Studies

Two authors (NT and AA) will independently assess the risk of bias in each of the studies. The assessment of the risk for bias will follow the principles outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* [33]. We will verify that studies minimize bias and address biases that were present. The bias assessment will provide the strengths and weaknesses of the study. Each study will be assessed for:

1. Adequate sequence generation to examine if investigators used a random component in their study design.
2. Allocation concealment to assess whether the study team member applying randomization was blinded to the treatment participants will receive.
3. Blinding (subjective outcomes) to ensure that the participants did not unknowingly affect results because of the knowledge of their treatment group.
4. Blinding (mortality) to safeguard that outcomes were not biased by the knowledge of participant deaths.
5. Incomplete outcome data (short-term and long-term outcomes) to evaluate whether the authors accounted for the missing time points and how it could have affected results.
6. Selective reporting to verify if investigators reported all results, not just the results that were significant.

Confidence in Cumulative Evidence and Data Synthesis

Confidence in Cumulative Evidence

Two authors (NT and AA) will independently appraise the quality of evidence for each of the studies. We will use the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) criteria to rate the quality of the studies [34]. High-quality evidence will demonstrate a very large effect, evidence of a dose response, precision, consistency, directness, and lack of publication bias. The quality will be lower if there is:

1. serious (−1) or very serious (−2) risk of bias;
2. serious (−1) or very serious (−2) inconsistencies;
3. serious (−1) or very serious (−2) indirectness;
4. serious (−1) or very serious (−2) imprecision; and
5. likely (−1) or very likely (−2) publication bias.

Data Synthesis Plan

If it is appropriate to quantitatively assess the data, we will summarize the difference in means of opioid use among the studies using CBT in children with SCD. We will only compare studies that meet our eligibility criteria. We will combine results of studies with homogeneous study designs for a meta-analysis. We also plan to assess studies for heterogeneity by making pairwise comparisons of studies that have used CBT with the outcomes of pain score or decreased opioid use. Statistical heterogeneity will be identified or quantified by using the inconsistency equation: $I^2 = (Q - df / Q) \times 100\%$ test, where Q is the chi-square statistic and df is its degrees of freedom. The results of the I^2 findings will be graded as follows: (1) 0% to 40% may not be important, (2) 30% to 60% has potential for moderate heterogeneity, (3) 50% to 90% has potential for substantial heterogeneity, and (4) 75% to 100% has sizeable heterogeneity. We will also consider the magnitude of effects and the strength of the associations ($P \leq .10$). If the potential for heterogeneity exists, we will run a random-effects meta-analysis that incorporates the heterogeneity. We will also take precautions in interpreting the results of the meta-analysis. If there is substantial evidence of heterogeneity, we will use a narrative approach for the review. If quantitative data analysis is not appropriate, we will use a narrative synthesis to describe: (1) eligibility criteria, (2) whether CBT reduces opioid use in

children with SCD versus only opioid use, (3) whether CBT is associated with pain intensity and emotional functioning in children with SCD, and (4) a summary of findings across the studies.

Results

We plan to report a summary of the findings across studies that meet eligibility criteria to present the extent to which adjunctive CBT is associated with decreased opioid use among children

with SCD. We expect to complete data analysis by December 2019 and publish results in the following calendar year.

Discussion

This systematic review will synthesize and report the current state of evidence on CBT and opioid use in pediatric SCD, which may inform clinical practice and health policy to support improved management.

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Authors' Contributions

ATA participated in conceptualizing and designing the review protocol and data collection instruments, drafting the initial protocol, and reviewing and revising the protocol. NT participated in conceptualizing and designing the review protocol and data collection instruments, drafting the initial protocol, and reviewing and revising the protocol. KS participated in conceptualizing and designing the review protocol and data collection instruments, drafting the initial protocol, and reviewing and revising the protocol. LIKQ participated in conceptualizing and designing the review protocol and data collection instruments, drafting the initial protocol, and reviewing and revising the protocol. All authors approved the final protocol as submitted and agree to be accountable for all aspects of the work.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy

GRADE: Grading of Recommendations, Assessment, Development and Evaluation

PedIMPACT: Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

RCADS: Revised Child Anxiety and Depression Scale

SCD: sickle cell disease

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Protocol

The Effectiveness of Internet-Based Self-Help Interventions to Reduce Suicidal Ideation: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Suicidal ideation is a highly prevalent condition. There are several barriers for individuals to seek treatment that may be addressed by providing internet-based self-help interventions (ISIs). Current evidence suggests that ISIs for mental disorders may only be effective in reducing suicidal ideation if they specifically target suicidal thoughts or behaviors.

Objective: The aim of this systematic review and meta-analysis is to investigate the effectiveness of ISIs that directly target suicidal thoughts or behaviors.

Methods: We will conduct a sensitive systematic literature search in PsycINFO, MEDLINE, the Cochrane Central Register of Controlled Trials, and the Centre for Research Excellence of Suicide Prevention databases. Only randomized controlled trials evaluating the effectiveness of ISIs for suicide prevention will be included. Interventions must be delivered primarily in a Web-based setting; mobile-based interventions and interventions targeting gatekeepers will be excluded. Suicide ideation will be the primary outcome; secondary outcomes will be completed suicides, suicide attempts, depressiveness, anxiety, and hopelessness. Study quality will be assessed using the Cochrane Risk of Bias tool. We will provide a narrative synthesis of included studies. If studies are sufficiently homogenous, we will conduct a meta-analysis of the effectiveness on suicide ideation and, if possible, we will evaluate publication bias using funnel plots. We will evaluate the cumulative evidence in accordance with the Grading of Recommendations Assessment, Development and Evaluation framework.

Results: This review is in progress, with findings expected by August 2019.

Conclusions: This systematic review and meta-analysis focuses on the effectiveness of ISIs for suicidal thoughts and behaviors. It will provide guidance to clinical practice and encourage further research by synthesizing the best available evidence.

Trial Registration: International Prospective Register of Systematic Reviews (PROSPERO) CRD42019130253; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=130253

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KEYWORDS

suicide; suicidal ideation; internet; computer-assisted therapy; randomized controlled trial; systematic review; meta-analysis

Introduction

Importance

Suicide is a severe public health problem. Globally, more than 800,000 people die because of suicide each year, and it is the second leading cause of death among those aged 15 to 29 years [1]. Suicide attempts are estimated to be 20 times more prevalent than completed suicides [2]. Globally, suicide rates have increased by 60% within the last 45 years [2].

Although there are effective suicide prevention strategies [3], many people at risk of suicide do not seek treatment, which may limit the effectiveness or impact of these strategies [4]. Surveys conducted worldwide ($N=55,302$ participants) by the World Health Organization show that only 39% of people with suicidal behavior had received any kind of therapeutic intervention for emotional difficulties in the preceding 12 months [5]. Treatment, including treatment of suicidal thoughts, was most prevalent in high-income countries (56% received treatment within the past 12 months) and less frequent in middle-income (28%) and low-income (17%) countries. Common barriers to treatment-seeking have been identified as (1) the wish to solve the problem by oneself, (2) the belief that one would get better without treatment, (3) the belief that the problem was not that severe, (4) stigma, (5) structural problems, for example, financial effort and low availability of treatment, and (6) low perceived need [5].

Internet-and-Mobile-Based Interventions

Over the past two decades, the development and evaluation of internet-and mobile-based interventions has been an emerging focus of mental health research. Previous meta-analyses have verified the effectiveness of digital interventions for a variety of mental disorders and health issues, including depression [6-10], anxiety [6] and post-traumatic disorder [11]. Internet-based interventions have now been integrated in clinical practice in several countries, including Australia, the Netherlands, Sweden, Norway, and England [12,13], demonstrating their value as a part of health care for at-risk individuals. Within the diverse field of digital interventions, internet-based self-help interventions (ISIs) are the most commonly developed and used. ISIs are stand-alone interventions that provide participants with evidence-based therapeutic material, which can be used self-reliantly [12]. ISIs can involve different levels of human support [14]. In guided ISIs, a clinician accompanies the intervention by providing feedback or guidance on the tasks and progress, often on a weekly basis [14]. Human support is typically limited to positive reinforcement, giving feedback and clarification of content instead of delivering additional therapeutic techniques [12].

The use of ISIs might address several of the barriers mentioned above: (1) The desire to “solve the problem by oneself” can be appropriately addressed by using guided or unguided self-help interventions [12,14]. (2) Individuals who assume that they will get better without treatment might still look for information or social support online [15], and psychoeducational content can be readily delivered through internet-based interventions. It has also been shown that suicidal individuals spend more time online than nonsuicidal users [16-18], which indicates that ISIs may

be very appealing to these individuals. (3) The perception of the problem as not that severe can be addressed by providing a low-threshold program within a stepped-care approach. As a first step, ISIs can be offered, and if the patient does not respond, further programs with more intensive therapeutic support can be provided [12]. (4) Individuals who face stigmatization might benefit from the anonymity that ISIs offer [12], (5) whereas structural barriers can be addressed by the accessibility and flexibility of ISIs. In addition, ISIs can be provided at low costs [19,20]. (6) Although offering self-help interventions does not address the barrier of low perceived need, online self-screening programs may increase the perceived need for treatment by providing feedback to participants [21]. In sum, ISIs may be an appropriate, low-threshold intervention for individuals at risk of suicide.

State of Research: Internet-Based Self-Help Interventions for Suicide Prevention

ISIs for suicide prevention have been developed in recent years. In response to the growth of electronic health (eHealth) interventions in mental health, several reviews and meta-analyses have been published which summarize the evidence of internet-and-mobile-based interventions for suicidality [21-25]. The umbrella term *internet-and-mobile-based suicide prevention* comprises widely divergent approaches, including social networking sites, videos, podcasts, email support programs, mobile apps, gaming interventions [26], self-screenings, text analyses [21], and self-help interventions based on psychological treatment approaches [12]. As a result, reviews have included a variety of interventions.

Overall, those reviews found mixed results and pointed out a paucity of high-quality evidence for the effectiveness of the reviewed interventions. Some reviews reported promising effects of ISIs on suicide-related outcomes [22,23], and one review concluded that there is no evidence for their effectiveness [25]. The most recent of these meta-analyses, by Witt et al [24], found that internet-and-mobile-based interventions (mainly developed for depression treatment) reduced suicide ideation at postintervention. Christensen et al [21] reported that self-help interventions for depression have specific effects on depressiveness but not on suicidal ideation, as there seem to be reductions in suicidal ideation in both depression and control conditions. They included only 1 study with an intervention directly addressing suicidality. It showed a significant effect on suicidal thoughts compared with the control group. The authors concluded that online programs that directly target suicidal ideation and behavior might be more effective than those programs that are designed for mental health more broadly. This is in line with the meta-analytic finding that interventions directly addressing suicidal thoughts and behavior show immediate post-treatment and long-term effects, whereas programs that solely address associated symptoms seem to be only effective in the long term [27].

However, there are some limitations concerning previous reviews in this field. First, ISIs were often not differentiated from other Web-based strategies or mobile-based interventions [22-24]. Differential effects are highly plausible owing to variations in treatment approaches, treatment dose, and

application context. Second, several reviews did not restrict study inclusion to controlled trials [21-24] and, third, did not assess risk of bias [21,23]. Fourth, none of the reviews assessed publication bias [21-23,25]. Finally, most reviews did not differentiate between studies investigating interventions that directly targeted suicide versus those that focused on other conditions such as depression or anxiety [22,24,25].

Objectives

Therefore, this review and meta-analysis will (1) focus on the effectiveness of ISIs directly targeting suicidal thoughts or behavior, (2) exclude Web-based interventions for other health conditions and mobile interventions, and (3) only include randomized controlled trials (RCTs), (4) perform the Cochrane Risk of Bias tool, (5) check for publication bias and (6) search a clinical trial register to give an overview of ongoing trials. As Web-based suicide prevention is a fast-growing field, this review will provide readers with a valuable up-to-date overview of the current state of research and identify gaps in the literature to benefit the design of future research investigations.

Methods

The review will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [28]. This protocol adheres to the PRISMA Protocols [29]. We registered the study with the International Prospective Register of Systematic Reviews (trial registration number: CRD42019130253). Protocol amendments will be tracked and reported in the final publication.

Eligibility Criteria

Population

There will be no restrictions for age groups, gender, or any other sociodemographic variables.

Interventions

We will include self-help interventions. They must be delivered predominantly in an online setting, defined as internet-based, online, Web-based, or any other equivalent. Although they are defined as stand-alone internet-based interventions, they may involve some additional human support (eg, guided interventions with written feedback). Interventions that use online tools as an adjunct to face-to-face therapy (eg, blended treatment) will be excluded. Treatment groups must receive a psychological intervention. According to the definition by Kampling et al [30], psychological interventions may comprise elements of cognitive behavioral therapy, psychodynamic psychotherapy, behavior therapy or behavior modification, systemic therapy, third wave cognitive behavioral therapies (eg, dialectical behavior therapy or acceptance and commitment therapy), humanistic therapies, integrative therapies (eg, interpersonal therapy) or other psychological-oriented therapies. The intervention must specifically target suicidal thoughts or behaviors. Interventions that only address symptoms associated with suicidality, for example, depressiveness or anxiety, will not be included. We will include universal, selective, and indicated prevention measures.

Comparators

The control group may receive treatment as usual, receive another active or passive treatment, receive placebo, consist of a waiting list group, or receive no intervention. However, controlled trials will not be pooled with comparative trials.

Outcomes

Studies will be included if they report a suicide-specific outcome, that is, suicide ideation, suicidal thoughts, or suicidal behaviors (completed suicide or suicide attempts). Suicide attempt is defined as self-injury with the intention to die, in contrast to nonsuicidal self-injury [31]. Outcomes have to be assessed quantitatively. Suicide ideation will be the primary outcome. The following variables will be included in the analyses as secondary outcomes: suicide and suicide attempt, depressiveness, anxiety, and hopelessness. If multiple measures are used, we will prioritize data extraction as follows: (1) validated questionnaires (eg, Beck Scale for Suicide Ideation), (2) clinician ratings, and (3) single item analysis of other rating scales (eg, Patient Health Questionnaire-9 [32]).

Study Design

Only published RCTs that are available in full text will be included. The articles have to be provided in English or German language.

Exclusion Criteria

Studies will be excluded if the intervention is exclusively mobile based (delivered via a mobile app). Interventions focusing on gatekeepers, for example, health care providers and teachers, will also be excluded. We will not restrict inclusion by year of publication.

Information Sources and Search Strategy

The systematic literature search will be conducted in the following databases: PsycINFO, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and the Centre for Research Excellence of Suicide Prevention (CRESP) Database. Search strings enabling a sensitive search (incorporating numerous Medical Subject Headings, subject terms, keywords, and publication types associated with internet, eHealth, suicide, or RCT) were developed for PsycINFO, MEDLINE, and CENTRAL (see [Multimedia Appendix 1](#)). As CRESP contains a manageable number of trials, we will screen all studies included in the database. We performed a pilot testing of the outlined search strategy. Hand searches identified 5 eligible trials [33-37]; 100% of these trials were identified by searching the databases using the search strings. In addition, a search in the clinical trial register, ClinicalTrials.gov (provided by the US National Library), will be performed to identify ongoing trials. Hence, this review will provide not only the current state but also the outline of emerging developments in the field. We will screen the reference lists of all included studies and relevant reviews articles for additional studies (backward search), and we will screen studies that cited the included studies and relevant reviews (forward search). In addition, we will perform hand searches. We plan to conduct the searches until April 30, 2019. Gray literature will not be included. Registered trials that have

not been published will be used to evaluate possible publication bias.

If it remains unclear whether a study meets the eligibility criteria or if relevant data or analyses have not been reported, we will contact the authors for clarification. We will also contact authors to ask for unpublished results when study protocols without a subsequent publication are identified.

Data Collection and Analysis

Study Records

A total of 2 reviewers (RB and MT) will independently screen the studies for eligibility in a hierarchical approach. The identified articles will be managed in CITAVI. In a first step, the reviewers will screen titles and abstracts identified in the databases. In a second step, they will screen full-text articles. Studies that do not meet the eligibility criteria will be moved to an exclusion folder. Potential discrepancies will be resolved in a discussion with a third researcher (LS). The selection process will be displayed in a PRISMA flowchart [28].

Data Extraction and Management

The following information will be extracted from the included studies: study identification items, study design, description of the intervention and control condition, technical characteristics, population, setting, treatment engagement/dropout, outcome variables, and results. We will use a data extraction form. All data will be double-checked by the second reviewer.

Assessment of Risk of Bias in Individual Studies

The risk of bias will be assessed with the Cochrane Risk of Bias tool [38] by 2 independent researchers (RB and MT). Potential discrepancies will be resolved in a discussion with a third researcher (LS). The following domains will be analyzed: (a) random sequence generation, (b) allocation concealment, (c) blinding of participants and personnel, (d) blinding of outcome assessment, (e) incomplete outcome data, (f) selective reporting and (g) other sources of bias.

In psychological interventions, blinding of participants or clinicians is not possible. This will result in a high risk of bias rating of (c). We will discuss findings in terms of risk of bias.

Qualitative Synthesis

We will narratively describe the relevant characteristics of included interventions and possible limitations of study designs. The relevant results will be reported in text as well as in a summary of findings table in line with the PRISMA guidelines [28].

Meta-Analysis

Only studies that provide a quantitative measure of suicide ideation will be included in the meta-analysis. We will analyze heterogeneity by providing I^2 statistics and, if possible, forest plots. According to the GRADE handbook, $I^2 < 40\%$ indicates

low, 30% to 60% indicates moderate, 50% to 90% indicates substantial, and 75% to 100% indicates considerable heterogeneity [39]. If studies fail to show sufficient homogeneity ($I^2 < 60\%$) in at least two trials [40], we will not undertake meta-analytic pooling. However, inconsistency may arise from differences in populations, interventions, outcomes, and study methods [39]. If appropriate, we will conduct subgroup analyses according to these categories. We will perform subgroup analyses for adults versus youth, guided versus unguided interventions, and varying control conditions, if possible. A random effects model will be applied. We will estimate standardized mean difference values and the respective 95% CIs. The RevMan software (Review Manager version 5.3 for Windows from the Nordic Cochrane Centre, The Cochrane Collaboration, 2014) will be used for calculation. If possible, sensitivity analyses will be conducted to examine the influence of trials with high risk of bias on the pooled effect size. If meta-analytic pooling is not appropriate, we will only describe reported data narratively.

Meta-biases: Confidence in Cumulative Evidence

Trial registrations and study protocols will be identified. This will enable us to determine whether a publication bias is likely, that is, if studies have been published selectively. If the number of retrieved studies is sufficient, we will use visual inspection of funnel plots to assess publication bias and inspect an international trial registry for unpublished studies.

The quality of evidence will be evaluated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [41] by 2 independent researchers (RB and MT). Discrepancies will be resolved in a discussion with a third researcher (LS). Dimensions of the GRADE rating will be risk of bias, inconsistency of results, indirectness of evidence, imprecision of effect size, and publication bias.

Results

This review is currently in progress. Data extraction started in April 2019. Our final paper is expected to be submitted in September 2019.

Discussion

Suicide ideation is a highly prevalent condition. Owing to low treatment-seeking [5], it is of great importance to provide individuals at risk of suicide with appropriate and low-threshold treatment options. This systematic review and meta-analysis will address a gap in research by evaluating the effectiveness of ISIs that are specifically designed for suicide prevention. This will provide crucial information for the implementation of ISIs into clinical practice. Hence, we will be able to provide recommendations to policy and research based on the current best available evidence.

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Authors' Contributions

LS and RB initiated the study. RB wrote the first draft of the manuscript. All authors were involved in the revisions and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Search strings for MEDLINE, PsycINFO and CENTRAL.

[[PDF File \(Adobe PDF File\), 131KB - resprot_v8i7e14174_app1.pdf](#)]

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Abbreviations

CENTRAL: Cochrane Central Register of Controlled Trials

CRESP: Centre for Research Excellence of Suicide Prevention

eHealth: electronic health

GRADE: Grading of Recommendations Assessment, Development and Evaluation

ISI: internet-based self-help intervention

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT: randomized controlled trial

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Protocol

Promoting Small Business Support of Youth Physical Activity in Low-Income, Minority Neighborhoods: Protocol for a Randomized Controlled Trial

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Abstract

Background: An unacceptably high percentage of our nation's low-income, minority youth (age<18 years) are not regularly physically active. One reason for this could be their lack of access to quality youth physical activity opportunities (YPAOs). Our previous research found that small businesses (<500 employees), which represent over 99.64% (27.9/28.0 million businesses in United States) of all employers, are powerful resources for creating and improving YPAOs. In accordance with the socioecological model and established philanthropic principles, we developed an alpha version of an intervention (alpha-i) for increasing small businesses' involvement with YPAOs.

Objective: The aims of this proposed study are to (1) create a beta version (beta-i) of the intervention and (2) conduct a pilot study of its impact on small business support for YPAOs and YPAO utilization by the youth in low-income, minority neighborhoods.

Methods: The alpha-i will be refined using information from focus groups and surveys conducted with small business owners and managers, YPAO providers, and parents and guardians of the youths from low-income, predominantly minority neighborhoods. A cluster randomized controlled trial will then be conducted for 1 year to examine the effects of the refined intervention (beta-i) on small business support for YPAOs in 10 low-income, minority neighborhoods. The control group of neighborhoods (n=10) will be provided with a standard practice intervention. The primary outcome for aim 2 will be the percentage of small businesses not supporting YPAOs at baseline that subsequently provide support for YPAOs at follow-up. We also will consider the US dollar equivalent of all types of support (monetary, goods/services, and time) donated for YPAOs by small businesses. In addition, we will examine the impact of the increased small business support for YPAOs on YPAO utilization by the youth.

Results: As of May 1, 2019, all YPAOs and small businesses in the study neighborhoods have been identified, and surveys have begun with these groups. In addition, 9 focus groups were completed, and the data have been transcribed. We anticipate that manuscripts regarding these aspects of the study will be submitted in fall 2019.

Conclusions: The proposed study is significant because it will provide evidence that an easily replicated approach can be used to increase small business support for YPAOs and that this support results in greater use of the YPAOs by youth. A logical next step will be to determine if YPAO changes resulting from increased small business support positively influence youth physical activity levels.

ClinicalTrial: ClinicalTrials.gov NCT03936582; <https://clinicaltrials.gov/ct2/show/NCT03936582>.

International Registered Report Identifier (IRRID): DERR1-10.2196/13141

KEYWORDS

health promotion; public health; exercise; children; ethnic groups

Introduction

Background

Health benefits can be gained by the youths (age < 18 years) who regularly participate in physical activity; for example, physical activity reduces the incidence of overweight, obesity, and chronic diseases [1-4]. Unfortunately, many youths fail to engage in adequate levels of physical activity. National data show that 3 out of 4 youths (aged 12-15 years) do not meet physical activity guidelines for moderate to vigorous physical activity (MVPA), and 7.6% are not involved in MVPA at all [5]. The problem is even more glaring for the minority youth. The 2013 Youth Risk Behavior Surveillance survey indicated that 21.5% of minority youth, compared with 12.5% of nonminority youth, were performing less than the recommended 60 min per week of MVPA [6]. In 1995, similar findings were reported—the minority youth participated in less MVPA than their nonminority peers [7]. This persistent difference has undoubtedly contributed to the disproportionately high burden of disease currently seen in the low-income, minority youth. Recent estimates indicate that 8.0% of African American children (aged 2-19 years) are considered severely obese versus only 3.9% of white children and the incidence of type 2 diabetes is a staggering 5 times higher [8-10]. Given their typically poor outcomes, it is unlikely that school-based physical education (PE) or physical activity interventions conducted in isolation (ie, individual level) will have a sufficient positive impact on physical activity [6,11]. Although over half of the high school youth are enrolled in PE, only 29% attend class on a daily basis and less than half are actually physically active during class [12]. Clearly, discovering innovative ways to enable and encourage the low-income, minority youth to be more physically active is a public health priority, requiring novel ideas and sustainable solutions.

The socioecological model has been used to explain why the youth are not more physically active. Briefly, the model suggests physical activity behavior is determined by intrapersonal (eg, self-motivation), interpersonal (eg, social support), and environmental (eg, availability of programs) factors [13]. Although intrapersonal and interpersonal factors have been studied extensively, they have not been shown to adequately explain youth physical activity or provide a basis for the development of effective interventions for the youth [14]. On the other hand, the evidence supporting a role of the environmental factors has grown exponentially in recent years [15-18]. Community sprawl, safety concerns, pedestrian-unfriendly street designs, and increases in sedentary activities (eg, television), among others, have a negative effect on youth physical activity and fitness [19-23].

Perhaps the strongest and the most influential environmental determinants of youth physical activity are the availability and adequacy of youth physical activity opportunities (YPAOs). They have been defined as programs and places available to the

youth with components/amenities that typically require/involve physical activity [24-28]. A park with sports fields or playgrounds or a dance class at a community center are good examples. Significant associations have been found between youth physical activity and access to affordable YPAOs, and lack of YPAOs has been cited by the youth as a major barrier to being active [24,29-35]. The quality of the YPAOs (eg, staff training and equipment) also plays a role and has been shown to be as vital for increasing youth physical activity as having access to YPAOs [21,36,37-40]. Health-related fitness, including body fatness, has been associated with YPAOs, and the youth involved with YPAOs learn sportsmanship, acquire new skills, improve social skills, and are more likely to participate in physical activity as adults [15,41-45].

YPAOs assume added importance if they are in one's local environment or neighborhood. Walking by the youth (aged 5-20 years) is positively associated with having access to nearby (<1 km distance from home) recreation or open spaces [46]. Middle school children engage in more physical activity if they have available after-school programs and high-quality local facilities near home [25]. Children provided with a safe schoolyard in their neighborhood become more physically active than children not granted such an amenity [21]. Others have shown that recreational facilities closer to home are more likely to be used than facilities located elsewhere and that local neighborhood characteristics, especially the presence of trails and places for physical activity, play a role in leisure activity patterns [24,26,47]. The presence of YPAOs varies between neighborhoods, with economically disadvantaged and minority neighborhoods having significantly fewer YPAOs than more affluent neighborhoods [48-52]. This deficiency, along with concerns about transportation and YPAO expenses, is expressed significantly more often by the parents of the minority youth than the parents of the nonminority youth [31]. Few YPAOs and associated expenses have been cited as critical barriers to reversing physical inactivity among the low-income, minority youth [53-56].

Small businesses (<500 employees) represent 99.64% (27.9/28.0 million) of all businesses operating in the United States. Total revenues typically exceed US \$1 trillion annually and over half a million new businesses start each month [57]. More than one-fifth of small businesses are minority-owned with revenues totaling nearly US \$700 billion [58]. Established philanthropic principles have been used to explain behaviors of different types of entities including small businesses [59-66]. Event sponsorship or sponsorship marketing refers to supporting various types of initiatives ranging from educational partnerships to YPAOs [59]. Small businesses heavily engage in event sponsorship compared with large businesses and they prefer to contribute to events connected to their local neighborhood [60-62,64]. It allows them to reach their target market more efficiently, expose their product/service directly to the market, give back to the neighborhood that supports them, and present an image of a

socially responsible organization [63]. These actions can lead to increased consumer support and ultimately greater revenue [65,66]. Not surprisingly, when small businesses decide to support an initiative, they tend to sustain that support [67].

The strong preference by small businesses for sponsoring local programs sets up a powerful force that, if utilized effectively, would have a dramatic and lasting impact on the quantity and quality of YPAOs and, ultimately, physical activity and health in low-income, minority neighborhoods. Supporting this contention are findings from our preliminary study showing that although a majority of small businesses do not currently support YPAOs (~60%), a large percentage (88%) of these non-YPAO supporters believe they should [67,68].

Objectives

In accordance with the socioecological model and established philanthropic principles, we developed an alpha version of an intervention (alpha-i) for increasing small businesses' involvement with YPAOs. We are now poised to create a beta version (beta-i) and conduct a pilot study of its *impact* on small business support for YPAOs and *YPAO utilization by the youth* in low-income, minority neighborhoods. To meet this objective, we will complete the following specific aims and address the specified hypotheses.

- *Aim 1:* Refine alpha-i components by conducting focus groups with small business owners, YPAO providers, and parents and guardians of the youth from low-income, predominantly minority neighborhoods. Results of the qualitative analysis will inform final tailoring of the intervention to create the beta-i that will be tested in aim 2.
- *Aim 2:* Determine the effect of the beta-i on small business support for YPAOs by conducting a cluster randomized controlled trial with randomization at the neighborhood level. The intervention neighborhoods (n=10) will receive the beta-i, whereas the control neighborhoods (n=10) will be provided a standard practice intervention for a period of 1 year.
- *Hypothesis 1:* The beta-i will result in a significantly greater increase in the percentage of small businesses providing support (eg, monetary donations) for YPAOs than a standard practice intervention.
- *Hypothesis 2:* The US dollar equivalent of all types of support (monetary, goods/services, and time) donated for YPAOs by small businesses exposed to beta-i will be greater than that donated by small businesses exposed to the standard practice intervention.
- *Aim 3:* Examine the impact of the increased small business support for YPAOs on YPAO utilization by the youth. The primary outcome will be the percent change in the number of youths participating in YPAOs from baseline to follow-up.
- *Hypothesis 3:* The percent increase in youth participants from baseline to follow-up will be significantly greater at YPAOs in the treatment neighborhoods receiving support

from small businesses than at YPAOs in the control neighborhoods.

Methods

Procedures for Aim 1

The timeline of activities completed in aim 1 is given in [Multimedia Appendix 1](#). The first set of activities involved identifying the study neighborhoods and the small businesses and YPAOs in these neighborhoods. Next, focus groups were conducted, and a local advisory board was formed. The focus group data were used by the local advisory board to refine the alpha components of the intervention we previously developed to create a beta version that was tested in aim 2 ([Multimedia Appendix 2](#) [69-76]).

Study Neighborhood Identification

We used a multistep process recommended for use in urban health research to identify 27 distinct neighborhoods in New Castle, Delaware (mainly Wilmington, the largest city in the state) meeting our inclusion criteria requiring a minority concentration greater than 50%, median household yearly income in the lower third of all neighborhoods in these areas, and a land use mix that is at least 30% residential and at least 15% retail/commercial [77]. From the pool of 27 neighborhoods meeting our inclusion criteria, 20 were randomly selected to participate in the pilot study of the beta-i. Pairs of neighborhoods separated by at least 0.5 miles constituted the randomization unit with 1 randomly assigned to the treatment and the other to the control (see *Interventions* section later in this paper for a description of the study arms). This helped reduce the risk of contamination.

Small Businesses and Youth Physical Activity Opportunities Identification

During November and December 2018, we identified all small businesses and YPAOs in the study neighborhoods using various approaches and sources we had used in previous studies (registries, internet/phone books, media, community tours, and community members) [52,67,68,78]. YPAOs were defined as programs and places available to the youth with components and amenities that typically involved physical activity [24-28,52,68]. Some examples of YPAOs we found were playgrounds, ballfields/courts, classes, sports leagues, and various types of structures (eg, jungle gym). These YPAOs were located mainly at parks, churches, and for-profit businesses, which is consistent with previous research [52,79]. We included school components (eg, athletics) because these are important YPAOs [80]. YPAOs not available to the public (eg, worksite exercise programs) or those not designed primarily for physical activity (eg, sidewalks/streets and stairs) were not included. A tracking system developed in our previous study will be used to detect new YPAOs that emerge and dissolve during the intervention [78]. The system involves monitoring local media and internet sources, canvassing neighborhoods, and obtaining feedback from YPAO providers. Follow-up procedures (eg, phone calls) will be carried out to confirm if a YPAO is actually new and baseline data on existing YPAOs will be referenced to quantify the emergence of new ones. The information

obtained on YPAOs was and will be carefully reviewed to eliminate duplication.

Focus Groups

Focus groups allowed us to obtain unique perspectives from neighborhood stakeholders, which were used to refine alpha-i components to better meet the needs/resources of the treatment neighborhoods. Participants were asked to consider components, provide recommendations, and suggest modifications. We specifically looked for input on our strategy for increasing support for YPAOs, how to efficiently handle administrative tasks, promoting YPAO provider fund use, ways to reduce barriers to using YPAOs, and long-term sustainability.

Between January and March 2019, we conducted 9 focus groups and analyzed the data. Each focus group was comprised 6 to 8 members recruited from the 27 low-income, minority neighborhoods that had met our inclusion criteria as outlined above. Participation was solicited from small business owners (3 focus groups), YPAO providers (3 focus groups), and parents and guardians of the youth (3 focus groups), using our personal contacts, referrals, flyers, and ads in local publications. Incentives (eg, food/drink, \$20 gift card) were used to encourage participation and all group sessions were held in one of the study neighborhoods. The number of groups we used was adequate for ensuring saturation, providing us with a comprehensive picture of the domains and helping achieve focus group goals [81,82].

Each focus group lasted about 90 min and was moderated by a research team member with extensive training in qualitative methodology. The moderator was assisted by a second scientist who documented focus group proceedings and other process data (eg, nonverbal behaviors) [83]. Using a focus group guide developed for this project, the moderator walked members through the topics to be covered and used probes to clarify select responses or solicit more detailed information [83]. Members were given a chance to ask questions to ensure they understood the process. At the end of each focus group, the team debriefed by reviewing notes and discussing particularly relevant areas (eg, presence of domineering members) [84,85]. Insights from the debriefing sessions were used to enhance the quality of the data by providing an explanation for areas that seemed ambiguous after all data were transcribed and coded. Each session was audiotaped with 2 electronic digital recorders for later transcription.

Preparation for Aim 2

The final activities that were completed in aim 1 involved the refinement of alpha-i components by the local advisory board, mainly using focus group and survey outcomes, and the formation of the beta-i. We also prepared for baseline data acquisition and developed the tracking mechanism that will be used to monitor donations to the fund and the distribution of donations. This will allow us to closely examine the cost of fund administration. We will be interested in the costs to solicit, maintain, and track donations, offer recognition (process and materials), identify YPAO providers, and distribute funds to YPAO providers. Information from donors and YPAO providers will include name, location, contact information, and a detailed

description of the donation (given or received). Because donations could be monetary (US dollars) and nonmonetary (goods/services and time), we will use the Statement of Financial Accounting Standards 157, Fair Value Measurements guide, to properly determine the US dollar value of all donation types. By the end of May 2019, the development of the beta-i was complete.

Procedures for Aim 2

The timeline of activities involved in aim 2 is presented in [Multimedia Appendix 3](#). During May and June, we completed baseline assessments on small businesses and YPAOs. The beta-i and the control intervention will then be implemented from July 2019 to June 2020. Follow-up assessments, which will mirror baseline assessments, will be conducted from July to August 2020. The project completion date is set for the end of August 2020.

Business Surveys

We developed the small business policy survey to capture the presence and development of small business support for YPAOs [67]. Using a test-retest design, we found high reliability coefficients (all>.95) for questions about YPAOs (eg, number supported and type), other physical activity promotion policies, and business/owner characteristics. In-person surveys were completed by trained personnel with a randomly selected sample of 244 small business owners. If an owner was not available, a supervisor or manager was interviewed if they indicated having the knowledge to answer our questions. We attempted to gather detailed information about the business (eg, marketing budget), the owner (eg, sex), and involvement with neighborhood initiatives. They were asked if they supported YPAOs and the cost, location, and reason for each YPAO supported. In the follow-up surveys, we will also include a series of open-ended questions to elicit information about the intervention and for the control businesses, questions about possible exposure to beta-i components and if this had influenced their YPAO-supporting activities. A thematic analysis, similar to the process outlined for the focus groups, will be done to analyze these short answer questions.

Youth Physical Activity Opportunity Provider Surveys

In-person interviews were conducted by trained personnel with a randomly selected sample of 44 YPAO providers. Our reliable YPAO survey was used to gather detailed information on the YPAO including the number of youth participants, descriptions of all features and amenities, programmatic information (eg, fees, operating times, and sessions per week), personnel qualifications, and start-up and operating costs including how costs were covered [52]. If a small business providing a YPAO was selected for the survey, we completed the YPAO survey with them in addition to the small business survey.

Interventions

As stated previously, the treatment intervention (beta-i) will be a derivative of the alpha-i intervention components given in [Multimedia Appendix 2](#). The control intervention is based on the finding that under normal circumstances, small business owners are seldom asked to provide support for specific initiatives in their neighborhood and they almost never receive

educational material about the benefits of supporting neighborhood initiatives. Usually they are just made aware of organizations (eg, nonprofits) accepting donations [67]. In keeping with this *standard of practice*, small businesses in the control neighborhoods will be offered a minimal intervention with an opportunity to donate to a fund supporting YPAOs. This fund will be established at our institution for credibility and tracking purposes. However, donors to the control fund will not be able to select specific YPAOs to support, donate directly to their neighborhood, or receive recognition for their donations. In addition, the email messages they receive will not utilize a marketing strategy and only contain basic information for donating along with contact information if they have any questions. A local advisory board will not be formed, and liaisons will not be used in the control neighborhoods. Email distributions in the control neighborhoods will coincide with those made in the treatment neighborhoods. Donations to the control fund will be given to groups not operating in the study neighborhoods to further their mission to provide the youth with low-cost obesity treatment options, such as YPAOs. Provided in [Multimedia Appendix 4](#) is a description of the interventions.

Procedures for Aim 3

Data for aim 3 will be collected at baseline and follow-up as per the measures described under aim 2 as well as additional measures described below and used to address our aim 3 hypothesis. These additional measures will be conducted at baseline and follow-up.

The System for Observing Play and Recreation in Communities

The system for observing play and recreation in communities (SOPARC) will be used according to the established protocols to count the number of youths using public YPAOs [86,87]. Briefly, each public YPAO will be visited by a trained observer who will first locate and map the size, location, and boundaries of all potential areas for leisure-time physical activity (ie, target areas). Then they will perform scans (ie, observation sweeps moving from left to right) of the target areas to obtain the desired information (eg, number and age group). Separate scans will be conducted for females and males. All parks will be assessed at baseline and follow-up 4 times a day on 4 separate days. The daily observation periods will be 7 am to 9 am, 11 am to 1 pm, 3 pm to 5 pm, and 7 pm to 9 pm and the 4 days will consist of 3 weekdays and 1 weekend day. This number of observations is the minimum needed to obtain robust estimates of park user characteristics [87]. Target areas will be assessed during each observation period according to a pre-established order determined by randomization and counterbalancing. During periods of moderate to severe precipitation, observations will be postponed until a later date that corresponds to the cancelled day/time period.

Physical Activity Resource Assessment

Trained field coders will use the Physical Activity Resource Assessment (PARA) to conduct concise (10-30 min) audits of YPAOs where surveys and SOPARCs were completed. The PARA is a reliable ($\rho >.77$) instrument for assessing characteristics of publicly available physical activity resources

including YPAO [50]. It will be used to gain further insight about the quantity and quality of YPAO amenities, features, and incivilities.

Training

Interviewers were trained according to the guidelines developed by The Gallop Organization [88]. Several procedures were used to assure the quality of data collected. Among these were attempts at participant maximization (eg, short introductions), refusal prevention and conversion training, and other quality control functions, such as maintenance of confidentiality, monitoring of interviewers' work, and validation of surveys to ensure respondents had actually been surveyed. Because the number of contact attempts and the patterns of businesses/YPAO operation hours are key factors impacting response rates, 2 attempts were made during each of the following periods: weekday mornings, afternoons, and nights; weekend mornings and afternoons. For the SOPARC and PARA, 2 observers/raters participated in a training session where they were given detailed instructions on the techniques [50,86].

Analysis

Process Evaluations

Process outcomes will inform us of intervention challenges and lessons learned. They will be derived from meeting minutes, debriefing sessions, study records (eg, budgets), small business surveys, YPAO provider reports, adult local advisory board member reports, liaisons, and study team evaluations. The primary process outcomes will be related to the local advisory board (eg, attendance), cost of fund administration and logistics of tracking donations and providing recognition, user satisfaction with donating methods, logistics of using electronic messaging (eg, spam blockers), and recruitment/retention of liaisons. This information will be used to inform planning of future implementations of the intervention and when interpreting/discussing outcomes from this study.

Qualitative Data Analysis Plan

An iterative, 2-phase thematic analysis will be conducted to capture the meaning behind the transcribed text with an overall purpose of creating an increasingly sophisticated and rich description about small business involvement with YPAOs. First, researchers will review the transcribed documents to develop a familiarity with the text and search for the patterns and the themes that occur frequently in a single session or are common across sessions. The data will then be coded by identifying passages that exemplify key concepts or ideas related to the major patterns and themes. The use of multiple reviewers will help establish construct validity and interrater reliability of the coding scheme and identified codes. During the second phase, a computer-assisted qualitative data analysis program (NVivo qualitative data analysis software; QSR International Pty Ltd. Version 12, 2018) will be used to check the rigor of the manual coding, help organize the large volume of data, analyze data, and provide a means for generating reports. Qualitative data analysis is typically iterative, recursive, and dynamic; therefore, we will move between the manual and the electronic process until we are satisfied that the coding scheme and results are representative of the participants' perspectives.

Furthermore, themes identified will be compared with the extant literature on the topic to further validate the findings [89].

Cost Analysis

The detailed information collected about YPAOs will be used to estimate the relative contributions made by small businesses toward their total yearly costs. Total yearly costs will be defined as all costs in the cost model incurred for the YPAO during the past 12 months (Multimedia Appendix 5). No discount rate will be considered for this short period. Cost-effectiveness analyses will be used to describe the total yearly costs incurred by small businesses for supporting YPAOs relative to the number of youths utilizing the YPAOs. Both 1-way and multiple way sensitivity analyses will be performed to measure the robustness of the evaluation.

Power Analysis

Our power analysis was based on the percent change in the proportion of small businesses supporting YPAOs at baseline that subsequently provided support for YPAOs during the intervention. Data to construct the primary outcome will be derived from tracking donations and small business surveys. Power formulas accounted for experimental condition, number of neighborhoods, number of businesses/neighborhoods surveyed, variance estimates of the outcome measure from preliminary studies, and a conservative estimate of the intraclass correlation coefficient (ICC). In our previous research, a 27% versus 8.0% increase in support for community physical activity initiatives by small businesses not supporting them at baseline was observed in the treatment and the control neighborhoods, respectively [78]. On the basis of our previous experience conducting research in neighborhoods and our desire to develop a sufficiently rich and diverse dataset, we tested whether 10 neighborhoods per condition would also provide sufficient statistical power for our primary outcome. Thus, the final power model was based on 10 neighborhoods per condition, 10 small businesses nested in each neighborhood, a difference in proportions of 19 percentage points, and an ICC of 0.05. It was determined that having 10 neighborhoods per condition would give us a statistical power of 86% to yield a statistically significant result. In a previous study, we completed interviews at 66.2% (98/148) of the small businesses visited [67]. Of them, 30.4% (45/148) refused and interviews could not be completed with an eligible individual at 3.4% (5/148) of businesses. For the proposed study, we expect an average of 50 small businesses per neighborhood or 500 per condition. Therefore, we will obtain a random sample at baseline of 185 small businesses per condition and expect to complete a baseline survey at 66.2% (122/185) per condition. Of these 122, we expect a loss-to-follow-up of 15% to 17%, giving us 104 businesses per condition or ~10 per neighborhood. This will allow us to achieve our goal of interviewing no less than 20% of the eligible businesses and obtaining a representative sample [84].

Approach to Analysis

Before developing statistical models, an examination of the univariate distribution of variables will be conducted (eg, scatter plots). Statistics, such as means or proportions, standard errors, ranges, and estimates of skewness and kurtosis will be derived

for the overall samples and stratified by condition and characteristics of small businesses and YPAOs using SAS 9.4 and used as guidelines in the application of both bivariate and multivariate analyses [85]. Data transformation procedures (eg, logarithmic) may be applied to quantitative variables whose distribution shows considerable departure from normality. In the case of discrete variables, results will provide guidance in recoding these variables appropriately for statistical modeling. Graphical data will be developed to provide visual comparisons of changes across time between the 2 study conditions on key measures of small business involvement and YPAO utilization by the youth. The primary outcome will be examined using a mixed-model, nested logistic regression analysis of proportions where (1) businesses are nested in neighborhoods and (2) neighborhoods are treated as a nested random effect within treatment conditions. Generalized models will be used to explore potential mediators/moderators of outcomes. For example, a model will be constructed with experimental condition (treatment vs control), neighborhood variables (eg, median income), and business variables (eg, number of employees and years in business) as the independent variables and mean percent change in small businesses donating as the dependent variable. In another model, donation amounts equated to US dollars will be used as the dependent variable. To accommodate the complex nature of the research design, the SAS PROC GLIMMIX and SAS PROC MIXED (SAS, 2015) procedures will be used.

Sample Size Determination for Aim 3

The primary outcome for aim 3 will be the percent increase in youth participants from baseline to follow-up. We hypothesize that the increase will be significantly greater at YPAOs in the treatment neighborhoods receiving support from small businesses than at YPAOs in the control neighborhoods. Previously in low-income, minority neighborhoods, we found an average of 46.7 (SD 37) youths participating in YPAOs [52,90]. With the proposed sample size of 10 neighborhoods per condition from aim 2, our pilot parameter estimates, an ICC of 0.05, and a desired power of at least 80%, we would need 35 YPAO assessments per condition to detect a difference of 0.5 percentage points between conditions at posttest. We expect a total of 140 YPAOs in our 20 study neighborhoods with 20% (28/140) being eligible for SOPARC assessments [52]. Given a 15% to 17% attrition rate and a response rate of 60%, we will randomly select 90 YPAOs for interviews to yield 44 YPAOs with baseline and follow-up data from the survey. These will be combined with the 28 YPAOs observed, giving a total of 70.

Potential Problems and Solutions

Attrition and Evaluation of Missing Data

Over the past 2 decades, our research team has developed methods to ensure low rates of missing data in our projects. One aspect of this study most likely to result in missing data is the longitudinal assessment of businesses/YPAOs. We will attempt to minimize missing data by maintaining contact with study businesses/YPAO providers and if dropout does occur, we will attempt to determine the reasons why and how much of their study participation was affected. We will examine characteristics associated with attrition and adjust models for attrition and/or baseline group differences.

Appealing to Small Businesses

We have been successful in the past in obtaining information from small businesses and soliciting their support for community physical activity initiatives. In the proposed study, we expect to elicit significant increases in support for YPAOs from small businesses in the treatment neighborhoods because the intervention contains numerous components that stimulate donations from small businesses.

Measuring Youth Physical Activity Opportunity Utilization

We do not foresee a problem recruiting YPAO providers to participate in the study. We were successful at obtaining detailed information from YPAO providers in a previous study and, in the proposed study, they will receive compensation for their participation and have the opportunity to receive donated funds [52].

Results

The study protocol was approved by our institutional review board on July 13, 2018. All preparatory activities (eg, hiring, training, and data collection procedures finalized) were completed on 31 October 2018. In addition, 20 study neighborhoods comprising 53 US census block groups meeting the inclusion criteria were identified and randomly assigned to treatment or control conditions (Multimedia Appendix 6). A total of 9 focus groups were completed with members from the study neighborhoods who were small business owners, YPAO providers, or parents and guardians. Recruitment was accomplished in a number of different ways—requests made at events (eg, business chamber meeting), business chamber networking, direct contact (eg, email, phone, and site visits), ad placements, and active recruitment at community locations. Focus group data have been transcribed and are currently being analyzed. It will be utilized in May 2019 to revise any components of the intervention and expected results will be published in fall 2019.

In December 2018, a database containing the names, addresses, and geolocations (eg, US census block group) of the 87,982 businesses currently licensed in Delaware was obtained from the Delaware Department of Finance: Division of Revenue. The database was edited to include only small businesses with a physical, nonresidential address located in 1 of our 20 study neighborhoods. During May and June, 2019, baseline surveys were completed with 244 owners and managers of small

businesses in the study neighborhoods. Data from small businesses will be analyzed in July 2019 and results will be disseminated in August 2019. In addition, a total of 96 YPAOs were identified in the 20 study neighborhoods, and interviews have been conducted with 35 nonpark YPAOs from May 6 to June, 2019. The park YPAOs (n=27) were examined in June, 2019 using the SOPARC and PARA methods to determine usages and presence/absence of amenities.

Discussion

We are 10 months into this study and have achieved the milestones set forth in the proposal. Preparation activities, including the identification of study neighborhoods and small businesses and YPAOs in these neighborhoods, and focus groups have been completed. The focus group data are currently being analyzed and we have just completed (June 2019) baseline surveying of small business owners and managers and YPAO providers. It is anticipated that findings will be disseminated in the fall of 2019.

Research in this area has typically been on policies targeting employee wellness programs at large corporations [91]. The proposed study will be the first to generate evidence on changing small business policies to mobilize their resources for YPAOs by applying previously proven strategies for stimulating support of community initiatives in a novel way. To our knowledge, we are the only group attempting to understand how the power of small businesses can be harnessed to promote healthy lifestyles in the youth. This effort will generate new knowledge about the alternative sources of support (eg, private sector) for YPAOs. Most existing descriptions of community-level physical activity interventions focus on support emanating primarily from governments and government-based institutions, such as public schools [92,93]. Increasing YPAO support from small businesses could result in a shift (reduction) in resource responsibility for youth physical activity promotion from these more traditional sources. A reduction in support from government-related entities may actually stimulate private giving for community initiatives [94,95]. Economists, public health personnel, and government officials would view such a shift as an improvement in the use of resources, as well as a cost-effective method for providing sustainable interventions to promote health [75,96]. Furthermore, having additional funds for health promotion in low-income areas opens the door for implementing novel approaches using the latest technology (eg, 3-dimensional printed physical activity models) and mobile health apps [97,98].

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Aim 1 activities.

[[PNG File, 16KB - resprot_v8i7e13141_app1.png](#)]

Multimedia Appendix 2

Intervention alpha components.

[[PDF File \(Adobe PDF File\), 92KB - resprot_v8i7e13141_app2.pdf](#)]

Multimedia Appendix 3

Aim 2 activities.

[[PNG File, 18KB - resprot_v8i7e13141_app3.png](#)]

Multimedia Appendix 4

Description of treatment and control interventions.

[[PNG File, 16KB - resprot_v8i7e13141_app4.png](#)]

Multimedia Appendix 5

Cost model.

[[PNG File, 10KB - resprot_v8i7e13141_app5.png](#)]

Multimedia Appendix 6

Characteristics of study neighborhoods [means (standard deviations)].

[[PNG File, 8KB - resprot_v8i7e13141_app6.png](#)]

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Abbreviations

- alpha-i:** alpha version of intervention
- beta-i:** beta version of intervention
- ICC:** intraclass correlation coefficient
- MVPA:** moderate to vigorous physical activity
- PARA:** Physical Activity Resource Assessment
- PE:** physical education
- SOPARC:** system for observing play and recreation in communities
- YPAO:** youth physical activity opportunity

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Protocol

Publicly Funded Home and Community-Based Care for Children With Medical Complexity: Protocol for the Analysis of Medicaid Waiver Applications

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Abstract

Background: Children with medical complexity are a group of children with multiple chronic conditions and functional limitations that represent the highest health care utilization and often require a substantial number of home and community-based services (HCBS). In many states, HCBS are offered to target populations through 1915(c) Medicaid waivers. To date, no standard methods or approaches have been established to evaluate or compare 1915(c) waivers across states in the United States for children.

Objective: The purpose of this analysis was to develop a systematic and reproducible approach to evaluate 1915(c) Medicaid waivers for overall coverage of children with medical complexity.

Methods: Data elements were extracted from Medicaid 1915(c) approved waiver applications for all included waivers targeting any pediatric age range through October 31, 2018. Normalization criteria were established, and an aggregate overall coverage score was calculated for each waiver.

Results: Data extraction occurred in two phases: (1) waivers that were considered nonexpired through December 31, 2017, and (2) the final sample that included nonexpired waivers through October 31, 2018. A total of 142 waivers across 45 states in the United States were included in this analysis. We found that the existing adult HCBS taxonomy may not always be applicable for child and family-based service provision. Although there was uniformity in the Medicaid applications, there was high heterogeneity in how waiver eligibility, transition plans, and wait lists were defined. Study analysis was completed in January 2019, and after analyzing each individual waiver, results were aggregated at the level of the state and for each diagnostic subgroup. The published results are forthcoming.

Conclusions: To our knowledge, this is the first study to systematically evaluate 1915(c) Medicaid waivers targeting children with medical complexity that can be replicated without the threat of missing data.

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KEYWORDS

Medicaid; children with medical complexity; home and community-based services; policy analysis; economic evaluation

Introduction

Children with medical complexity (CMC) are a growing population of medically fragile children (between birth and the age of 21 years) with complex, multisystem disease states; technology dependence; severe functional limitations;

complicated treatment regimens and therapies; high utilization of care; and numerous surgical interventions [1-5]. CMC are believed to be extremely susceptible to inequities in health due to access limitations and extreme out-of-pocket financial burden for families [6]. Caring for CMC within a fragmented health care system can be challenging for health care providers [7,8]. Because of numerous hospitalizations, CMC must have care

transitions that are coordinated from intensive and acute care settings to ambulatory and community health resources and home care [9]. Caring for CMC at home is a resource- and emotionally intensive experience for families and often results in one partner remaining at the home to provide 24-hour care [3,5,10-13].

There are long-term care funding opportunities for home- and community-based care of CMC; however, each state interprets the eligibility and service provision differently. In many states, long-term care services and support for CMC are provided through the Medicaid Home and Community-Based Services (HCBS) 1915(c) Waivers (implemented through section 1915 of the Social Security Act) and are named such because they allow states to waive certain Medicaid eligibility criteria [14]. HCBS waivers provide states the flexibility to define populations that are high risk based on age and medical condition(s) and to disregard income and resource rules that are traditionally used for Medicaid qualification [15]. All waiver programs must not cost the federal government any more than that if the states did not have the waiver (ie, cost neutrality) [16]. In order to guarantee cost neutrality, states often limit the number of people served under a waiver [16]. Based on the 2013 data, all states reported using cost control measures when implementing the 1915 waivers, such as restrictive functional limitation standards, enrollment limits, or waiting lists, and the average waiting time for services exceeded 2 years [17]. Complicating this financing structure is the fact that children requiring HCBS can be covered through different sources of public and private insurance, which makes overall coverage determination challenging to assess from a policy context [18-25].

To date, no systematic evaluations exist for the Medicaid waiver programs targeted toward children, and there is limited guidance for state policy development and implementation. Previous economic and policy evaluations of the HCBS waiver programs have primarily focused on adult populations and even then, the literature has been incredibly sparse [26,27]. To our knowledge, there is only one systematic evaluation that included services targeted to children and specifically focused on evaluation of 1915(c) waivers for children who received a diagnosis of autism [15,28,29]. Proof-of-concept economic and policy evaluations exist for individual components of home and community-based Medicaid waivers for adults, but there are virtually no data on how various states interpret coverage of services for CMC [14,26]. Given the paucity of data evaluating state Medicaid waivers for children with the most intensive medical needs, this study will facilitate a formal policy evaluation and analysis supporting a comparative approach to evaluate scope of services. Therefore, the purpose of this analysis was to develop a systematic and reproducible approach to evaluate the scope of coverage and services offered through 1915(c) Medicaid waivers for children.

Methods

Study Design

This study used a cross-sectional comparative analysis approach involving secondary data collected from 1915(c) Approved

Applications that are stored on the Medicaid state waiver website [30]. Each state's Medicaid office initiates an application for individual waivers to the Centers for Medicare & Medicaid Services, where each application is over 300 pages long and has a uniform structure. Once they are approved, most are considered active for 5 years.

The 1915(c) waivers were included in this analysis if they included children (ages 0-21 years) in the age eligibility criteria across any of the following subgroups that can be defined under the waiver of Section 1902(a)(10)(B) of the Social Security Act: disabled-general (physical or other); disabled-other subgroup (medically fragile, technology dependent, brain injury, and HIV/AIDS), intellectual disability/developmental disability (autism, intellectual disability, and developmental disability), and mental illness (serious emotional disturbance). Relevant waivers were included in this study if they were current and had not expired by October 31, 2018.

Data Extraction Process and Variable Transformation

We used a systematic data extraction template to ensure uniformity in the process followed by the three authors (Textbox 1). Elements that were included in the abstraction and analysis included pediatric age ranges, ability to transition to adult care services, cost neutrality components (individual cost limits and capitation), individual services offered through the waiver, ability of time-eligible clients to stay on the waiver, and dollars allocated per person. Scope of services were specifically defined using standard HCBS taxonomy including case management; education services; environment, home, or vehicle modifications; specialized equipment; counseling support for the child; counseling support for the caregiver; personal care/day habilitation; respite care; therapies; and skilled or private duty nursing. These domains were chosen based on theory-based clinical relevance and elements central to the administration and policy relevance of the waivers themselves (ie, overall economic allocation of dollars per individual for an amount of time). Due to the heterogeneity in how states define enrollment and transition plans, the data were maintained as the original text data for subsequent secondary qualitative content analysis [31].

Criteria that were obtained for normalization and thus could be compared across states are defined in Textbox 1 along with the source location in the Medicaid waiver application. All variable transformations are also described in Textbox 1. Two-thirds of the waivers had two reviewers to ensure quality control in the data extraction process, with 100% concordance. One advantage of our methodological approach is that the normalization criteria and coverage score calculation can be achieved without the threat of missing data, because all the elements are required components of the waiver applications. Despite this, we are limited in this approach on sole reliance on the elements provided in the waiver applications and the projected spending and enrollment per waiver rather than actual spending and enrollment. Finally, an additional limitation was that wait list information could not be incorporated in the normalization score due to heterogeneity in how states report wait list numbers.

Textbox 1. Final criteria used and variables created for waiver scores that were compared across 1915(c) waivers.

Domain (original data abstraction in 1915 [c] waiver application) and features and operationalization

Descriptive feature (Section 1, Request information A-F)

- State
- Waiver name
- Expiration
- Level of care

Target group (Appendix B-1: Specification of the Waiver Target Group[s])

- Disabled (general)
- Disabled (specific subgroups)
 - Medically fragile
 - Technology dependent
 - Brain injury
 - HIV/AIDS
- Intellectual disability/developmental disability
 - Autism
 - Intellectual disability (ID)
 - Developmental disability (DD)
- Mental illness
 - Serious emotional disturbance

Target group was described descriptively and transformed into (yes/no) for each target group descriptor

Age coverage (Appendix B-1: Specification of the Waiver Target Group[s])

- Minimum age
- Maximum age (with either actual age or “not applicable” as age maximum if there was no age maximum presented)

The variable was then transformed into a percent pediatric coverage variable representing the percent of the age coverage that ensures those aged 0 through 21 years are covered. For example, if an autism waiver only covers children aged 1 through 6 years, then 5/21 or 23.8% of pediatric ages are covered.

Transition (Appendix B-1: Specification of the Waiver Target Group[s])

Due to the heterogeneity in how transition plans were described (they are a required element in the application and many were vague without specifying a specific adult waiver the child could transition to), *transition* was only given a point in the overall score if the child could age into the same waiver as an adult (ie, where there was no maximum age or the maximum age was 64 years)

Cost containment strategies

- Individual cost limit (yes/no): Appendix B-2: Individual cost limit. Variable transformed into either “no” cost limit or “yes” cost limit (which includes cost limit in excess of institutional costs, institutional cost limit, lower than institutional cost, or cost limit defined by the state). No individual cost limit=1 point
- Limitation in number served (yes/no): Appendix B-3: Number of individuals served Part B - Limitation on number of participants at any time. Not used in final calculation because it appears that most states limit the number on the waiver even if they do not indicate this; determined to be an unreliable indicator
- Additional limits on amount of waiver services (yes/no): Appendix C-4: Additional limits on amount of waiver services. No additional limits on amount of waiver services (ie, “not applicable in application”)=1 point

Raw number of home and community-based services offered (Appendix C-1: Summary of services covered; C-1/C-3 Participant services and service specifications)

Home and community-based services were represented across child/family-centric domains as yes/no in the following domains:

- Case management/care coordination/transition
- Education

- Environment/home or vehicle modifications/transportation
- Specialized equipment/assistive or adaptive technology
- Counseling/psychological support/behavior
- Caregiver/parental support/counseling/family training
- Personal care/day habilitation
- Respite
- Therapies including physical therapy, occupational therapy, vision therapy, speech, and audiology
- Nursing: skilled nursing or private duty
- Medical treatment, dietary assistance, and dental care

Created *breadth of service categories offered*, which is the number of service domains divided by the total (n=11)

Coverage of individuals served (includes both dollars allocated and time on waiver): Appendix B-3: Number of individuals served; Appendix J: Cost-neutrality demonstration; J-1: Composite overview and demonstration of cost-neutrality formula and J-2: Derivation of Estimates

- Individuals served (years 1-5); calculated median individuals served, which is the median of those served in years 1 through 5
- Composite dollar coverage per person per year
- Length of stay on waiver, derived from J-2 derivation of estimates per year. An overall dollar per person per year was calculated by taking the “composite dollar coverage per person per year” multiplied by the (length of stay on waiver divided by 365 days). A mean rate was also calculated as an average of years 1 through 5.
- Increase in waiver capacity over time (yes/no). Does the waiver increase in the number of individuals served, waiver length of stay, or composite dollar coverage over the 5-year waiver length? Yes=1 point.

Wait list (directly from state officials and crowdsourced from Kidswaivers.org)

Due to the lack of ability to compare across states, the wait list was left out of the aggregate coverage score calculation. Wait list was obtained both directly from Medicaid state administrators and from a crowdsourced resource, Kidswaivers.org. Some wait lists were reported as the number of children; however, many were combined children/adults and were not comparable.

Analyses

Central to the study’s analytic strategy was the development of normalization criteria used to assess the overall scope of coverage of each waiver. Following data extraction, we calculated the overall coverage score based on a summation of the individual criteria for each waiver. Specifically, the overall coverage score was calculated as (Percent pediatric covered percent/100)+Transition (1 point if children can age into the existing waiver)+Individual cost limit (1 point if there is NO cost limit)+(Raw services/median raw services)+(Breadth of service categories percent/100)+Additional limits on amount of waiver services (1 point if there are NO additional limits)+Increase in waiver capacity (1 point if there IS an increase in waiver capacity over the 5-year window)+(Overall rate per person per year/median rate per person per year). Individual waiver scores were then summed and aggregated to the level of the state in order to quantify variations in scope of coverage by state and across states. States were ranked from highest to lowest coverage.

Results

This project was funded in 2017, and data extraction was conducted in two phases: (1) waivers that were considered nonexpired through December 31, 2017, and (2) the final sample

that included nonexpired waivers through October 31, 2018. Overall, 142 eligible waivers across 45 states were included in the final analysis, which is still ongoing. Five states chose other funding mechanisms and did not use the 1915(c) waivers for children. By following the process outlined for data extraction, there were no missing data for any of the waiver elements included in this analysis. Study analysis was completed in January 2019, and after analyzing each individual waiver, the results were aggregated at the level of the state and for each diagnostic subgroup. The published results are forthcoming.

While defining the HCBS scope of services for children, we established that existing criteria for HCBS taxonomy developed by Peebles and Bohl (developed for all HCBS, not specific to pediatrics) [32] should be reconsidered for waivers targeted toward children and families. Some HCBS services do not have the same level of applicability for children (eg, adult day services) and could be eliminated for waivers targeting children, while other categories could be further expanded more fully to explicate services that are most pertinent (ie, expanding education into a category and expanding caregiver support so that respite can be a category). All recommendations for child- and family-centric HCBS taxonomy are found in [Table 1](#); these involve recommendations for modifying the existing adult HCBS taxonomy specifically for pediatric and family-centered services.

Table 1. Recommendations for changing existing adult home-and community-based service taxonomy to accommodate children's waivers.

Existing adult HCBS ^a taxonomy as defined by Peebles and Bohl [32]	Recommendations for child/family-centric taxonomy orientation
Case management	In addition to case management, consider adding Care coordination and Transition coordination
Around-the-clock services such as group living (residential habilitation and mental health), shared living, in-home residential habilitation	Group living and shared living are not readily applicable to children's waivers because the vast majority of children reside in the home setting. However, there are some situations where these elements would be applicable.
Supported development such as job development and ongoing supportive development	These elements can remain, and supported development and can be targeted toward adolescents and young adult on child waivers.
Day services such as day habilitation, education services, day treatment, adult day health, medical day care, and community integration	These elements can remain but are not frequently encountered due to the majority targeting adult day health, etc. For child-based waivers, consider splitting out "education" as a stand-alone waiver element and one that has the ability to be synergistic with the 1115 waivers.
Nursing such as private duty nursing and skilled nursing	These elements can remain and are readily applicable.
Rent and food expenses for live-in caregiver	These were dropped from the HCBS taxonomy due to low percent reporting [32].
Home-based services such as home health aide, companion, personal care, and homemaker	Consider combining these with "day services" for child waivers.
Caregiver support such as respite and caregiver counseling/training	Consider breaking out these categories for further clarification due to the importance of the caregiver for children and families. Consider: (1) caregiver/parental support, counseling, and family training and (2) respite.
Mental health and behavioral health such as mental health assessment, crisis intervention, behavior support, and psychosocial rehabilitation	These elements can remain and are readily applicable.
Other health and therapeutic service such as prescription drugs, dental services, occupational therapy, physical therapy, respiratory therapy, cognitive rehabilitative therapy, speech, hearing, and language	Due to the nature of target groups, waivers that include children should consider breaking these out into two categories: (1) Therapies including physical therapy, occupational therapy, vision therapy, speech, and audiology and (2) Medical treatment, dietary assistance, and dental care.
Services supporting participant direction and participant training such as financial management services and information and assistance in support of participant direction	Not readily applicable to children's waivers or families.
Equipment, technology, and modifications such as personal emergency response system, home/vehicle adaptations, and supplies	These elements can remain and are readily applicable.
Nonmedical transportation	We condensed nonmedical transportation into environment/home/vehicle modifications because the priority for the child/adolescent would be vehicle modification.
Community transition services	Not readily applicable to children's waivers or families.

^aHCBS: home-and community-based service.

Discussion

We present a novel analytic methodology to systematically evaluate 1915(c) Medicaid waivers targeting CMC that can be replicated and updated as new waivers are approved. Even though there was uniformity in the Medicaid applications, there was high heterogeneity in how waiver eligibility, transition plans, and wait lists were defined. To accommodate this heterogeneity, normalization criteria for cross-waiver comparison were developed based on the ability to conduct analysis without threats of missing data, which required these important elements to be excluded in the overall coverage score. Greater data harmonization across states can allow expansion of the overall coverage score over time if these elements can be captured in systematic and reproducible ways. Additionally, another major methodological finding was the inability to capture CMC alone by focusing on the "disabled" target groups.

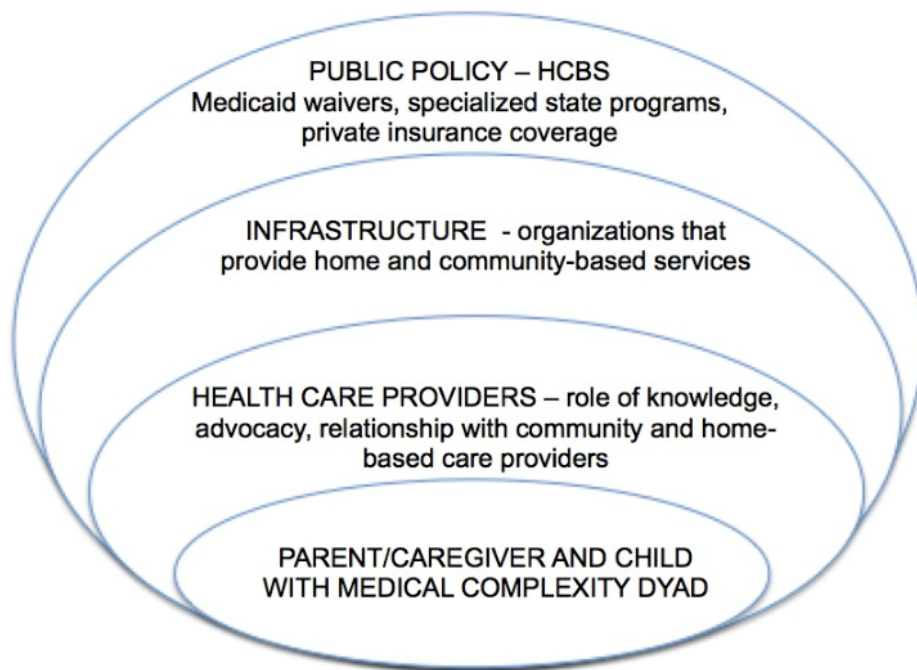
This unanticipated challenge resulted in a broadened approach by including all waivers targeting children. The overall result of this decision will lead to a much more robust data set and likely to greater policy implications and translation.

The 1915(c) Medicaid waivers are not the only mechanism available to fund home and community-based services for CMC, but they are, by far, the most widely used [14,33]. Even if states use a combination of 1915(c) and 1115 demonstration waivers (experimental or pilot programs that promote the objectives of Medicaid), moving to Medicaid managed care or other funding pathways, the overall coverage score can still be used as part of a composite score representing access to HCBS [18,20,34]. Although the overall coverage score represents an important first step in understanding access and differences in state interpretations, several research gaps exist. Using the socioecological model outlined in Figure 1, we believe there is a need for better links between public policy, infrastructure,

health care providers, and a family-centered approach to extend this research by assessing quality outcomes related to HCBS; understanding of family-centered needs regarding timing, frequency, service extensions, preferences with respect to medical homes [35,36], and transition; and formal economic

and policy evaluations of components of waiver services to understand their efficacy as well as studies related to the impact of such waivers on family functioning and economic sustainability (ie, return on investment).

Figure 1. Socioecological model outlining research needs of care of children with medical complexity transitioning from hospital to home. HCBS: home and community-based services.



Conflicts of Interest

Non declared.

Multimedia Appendix 1

Peer-reviewer report from the Lucile Packard Foundation for Children's Health.

[[PDF File \(Adobe PDF File\), 1MB - resprot_v8i7e13062_app1.pdf](#)]

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Abbreviations

CMC: children with medical complexity

HCBS: home and community-based services

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Protocol

An Electronic Health Intervention for Dutch Women With Stress Urinary Incontinence: Protocol for a Mixed Methods Study

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Abstract

Background: Stress urinary incontinence (SUI) is a common problem with a great potential influence on quality of life. Although SUI can be treated effectively with pelvic floor muscle training (PFMT), only a minority of women with this complaint seek help. An internet-based electronic health (eHealth) intervention could make care more accessible. The Swedish eHealth intervention *Tät-treatment of Stress Urinary Incontinence* offers PFMT and has shown to be effective in reducing symptoms in women with SUI. This intervention might be helpful for Dutch women too, but its adoption needs to be studied as the Netherlands differs from Sweden in terms of geographical characteristics and health care organization.

Objective: The objective of this protocol is to investigate the barriers and facilitators to the adoption of an eHealth intervention for Dutch women with SUI and the effects of this intervention.

Methods: We are conducting an explanatory sequential mixed methods study among 800 Dutch women with SUI who participate in the translated version of *Tät-treatment of Stress Urinary Incontinence*. This eHealth intervention takes 3 months. A pre-post study is conducted using surveys, which are sent at baseline (T0), 3 weeks after baseline (T1), posttreatment (T2), and 3 months posttreatment (T3). After the intervention, semistructured interviews will be held with 15 to 20 participants. The primary outcomes are barriers and facilitators to using the *Tät-treatment of Stress Urinary Incontinence*. This will also be analyzed among groups that differ in age and severity of incontinence. A thematic content analysis of the qualitative data will be performed. The secondary outcomes are: (1) effect on symptoms of urinary incontinence, (2) effect on quality of life, and (3) factors that are potentially associated with success. Effects will be analyzed by a mixed model analysis. Logistic regression analysis will be used to study what patient-related factors are associated with success.

Results: Enrollment started in July 2018 and will be finished by December 2019. Data analysis will start in March 2020.

Conclusions: An eHealth intervention for Dutch women with SUI is promising because it can make treatment more accessible. The strength of this study is that it explores the possibilities for an internet-based-only treatment for women with SUI by using both quantitative and qualitative research methodologies. The study elaborates on existing results by using a previously tested and effective eHealth program. Insight into the barriers and facilitators to using this program can enhance the implementation of the intervention in the Dutch health care system.

Trial Registration: Netherlands Trial Registry (NTR) NTR6956; <https://www.trialregister.nl/trial/6570>.

International Registered Report Identifier (IRRID): DERR1-10.2196/13164

KEYWORDS

eHealth; urinary incontinence; women; mixed methods design; pelvic floor muscle training; study protocol

Introduction

Stress urinary incontinence (SUI) is a common problem in women, which has a significant impact on their lives. SUI is defined by the International Continence Society as the complaint of any involuntary urinary leakage on effort or exertion, or sneezing or coughing [1]. Other types of urinary incontinence are urgency urinary incontinence (UUI), which is the complaint of an involuntary leakage accompanied by or immediately preceded by urgency, or mixed urinary incontinence (MUI), which is the combination of both stress and urgency incontinence [1]. SUI is the most prevalent type of urinary incontinence, with prevalence figures ranging from 10% to 39% [2]. Urinary incontinence is associated with a negative impact on quality of life and mental well-being [3], and it affects participation in social activities [4].

Despite the availability of effective treatment options for SUI, only a minority (15% to 38%) of women seek help [5,6]. Pelvic floor muscle training (PFMT) is effective and is recommended as the first-choice therapy for SUI [7,8], which can be provided by a general practitioner (GP) or by a pelvic physiotherapist. Various factors prevent women from help-seeking, such as feeling ashamed, considering urinary incontinence as a consequence of giving birth or of ageing, or lack of knowledge about the treatment options [6,9,10]. Furthermore, GPs encounter difficulties in providing adequate treatment to these women [11,12]. They acknowledge that they experience time restrictions in explaining PFMT and that they lack knowledge and skills for dealing with PFMT [11-13]. Thus, improvement of care for women with SUI is needed.

The delivery of web-based self-help therapy, electronic health (eHealth), is expanding rapidly and has proven to be effective for a wide range of health problems [14]. eHealth appears to be well accepted by women because they prefer the anonymity and flexibility of Web interventions [15]. The feasibility of a Web program as the access point for SUI care seemed to be promising [16]. Various Swedish studies have shown eHealth to be both cost-effective and effective in reducing urinary incontinence symptoms [17-19]. In total, 2 randomized controlled trials showed that symptom severity and incontinence-related quality of life improved significantly after women received an internet-based intervention or mobile phone app intervention with PFMT [17,19]. These treatment effects remained stable after a 1- and 2-year follow-up [20,21], and two-thirds of these women were satisfied with the effect after 2 years [20]. Women appreciated the intervention because they felt that their complaints had been acknowledged [22]. eHealth was not a panacea for all women, however, and a group of women (9% to 22%) sought other treatment after they had participated in the intervention [20,21].

The results from these studies cannot be generalized because a country such as the Netherlands differs from Sweden in

geographical characteristics and, hence, in the way its health care provision is organized. Compared with the Netherlands, Sweden has a large number of inhabitants who live in rural areas, which can restrict the access to the health care facilities, such as physiotherapy [23,24]. Although the Swedish Health and Medical Services Act states that health services should be close by and easily accessible to all Swedish citizens, this is challenging in rural areas, even more so since the health care system was marketized in 2010 [24]. This challenge in access to care may have stimulated the uptake of eHealth in Sweden, which is reflected by the country's long tradition of using telemedicine, one of the first eHealth apps [25]. Due to these differences, therefore, it is questionable whether Dutch women need eHealth for SUI.

Therefore, we perform a mixed methods study with *Tät-treatment of Stress Urinary Incontinence*, an internet-based intervention offering PFMT, for Dutch women with SUI. In this study, we investigate barriers and facilitators to the adoption of an eHealth intervention among Dutch women with SUI who receive the intervention. We also investigate the effects of the intervention on urinary incontinence and quality of life. We expect that this study will provide information that will guide health care providers and policymakers in implementing an eHealth intervention for Dutch women with SUI.

The main objective is to investigate barriers and facilitators to the adoption of an eHealth intervention among Dutch women with SUI. The secondary objectives are to examine the effects of the intervention on symptoms of urinary incontinence and quality of life, and to study factors that are potentially associated with treatment success.

Methods

Study Design

We use an explanatory sequential mixed methods design to study the barriers and facilitators to the adoption of an eHealth intervention among participating women and to gain an in-depth understanding of their experiences with the intervention [26]. We are also interested in exploring whether the barriers and facilitators differ between women who vary in age and symptom severity. The quantitative strand is an observational pre and poststudy with women who participated in the Dutch version of *Tät-treatment of Stress Urinary Incontinence* [27]. All eligible women are given the opportunity to participate, and data are collected at baseline, during the intervention (3 weeks after baseline), immediately after the intervention (3 months after baseline), and at follow-up (6 months after baseline). After the eHealth intervention has finished, a qualitative study will be conducted with semistructured interviews to gain more insight into the women's experiences with the intervention. The Consolidated Criteria for Reporting Qualitative Research will be used to report these qualitative results [28]. The CONSORT-eHealth (Consolidated Standards of Reporting

Trials of Electronic and Mobile Health Applications and onLine TeleHealth) criteria that are applicable to this study will be applied to report our results [29].

Setting and Study Population

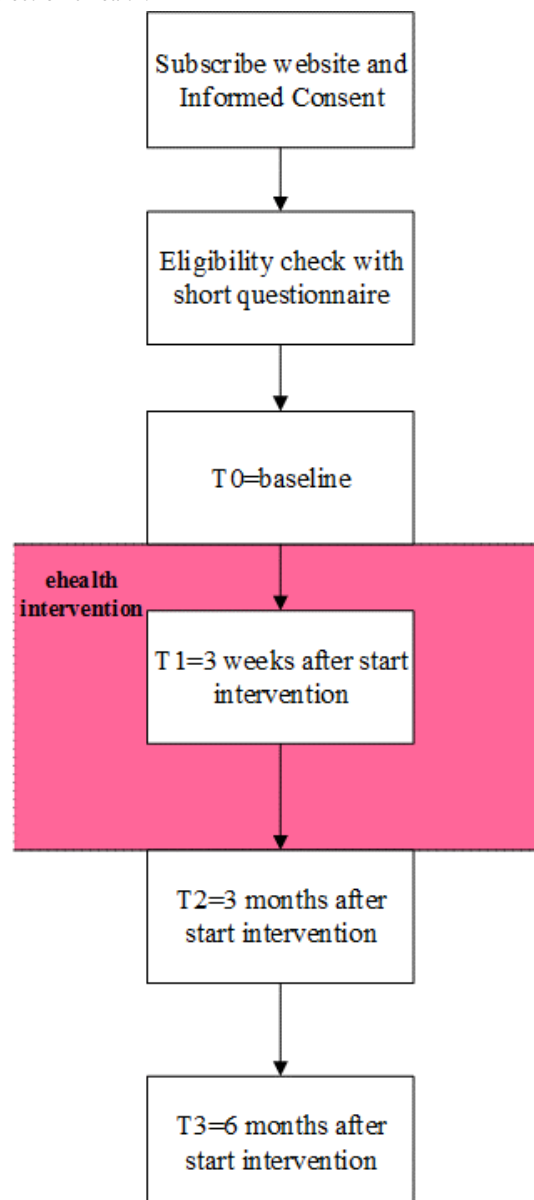
Dutch women can subscribe to the intervention on our website (baasoverjebblaas.nl [27]) between July 2018 and December 2019 without needing referral by a health care provider. After providing informed consent (see recruitment and informed consent), they have to fill in a short questionnaire, after which the researcher checks their eligibility (Figure 1).

The following inclusion criteria are applied: women aged >18 years reported having SUI, being capable of understanding Dutch language, and having internet access. Questions to discriminate between different types of urinary incontinence (SUI, UUI, or MUI) were based on the Questionnaire for female Urinary Incontinence Diagnosis, which has proved to be an adequate tool for self-assessment [30]. Women who reported having MUI are included and informed that the intervention is

specifically designed for SUI, but that PFMT can also have a positive effect on their UUI component. Eligible women receive the baseline questionnaire, and immediately after completion, they receive a unique token that provides them with access to the intervention.

Women are excluded if one of the following criteria applies: participation in another therapy program or trial for SUI; surgery for urinary incontinence in the last 6 months; PFMT from a pelvic physiotherapist in the last 6 months; pregnancy; vaginal delivery in the last 6 months; neurological disease affecting lower limbs (eg, Parkinson, Multiple Sclerosis, and cerebrovascular incident); and malignancy in lower abdomen currently or in the past 5 years (colon, uterus, cervix, bladder, ovary, or vagina). In case of ineligibility, an email is sent to these women, and, if applicable, we advise them to seek help from their GP or to take a look at a certified self-help website, thuisarts.nl [31]. Excluded women will not be given access to the intervention.

Figure 1. Flowchart of the study. eHealth: electronic health.



After the intervention, a subset of 15 to 20 women will be asked to participate in semistructured interviews. We will use purposive sampling to study women with variability in age, education level, symptom severity, impact on quality of life, and intervention adherence. We endeavor to interview women immediately after their participation in the intervention to avoid recall bias.

Conceptual Framework

In implementation science, there are multiple outcome variables that can be studied depending on the phase of the implementation, such as acceptability, adoption, feasibility, or sustainability [32]. Various models indicate that an innovation needs to go through multiple stages to make it sustainable [33,34]. The objective of this study is to examine whether the intervention will be adopted by the users. It is known that various factors are determinative for the adoption of new technologies, but the interaction between different factors is also relevant. Ammenwerth et al created the Fit between Individuals, Task, and Technology (FITT) framework, which takes the interaction between different components into account (Figure 2) [35].

According to this framework, the adoption of information technology depends on the fit between attributes of users (eg, motivation and computer anxiety), attributes of technology (eg, usability and performance), and attributes of tasks (eg, complexity). The framework was retrospectively used to study the adoption of a nursing process documentation system and to describe the barriers and facilitators to the 3 attributes in the FITT framework. We will use the same FITT framework in this study to guide our description of the barriers and facilitators to the adoption of *Tüt-treatment of Stress Urinary Incontinence*.

On the basis of the known modifiers of PFMT adherence, we hypothesize that the relevant attributes of individuals with regard to this intervention are knowledge, cognitive analysis, planning and attention, and prioritization [36]. Cognitive analysis and planning and attention mean that PFMT adherence depends on the belief of women that the exercise is worth the effort. Furthermore, PFMT requires conscious planning and attention to remember the exercises. The task in our framework will be the participants' feelings about PFMT and the physical skills they gained during the intervention [36]. On the basis of a behavior change model for internet interventions, finally, we believe that the relevant attributes for technology (the website) are its appearance, behavioral prescriptions, the burden of using the website, training content, and delivery of the message (eg, text and audio) [37].

Recruitment and Informed Consent

The intervention is an open-access website that enables all women who search for information over Web about urinary incontinence to subscribe to this study. The website provides information about different types of urinary incontinence and about the content of the intervention by means of written text and a video. In addition, we recruit women through

advertisements in local papers, posters in waiting rooms of primary care practices or pharmacies, and through other websites displaying a referral link to our website. We explain that the intervention is part of our research project at the Department of Primary and Community Care at the Radboud University Medical Center.

Women who register are requested to fill in their surname (or pseudonym), email address, age, and phone number (optional). Then, they are shown a webpage with information about the study, and they need to tick the *I agree to participate* box at the bottom of that page. This click automatically generates an email with a confirmation link that needs to be clicked to give informed consent. The baseline questionnaire contains 1 item that asks participants for permission to be contacted for an interview after the intervention.

Intervention

The eHealth intervention is based on the Swedish internet-based module named *Tüt-treatment of Stress Urinary Incontinence* [38], which was developed at Umeå University in Sweden. The authors (E S, M S, and the eContinenence Group) gave their full permission to translate the content, adapt the program to our platform, and conduct an implementation study (noncommercial license by TÄT.nu—eContinenence Group on 13 February 2017). The Dutch version of the website was technically constructed by a Web developer and was pilot tested by a group of women who varied in age, education level, and profession. Version 1.0 of our website is currently hosted over Web, and we aim to keep it *frozen* during the entire study period (Figure 3).

The core content of the website is about PFMT, which is explained by text, audio fragments, and images. Webpages with information and exercises can be downloaded and printed. Next to training, information about urinary incontinence is also provided as well as lifestyle advice to reduce the impact of risk factors for SUI; the negative effect of obesity on SUI, for example, is addressed, and lifestyle advice is provided. In total, 4 different pelvic floor muscle exercises are addressed in 8 escalating modules. Each module contains background information, a training program, and a test exercise that enables women to check whether they gained the correct skills. Depending on the module, participants are recommended to train 2 to 3 times a day for 2 to 12 min, in line with existing guideline recommendations (Figure 4) [7,39].

After completing a module, participants are requested to fill in a training report with 2 questions about the frequency and time they spent on this module. Access to the next module will automatically be provided after the report has been filled in. The intervention will take 3 months, but women can take it at their own pace. Women receive a message 3 months after their first login that their account will be inactivated within a week but that they can download the exercises to continue their training. We decided to inactivate the Web portal to have a cut-off point for the intervention and to achieve a proper measurement of the women's login activity.

Figure 2. The Fit between Individuals, Task, and Technology framework.

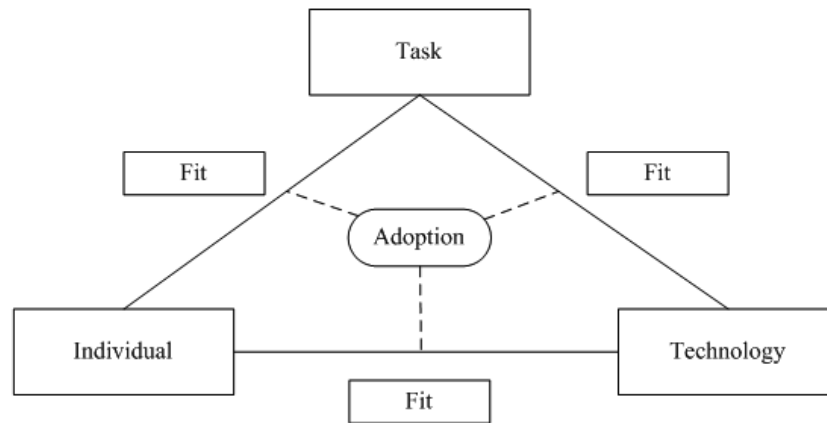


Figure 3. Homepage layout of the Dutch version of *Tät-treatment of Stress Urinary Incontinence*.

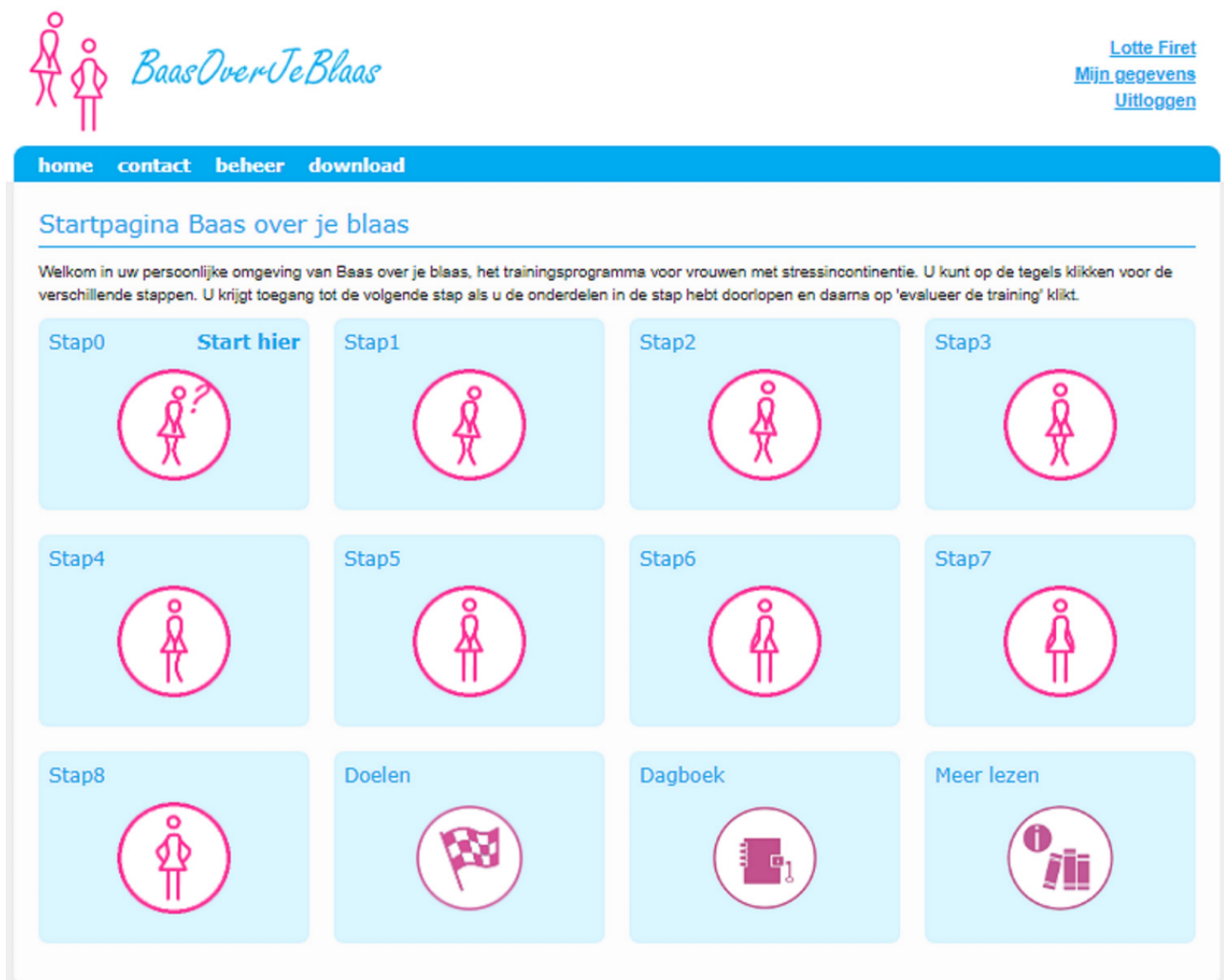


Figure 4. Intensity of pelvic floor muscle training per module in the intervention.

1	2	3	4	5	6	7	8
2 minutes 3 times per day	2 minutes 3 times per day	3-4 minutes 3 times per day	3-4 minutes 3 times per day	4 minutes 3 times per day	7-8 minutes 2 times per day	7-8 minutes 2 times per day	12 minutes 3 times per week

During the intervention, there is no face-to-face contact, but the researcher (a GP in training and researcher) is available for both content-related and technology-related questions through a secured email system. Technology questions are discussed with the Web developer. To stimulate adherence, email reminders are sent if participants do not log-in for 1 week. The content of the reminder is related to the content of the module in which participants are training at that time. A maximum of 2 reminders for each module will be sent, and women are able to unsubscribe themselves. Women who notice no effect of the training or who are unable to contract their pelvic floor muscles are advised to consult their GP for further treatment. This is explained in the intervention as well as in the outro of the questionnaire that is sent 3 weeks after the start of the intervention.

The website is password-protected and allows participants to create their own portal where personal learning goals or training reports can be filled in. Women can create or reset their own password. The eHealth intervention is provided at no cost to participants, and they are not reimbursed for participation.

Outcomes of Interest

The primary outcome of the study will be the barriers and facilitators to the adoption of *Tät-treatment of Stress Urinary Incontinence*. This outcome will be examined from the perspective of women participating in the eHealth intervention. The secondary outcomes are the effects of the interventions and have been divided into the following 3 items: (1) the effect of an eHealth intervention on symptoms of urinary incontinence, (2) on quality of life, and (3) factors associated with a successful treatment defined by the first secondary outcome.

Data Collection

We will collect quantitative and qualitative data from women who participated in the intervention (Table 1).

Questionnaires

Participants are asked to fill in Web-based questionnaires at baseline and at 3 weeks, and 3 and 6 months after baseline (T0, 1, 2, and 3, respectively; Figure 1). They receive a link to the Web questionnaire by email, and they can save their answers and complete the survey at another point in time. Questionnaires can only be completed if all required fields are filled in, and the survey is locked after that, allowing no changes. These data are collected and stored by Castor EDC [40], which is a certified cloud-based Electronic Data Capture platform. Participants who do not complete the questionnaire within 1 week receive a reminder by email.

Primary Outcome: Barriers and Facilitators

The barriers and facilitators to the adoption of the eHealth intervention are evaluated by means of questionnaires sent before, during, and after the intervention (T0-T3; Table 1). T0 includes questions about demographic characteristics, medical background, previous help-seeking behavior, and treatment for SUI. Reasons for not seeking help are explored with an open question.

The questionnaire during and after the intervention (T1-T2) contains 5 closed questions about the understandability of the training information (2 times), adherence to the intervention, conditions that would enhance adherence (if applicable), and the possibility to ask questions during the intervention. Some of these questions contain response options that trigger a follow-up open question, for example, to explore reasons for nonadherence or low adherence. T1 and T2 also include 5 closed questions about positive and negative experiences with the intervention (both asked twice) and about suggestions for the intervention's further improvement.

After the intervention (T2 and T3), we ask women multiple, self-generated questions to evaluate if they sought help since the start of the eHealth intervention or if they intend to seek help from a health care professional for urinary incontinence. The health care professionals who are mentioned in the answer options are the GP, the pelvic physiotherapist, or the specialist (urologist or gynecologist). Reasons for either seeking or not seeking help are explored with open questions that show up depending on the participants' response to previous questions. We also assess whether participants receive another treatment during or after the eHealth intervention, and, if applicable, what kind of treatment this was. Nonresponders are approached by email first, and, second, by telephone to explore their reasons for not completing the questionnaire. They are also asked if they have any suggestions for improvement.

Secondary Outcome: Effect of the Electronic Health Intervention on Symptoms of Urinary Incontinence

At baseline (T0), the situation regarding urinary incontinence is assessed by self-generated questions about symptom duration and about perceived discomfort by a 7-point Likert scale. The effect of the eHealth intervention on incontinence severity is assessed by the International Consultation on Incontinence Questionnaire Short Form (ICIQ-UI SF) at T0, T2, and T3. The ICIQ-UI SF is a validated and a highly recommended 6-item questionnaire to assess the frequency, amount of leakage, and impact on daily life [41]. The total score ranges from 0 to 21, and patients can be divided into 4 categories of severity (overall score: 1-5=slight, 6-12=moderate, 13-18=severe, and 19-21=very severe).

To assess patient-reported improvement, the Patient Global Impression of Improvement (PGI-I) [42] is used. The PGI-I contains one question: "Check the one answer that best describes your urinary incontinence situation, compared with how it was before you began with the study" with 7 response options, ranging from *very much better* to *very much worse*. A successful effect of the eHealth intervention is accomplished if women report that their urinary incontinence is *much* or *very much* improved. This definition is based on the results from a systematic review that reported the definition of success used by studies on both surgical and nonsurgical interventions for SUI [43]. The frequency of using incontinence pads is compared before and after the intervention by one question.

Table 1. Data collection. T0: baseline; T1: 3 weeks after baseline (during treatment); T2: 3 months after baseline (posttreatment); T3: 6 months after baseline (posttreatment).

Data categories	Data variables	Quantitative data collection (content of instrument)	Qualitative data collection
Demographic data	Age, education level, marital status, residential area, recruitment method	T0 questionnaire	— ^a
Medical background	Parity, vaginal delivery, gynecological surgery, chronic diseases, defecation problems, symptoms of prolapse, medication use, BMI ^b , smoking, alcohol use, general physical and mental health status	T0, T2, and T3 questionnaires	—
Barriers and facilitators to using eHealth ^c	Positive and negative experiences, understandability, reasons for (non) adherence, support, previous help-seeking behavior, previous treatment received, help-seeking during/after intervention, intent to seek help	T0, T1, T2, and T3 questionnaires	Interview after intervention
Effect of eHealth on urinary incontinence	Baseline information (duration, discomfort) severity, improvement, use of incontinence pads, BMI	T0, T2, and T3 (ICIQ-UI SF ^d , PGI-I ^e) questionnaires	Interview after intervention
Effect of eHealth on quality of life	Urinary incontinence related and general quality of life	T0, T2, and T3 (ICIQ-LUTSqol ^f , Short Form-12) questionnaires	—
Factors associated with success	Age, education level, physical activity, menopausal status, prior surgery for urinary incontinence, (expected) ability to do PFMT ^g , expectation of treatment success, symptom severity, improvement of pelvic floor muscle strength, BMI change, adherence to intervention, adherence to PFMT during intervention, adherence to PFMT after intervention	T0, T1, T2, T3 (ICIQ-UI SF, PGI-I) questionnaires, website data (login data, training reports)	Interview after intervention

^aNot applicable because data are collected through questionnaire only.

^bBMI: body mass index.

^ceHealth: electronic health.

^dICIQ-UI SF: International Consultation on Incontinence Questionnaire Short Form.

^ePGI-I: Patient Global Impression of Improvement.

^fICIQ-LUTSqol: ICIQ-Lower Urinary Tract Symptoms Quality of Life.

^gPFMT: pelvic floor muscle training.

Secondary Outcome: Effect on Quality of Life

Quality of life is assessed at T0, T2, and T3 by 2 validated questionnaires: one that is designed specifically for Lower Urinary Tract Symptoms Quality of Life (ICIQ-LUTSqol) and another that is designed for quality of life in general Short Form-12 (SF-12) [44,45]. The ICIQ-LUTSqol contains 19 items about condition-specific issues, such as physical and social limitations relating to incontinence. The total score ranges from 19 to 76, with a higher score implying a greater impact on quality of life. The SF-12 is a shortened version of the SF-36 and aims to assess physical and mental well-being with 12 items. The total score ranges from 0 to 100, with a higher score corresponding to a better quality of life.

Secondary Outcome: Factors Associated With Successful Treatment

Several factors will be analyzed for their potential association with intervention effect. The dependent variable is *success*, defined as *very much* or *much* improvement on the PGI-I scale. Characteristics with a potential association are collected at baseline, during, and after the intervention. The content of these characteristics is based on previous studies and includes a wide range of items because the literature is inconsistent on this topic [46-49]. Baseline characteristics that are collected are age, education level, physical activity, menopausal status, previous

surgery for urinary incontinence, self-rated ability to do PFMT, expectation of treatment success, and symptom severity (ICIQ-UI SF). Physical activity will be self-assessed using a standard question with 4 levels of activity. The ability to perform PFMT will be assessed on a 10-point Likert scale. The expectation of treatment success will be assessed by using a 5-point Likert scale (1: incontinence definitely stops to 5: no improvement of incontinence), based on the one used by Nyström et al [49].

Characteristics that are collected during and after the intervention include adherence to the intervention, adherence to exercises, symptom severity (ICIQ-UI SF), self-rated improvement of pelvic floor muscle strength, difference in bodyweight compared with baseline, and the frequency of PFMT after intervention. Adherence to the intervention and to the exercises is collected by the website instead of the questionnaire (see website data). Self-rated improvement of pelvic floor muscle strength is assessed during and after the intervention. Participants are asked 3 questions about their ability to contract the pelvic floor muscles 3 weeks after the start of the intervention (T1). At T2 and T3, participants assess the improvement of their pelvic floor muscle strength on a 5-point Likert scale, with answers ranging from *very much worse* to *very much better* to the question “How is your pelvic floor’s tightening capacity now compared to before the start of the

study?" [49]. At T3, 3 months after completing the intervention, participants are asked about the frequency of PFMT with an item that was based on a previous research [46]. Answers to these questions are: *never, sporadically, less than once a week, regularly, 1-3 times a week, regularly, more than 3 times a week, or regularly, daily*.

Website Data

During the intervention, website usage is assessed by collecting website statistics. According to previous research, website usage can be defined by frequency, duration, and activity [50]. Frequency is the number of logins per participant during the 3-month intervention period. Duration is the total time spent on the website, calculated by the time between login and logout, multiplied by login frequency. Activity is the number of Web pages opened within the website. As a logout cannot always be registered accurately, we will not be able to measure duration, and we have chosen, therefore, to approach duration by registering the first and last login data. Frequency is assessed by registering the total number of logins, and activity is assessed by registering the frequency and the type of Web pages that are visited, and the module number that the participants reached.

Adherence to the intervention is defined as the extent to which participants made use of the intervention. We defined 3 groups: nonadherence, intermittent adherence, and continuous adherence, based on previous research [50] and on intervention content. Nonadherence refers to the proportion of participants who never log in after they receive the email with a login token. Intermittent adherence is the proportion of participants who make it up to module 5. Continuous adherence refers to the participants who end up between modules 6 and 8. We set the cut-off point for intermittent and continuous adherence after module 5 as no new pelvic floor exercises are introduced after module 5.

Exercise adherence is measured using the training reports that have to be completed during the intervention to continue to the next module. In each training report, participants need to fill in how many minutes and how often they trained for that particular module. Exercise adherence is defined as the percentage of time spent on PFMT out of expected time spent on PFMT and will be categorized in 3 levels: high (>80%), moderate (20% to 80%), and low (<20%) adherence [48]. The expected time spent on PFMT is based on the prespecified training schedule (Figure 4).

As part of the intervention, participants can fill in their short-term and long-term goals for the training program, and they can make notes in their own diaries, but both are nonobligatory. Both functionalities aim to enhance adherence.

Semistructured Interviews

After completing the intervention, participants will be asked to participate in a semistructured interview, allowing them to provide feedback in a more narrative form. We undertake to select a subset of 15 to 20 participants with variety in age, education level, urinary incontinence severity, and adherence to the intervention to participate in the interviews. To explore reasons for nonresponse, women who dropped out during the intervention will be interviewed as well. The topics in the

interview guide have been divided into the 3 components of the FITT framework [35], a previous qualitative study on eHealth for urinary incontinence [22], and on research group expertise. The following topics will be addressed:

- Individually:
 1. Reason for participation.
 2. Previous experiences with help-seeking, receiving treatment (if applicable).
 3. Expectations of the intervention.
 4. Knowledge of the condition and PFMT.
 5. Cognitive analysis, planning and attention.
 6. Prioritization.
 7. Attitudes toward support during this intervention (advantages/disadvantages of absence of personal contact, attitudes toward email reminders, and suggestions).
 8. Computer skills.
 9. Effects of the intervention (on symptoms and consulting a health care provider).
- Task:
 1. Feelings about PFMT.
 2. Experiences with intervention adherence (including attitudes toward how to enhance adherence, integrating PFMT into daily life).
 3. PFMT complexity (also taking into account previous experiences with PFMT).
 4. Effect on skills gained during the training (ability to contract the pelvic floor muscles).
- Technology:
 1. Appearance.
 2. Behavioral prescriptions.
 3. Burden of using the website.
 4. Content.
 5. Delivery of the message.
 6. Stability of the website and technical problems.
 7. Privacy aspects.

Analysis

Quantitative Data: Questionnaires and Website Data

Descriptive statistics will be used to analyze the characteristics of the participating women, and they will also be described for groups who differ in intervention adherence. The questionnaires include a mixture of open and closed questions that address barriers and facilitators to adopt the eHealth intervention. Responses to open questions will first be analyzed qualitatively, divided into barriers and facilitators, and then be categorized into one of the 3 components of the FITT framework [35].

On the basis of this mapping, different barriers and facilitators will be analyzed for groups that differ in age and urinary incontinence severity with a chi-square test. Treatment effects (T0 vs T2 and T0 vs T3) on the ICIQ-UI SF, ICIQ-LUTSqol, and SF-12 will be analyzed using a mixed model analysis. Missing answers are not likely as Castor EDC does not allow completion of the questionnaire before all required fields have been filled in. Nevertheless, if there are any missing values, they will be replaced with the corresponding answer at baseline

and vice versa. If more than 3 answers are missing in a row, the participant will be excluded from further analysis. Descriptive statistics will be used for the analysis on the PGI-I.

Logistic regression analysis will be used to assess the association between different variables and treatment success. Before a definitive model is constructed, the variables will be tested for their unique correlation with the dependent variable, and variables with very-skewed distribution will be excluded or categorized further. Univariate analyses will be performed, and variables with a significance level of $P < .2$ will be included in the multivariate regression model. Variables will then be excluded step by step in order of the highest P value until only statistically significant ($P < .05$) variables remain in the multivariate model. The number of variables in the multivariate model will depend on the definite number of participants included in the study. IBM SPSS Statistics 25 software will be used for the analyses.

Qualitative Data: Semistructured Interviews, Website Data, and Email

The data that will be collected from the semistructured interviews will be analyzed thematically. With thematic analysis, one strives to identify patterns (themes) that together provide an answer to the research question [51]. Several steps need to be taken to find themes within the data. First, the researchers need to familiarize themselves with the data. They do this by transcribing the audio-recorded semistructured interviews verbatim and by profoundly reading the transcripts. Thereafter, the transcribed interviews will be analyzed using the ATLAS.ti version 8 program. In all, 2 researchers will analyze the interviews independently by applying codes to the transcripts. We will endeavor to compare and discuss the codes after each of the first 3 interviews to check whether the interview guide needs to be adopted. Then, we aim to have the researcher compare codes after 5 interviews. In case of a disagreement, a third researcher will read the transcripts and give his/her opinion. When no new codes emerge, we conclude that data saturation has been reached, which means that no new participants need to be interviewed. Data analysis continues with merging codes into categories. Categories will be discussed in the research team with the aim of constructing themes. During these discussions, the themes will be reviewed and definitions and names for the themes will be constructed.

Document analyses will be conducted with the qualitative data from the emails sent by participants during the intervention and with data from the website (short-and long-term goals for the training and the diary). These documents will not be available from all participants as email contact, diary, and goals are not compulsory.

Integration of Quantitative and Qualitative Data

After analyzing the quantitative and the qualitative results, we will combine these results to provide an answer to the primary outcome: barriers and facilitators to the adoption of eHealth for SUI. We will use the FITT framework by describing the *fit* between individual and task, individual and technology, and task and technology [35].

Sample Size Calculation

No sample size calculation is needed to provide a reliable answer to our primary outcome. However, a reasonable number of participants is needed to compare groups that differ in barriers and facilitators to the adoption of the eHealth intervention. We decided, therefore, to perform a power calculation based on one of the secondary outcomes: self-rated improvement on symptoms as assessed by the PGI-I. Improvement or success was defined as answering *very much* or *much* to the PGI-I question. Previous studies using the same definition showed that 34% to 56% of participants in PFMT trials improved after the intervention [19,46,47,49]. We used a percentage of 40.9% for the power calculation as this value was derived from the Swedish trial on which our eHealth intervention is based [19]. The power calculation is based on the precision in estimating the percentage of people with very much/much improvement at a certain point in time. To estimate this percentage with a 10% accuracy, the number of 93 women is needed (95% CI 35.9-45.9%).

We expected high drop-out rates as previous research on self-help internet interventions showed rates between 2% and 83% [52,53]. The Swedish eHealth trial *Tät-treatment of Stress Urinary Incontinence* had a 30% drop-out rate. As there is less personal contact during the selection phase in this study, we expected higher drop-out rates, and we took a worst-case scenario into account with a drop-out rate of 80%. To get a number of 100 women completing the questionnaires, therefore, our goal was to include 500 women. After the commencement of this study, we discovered that 40% already dropped out between the moment of registration on the website and the start of the intervention. Therefore, we wrote an amendment to the research ethics committee, who approved our request to include 800 participants.

Ethical Approval

Ethical approval has been requested and granted (file number 2016-2721) by the research ethics committee of the Radboud University Medical Center, Nijmegen, the Netherlands. This study is conducted in accordance with the Medical Research Involving Human Subjects Act. The committee declared that the risks associated with participation in this trial are negligible according to the Netherlands Federation of University Medical Centers. Handling of personal data will comply with the General Data Protection Regulation (Dutch: Algemene verordening gegevensbescherming).

Results

Enrollment of participants in the eHealth intervention started in July 2018 and will last until December 2019. Data analysis will start in March 2020.

Discussion

Relevance

The mixed methods design in this study allows for a comprehensive and in-depth understanding of the barriers and facilitators to the adoption of an internet-based intervention for

women with SUI. The quantitative strand of this study further facilitates an analysis of the effects of the intervention on urinary incontinence symptoms, quality of life, and the factors associated with successful treatment. From previous research, we know that Swedish women were satisfied after using the intervention. Due to geographical and organizational differences with Sweden, however, we do not know whether Dutch women with SUI will also be satisfied with this eHealth intervention. It is important, therefore, to study what factors facilitate or hamper the use of the intervention in the Netherlands. These results can be used to guide health care providers and policymakers in implementing this intervention in the Dutch national health care system. Due to its anonymous and flexible character, eHealth has the potential to improve care for women with urinary incontinence as it lowers the threshold to help-seeking [15]: given that a minority of women with urinary incontinence seek help in regular care [5,6], eHealth might reach those women who would otherwise remain untreated.

Strengths and Limitations

One of the strengths of this study is that it elaborates on an intervention—proven to be effective—for women with SUI [19]. We translated the content of the program and adapted it to our platform. Although our main objective is not to study the effects of the intervention, we used some of the same validated questionnaires that were used in the Swedish trial to investigate the effect on symptoms and quality of life as a secondary outcome. Another strength is that we used a mixed methods design, which is suitable for describing factors that influence implementation [32]. The use of an existing framework (FITT) further strengthens the study as it helps us include all relevant barriers and facilitators to the adoption of *Tät-treatment of Stress Urinary Incontinence*. This FITT framework will also guide the data analysis.

However, we may not detect all variables as we mostly use open questions in the questionnaire, which do not guide participants to address specific items. We hope to fill this gap with the

qualitative strand in this study. Another potential limitation of this study is that we are unable to study the barriers and facilitators among nonresponders or drop-outs, which might lead to selection bias. To mitigate this risk, we have embedded a brief questionnaire at T1 with questions about positive and negative experiences because we expect that more women will respond shortly after registration than at T2 or T3 [53]. Another limitation, finally, could be the absence of a diagnostic procedure by a health care provider. It is known that women can diagnose themselves with the help of questionnaires [30,54], but some women might be mistaken in their diagnosis and take the intervention without effect, causing treatment delay. In this study, we have attempted to decrease this risk using different methods: the researchers check the answers in the selection questionnaire and email those participants whose diagnosis is unclear, women with questions about their diagnosis can contact us by email, and 3 weeks after the commencement of the intervention, we recommend women to consult their GP who are unable to identify and contract their pelvic floor muscles. We believe that it is inevitable that eHealth must be studied without accepting the absence of hands-on diagnostics, but we tried to guide our participants properly by embedding a safety net.

Conclusions and Implications

In this study protocol, we described the methods for investigating the barriers and facilitators to the adoption of *Tät-treatment of Stress Urinary Incontinence* by patients with SUI. The study expands previous results by using a tested and effective eHealth program. To gain a deeper understanding of the use and uptake of this intervention, we have chosen a mixed methods design. The results of this study are expected to be relevant to policymakers, health care professionals, and patient organizations who play a part in implementing this intervention into the health care system. Insight into the barriers and facilitators to adopting this program can enhance implementation of the intervention in the health care system in the Netherlands.

Conflicts of Interest

None declared.

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Abbreviations

eHealth: electronic health

FITT: Fit between Individuals, Task, and Technology

GP: general practitioner

ICIQ-LUTSqol: Lower Urinary Tract Symptoms Quality of Life

ICIQ-UI SF: International Consultation on Incontinence Questionnaire Short Form

MUI: mixed urinary incontinence

PFMT: pelvic floor muscle training

PGI-I: Patient Global Impression of Improvement

SF-12: Short Form-12

SUI: stress urinary incontinence

UUI: urgency urinary incontinence

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Protocol

Using a Triple Aim Approach to Implement “Less-is-More Together” and Smarter Medicine Strategies in an Interprofessional Outpatient Setting: Protocol for an Observational Study

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Abstract

Background: Increased awareness of the world's problematic growing health care expenditure and health care shortages requires sustainable use of available resources. To promote cultural changes in medical mindsets, societies representing medical specialties have developed new Choosing Wisely strategies. The Valais Medical Society and the Valais Pharmacy Association have developed an interprofessional collaboration project entitled “Less-is-more Together-PPI” to analyze and optimize change management practices focusing on the prescription and deprescription of proton pump inhibitors (PPIs).

Objective: This study aims to enhance interprofessional collaboration between physicians, pharmacists, and patients to optimize PPI use, avoid unnecessary treatments and improve therapeutic adherence to indicated therapies, and to analyze hindrances and facilitators to implementing interprofessional Less-is-more strategies in the field.

Methods: Home-dwelling adults domiciled in Valais and prescribed PPIs in the last 6 months will be invited to participate in this observational study. The studied subpopulation will be constituted of consenting patients whose physicians and pharmacists also voluntarily agree to participate. The process of collecting, pooling, transmitting, evaluating, and protecting data has been validated by the Human Research Ethics Committee of the Canton Vaud.

Results: The Primary Triple Aim outcome measures will be (1) population health: patient's assessment of their own health, functional status, and disease burden using a monthly questionnaire for 6 months; Behavioral/physiological factors will be investigated using a final questionnaire at 6 months, (2) experience of care: assessment using a final questionnaire for participating patients, pharmacists and physicians, and an analysis of negative/positive experiences via 6 follow-up questionnaires, and (3) Per capita cost: participants' fluctuating or decreasing PPI intake (number of pills/dosage) and an analysis of participants' different categories following their medical prescription, in relation to possible bias effects on the overall drug intake of the population studied. Secondary outcomes will be participation rates; patient, physician, and pharmacist follow-up; and evaluations of participants' experiences and their perceived benefits, as well as whether the interprofessional process can be improved.

Conclusions: This project seeks a deeper understanding of how Less-is-more and smarter-medicine strategies are perceived by patients and health care providers in their daily lives in a very specific context. It will reveal some of the hindrances to and facilitators for efficient cultural change toward a more sustainable health care system. The results will be useful to optimize and scale up further Choosing Wisely approaches.

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KEYWORDS

pharmacists; family physicians; prescription; deprescription; polypharmacy; evidence-based medicine

Introduction

There is growing awareness that the world's ever-increasing health care expenditure and lack of global health care coverage will require a more sustainable use of available resources. With this in mind, Choosing Wisely strategies have been developed to promote a cultural shift in medical mindsets, mainly by societies of medical specialists. To date, little is known about the implementation and impact of these strategies [1,2]; however, there is nevertheless rising pressure to impose more sustainable health care strategies, including specific restrictions, coming from political and health insurance lobbies [3].

Choosing Wisely was an initiative of the American Board of Internal Medicine (ABIM), which sought greater dialogue between patients and physicians on avoiding unnecessary medical tests, treatments, and procedures [4,5]. The initiative was sparked by a 2010 *Perspective* article calling on American medical societies to identify 5 tests or treatments that were overused in their specialty and failed to provide any meaningful benefit to patients [6]. Some estimates have suggested that as much as 30% of all health care spending is wasted [7]. In 2012, the ABIM Foundation and Consumer Reports launched the Choosing Wisely campaign, inspired by the idea that professional societies and health care providers should take the lead in defining and motivating efforts to reduce the use of low-value care [6]. Since its launch, Choosing Wisely has grown rapidly and spread to 20 countries, with over 70 participating medical societies. Multiple national organizations, representing various medical specialties, have identified the tests or procedures that are commonly used in their field but whose necessity is questionable [2].

The latest report from the Organisation for Economic Co-operation and Development showed that the Swiss are among those who spend the most on health care [7]. In 2012, the Swiss Academy of Medical Sciences developed a roadmap on the theme of sustainable medicine [6]. In 2014, The Swiss Society of General Internal Medicine took the lead by introducing a program entitled Smarter Medicine—Choosing Wisely Switzerland [3]. A top-5 list overused in ambulatory general internal medicine was launched, which included a recommendation to avoid or discontinue proton pump inhibitors (PPIs) [3]. To give the Less-is-more Together approach a wider and not only medical audience, Choosing Wisely Switzerland's leadership was transferred to a broader interprofessional alliance in 2017 [8]. *Less-is-more* is described as an invitation to recognize the potential risks of overuse of medical care that may result in harm rather than in better health [9]. Its ambition

remains to move from a concept of maximum medicine to one of optimal medicine by relying on research and teaching grounded in evidence-based medicine. Faced with this context, the Valais Medical Society and the Valais Pharmacy Association launched a joint study to evaluate the extent to which interprofessional collaboration could affect the implementation of a smarter-medicine guideline in an outpatient setting under real-life conditions. The study focused on optimizing PPI use within the framework of the Smarter Medicine—Choosing Wisely Switzerland program [8].

Why Should Proton Pump Inhibitor Use be Challenged?

The challenge of PPI prescription is that sometimes long-term intake is mandatory for medical reasons, but at other times short-term or on-demand-treatment would be sufficient. For various reasons, short-term treatments sometimes become long-term ones, but this situation deserves to be challenged [10]. PPIs reduce stomach acid production by inhibiting the H⁺/K⁺-ATPase pump. They are indicated for the treatment of gastroesophageal reflux disease, esophagitis, peptic ulcer disease, Zollinger–Ellison syndrome, *Helicobacter pylori* eradication, secondary prevention of gastrointestinal bleeding under aspirin, and prevention of gastroduodenal lesions induced by nonsteroidal anti-inflammatory drugs [11,12]. First introduced in 1987, PPI use has increased significantly in the last 20 years, and they are now widely prescribed in Western countries, following specific recommendations and requirements [13]. Certain recommendations that aimed at older adults probably contributed to the increasing quantities of PPIs prescribed (around 10% per year in the 2000s) [10,14]. PPI treatments are generally considered to create few tolerance problems, but in recent years the scientific literature has described some side effects because of long-term use [15,16]. Studies have shown associations between PPIs and enteric infections [17,18], pneumonic pathologies [18,19], calcium malabsorption leading to an increased risk of osteoporotic fractures [20,21], and iron or vitamin B12 malabsorption causing anemia [18,21,22] and hyponatremia [23]. The use of PPIs for older adults has been associated with functional decline, more hospitalizations, and early death [24–26]. Another problem with prescribing PPIs, mainly among elderly polymedicated patients, is the existence of drug interactions that can lead to greater numbers of adverse effects of inactivated drugs (eg, citalopram) and, conversely, the decreased efficacy of prodrugs metabolized by this cytochrome [18,27,28]. PPIs may increase (eg, digoxin) or decrease (eg, ketoconazole) the absorption of certain drugs depending on gastric pH [28,29]. Despite the publication of

multiple recommendations on good PPI prescribing, several studies report that they are poorly adhered to [30,31]. Several European studies have found a high frequency of inappropriate PPI prescriptions in hospitals and outpatient practices [32-34].

Using an interprofessional approach, these experiments will involve primary care physicians, pharmacists, and patients in canton Valais with a view to optimizing PPI prescription.

The Observational Study: Less-is-More Together—Proton Pump Inhibitors in Valais

Challenged by the Smarter Medicine Program: Choosing Wisely Switzerland, the Medical Society of Valais and the Valais Pharmacy Association developed an observational study within the broader framework goal of optimizing the prescription and deprescription of PPIs among community-dwelling adults relying on interprofessional resources. This prescription/deprescription program aims to develop a more appropriate intake of PPIs based on the most recently published evidence-based guidelines [35] and, where possible, to move toward the deprescription of PPIs. The present project will focus on exploring the opportunities for increased collaboration between family physicians and community pharmacists, while also proactively integrating community-dwelling adult outpatients. The observational study framework will be built on the evidence-based PPI Bruyère Deprescribing guidelines [35]. Our observational study will investigate a simple community-engagement model to raise awareness of and promote the uptake of deprescribing initiatives, with the goal of scaling-up similar activities across the canton.

Study Aims

The study's primary aim is to enhance interprofessional collaboration between physicians, pharmacists, and patients to optimize PPI use, avoid unnecessary treatments, and improve therapeutic adherence where indicated. Secondary aims involve analyzing the factors hindering or facilitating the implementation of interprofessional Less-is-more Together strategies, drawing together feedback from patients and health care professionals and deciding how the impact of such projects can be measured efficiently.

Methods

Design

The Less-is-more Together—PPI study is framed as an observational study being the first step in a small-sample *plan-do-study-act* cycle, following the Institute of Health Improvement's Triple Aim Initiative approach [36].

Research Population

Home-dwelling adults in Valais who were prescribed any type of PPI in the last 6 months will be invited to participate in this observational study, if their community pharmacists and their primary health care physicians are willing to participate. The study's final subpopulation will be made up of consenting patients who have been prescribed PPIs, for various medical indications, in the 6 months before the project's initiation and whose physician and pharmacist both voluntarily agree to participate. To enable scientific follow-up and analysis of the

outcomes of this particular smarter-medicine goal, patients were stratified according to known, evidence-based, deprescription strategies introduced in this framework by the Less-is-more Together—PPI project.

Recruitment and Data Collection Procedure

Information on the project and the PPI guidelines of the Less-is-more Together—PPI project will be spread to the population by the local media but also specifically to individual members of the canton's medical and pharmacy societies. Before participant recruitment and data collection, the study protocol is been approved by the Cantonal Research Ethics Committee, Vaud/Valais (CER-VD: 2018-00943). Written informed consent will be obtained from all participants before data collection commences, confidentiality will be ensured and preserved in all cases, and the study will also fulfil the provisions of the Declaration of Helsinki. Data collection will be organized into 2 phases: data collection from pharmacists' electronic records of home-dwelling adults with a PPI prescription in the last 6 months and a prospective data collection.

In collaboration with participating primary care physicians and community pharmacists, electronic patient/client records will be searched for all the PPI prescriptions dispensed in the last 6 months. Each patient's age, sex, place of residence, his pharmacist, and prescribing physician will be identified for use as the basic sample in the prospective study. Data will be extracted from eligible patients' records according to procedural guidelines, entered into the database, and checked for plausibility and completeness. Participating pharmacies will send lists of eligible patients and their PPI prescriptions in the preceding 6 months to their respective primary health care physicians. The physicians will then apply the following procedure:

- Exclude patients who lack the faculty of judgment to participate in the study or patients with more than 1 pharmacist
- Group PPI users according to 1 of the 3 Bruyère categories [35]
- In case of changes to the PPI prescription during the study, the physician will communicate with the participating pharmacist (physician will send a new prescription by email and will adapt the PPI classification)
- Answer the end-of-project satisfaction questionnaire

Physicians will categorize the participating community-dwelling adult's PPI indication [35] as follows:

1. Medical indication for regular prescription of PPIs at a minimum dose
2. Prescription with the aim of only taking PPIs "on demand"
3. Deprescription is possible, but the indication for possible dose reduction remains unclear
 - Decrease the PPI dose while maintaining a regular minimum dose intake (> 6 months)
 - Progressive decrease in prescribed PPI dose with the aim of stopping in the next few weeks (< 6 months)
 - Cessation of regular PPI intake and use only "on demand"
 - A complete cessation of the PPI prescription and intake

The participating physicians will be asked to categorize their patients based on the deprescription guidelines/flow chart published by *deprescribing.org*—the PPI deprescription algorithm [35].

Prospective Data Collection

Sample

The convenience sample will be composed of eligible patients with a PPI prescription given by a primary care physician and followed up by participating pharmacists in the Valais region. To have sufficient statistical power, based on an 80% probability of not rejecting the null hypothesis (type-II error) and on reaching a statistical significance level of 0.05 (type-I error), a minimum of 500 patients will be required.

Recruitment

Physicians

The research team will contact all the primary health care physicians in the Valais Medical Society to request their collaboration in our research project. A flyer will explain the study's aims, the participants involved, data collection procedures, and the researchers' expectations for participants ([Multimedia Appendix 1](#)).

Pharmacists

The research team will also contact all the pharmacists in the Valais Pharmacy Association to request their collaboration. They will receive the same flyer. Participating pharmacists will extract the details of all the patients eligible for participation in the project from their databases. All patients who have been prescribed a PPI during the last 6 months, in agreement with their treating physicians (who also accept to participate in the study), will be listed and invited to participate. Patients will be contacted personally by the pharmacist and informed about the study. The patient will receive a comprehensive explanatory flyer and be invited to fill in the form to confirm their consent to participate ([Multimedia Appendix 2](#)). Attending physicians will be notified about participating patients and group them according to therapeutic categories (see above).

Patients

The physicians will prospectively recruit patients based on the retrospective analysis of electronic patient/client records by community pharmacists. Patients with a PPI prescription written by a participating primary health care physician will be invited to participate in the study. A patient-oriented flyer will explain the study's aims, data collection procedures, and researchers' expectations ([Multimedia Appendix 2](#)).

Data Collection

Home-Dwelling Adult Patients

Data collection on PPI prescribing and deprescribing will be organized over 6 months. After consenting to participate in the study, home-dwelling adult patients will receive the first self-administered questionnaire on PPI-use and its effects on their clinical symptoms. Self-administered questionnaires 2 to 6—on PPI use, clinical symptoms, and prescription/deprescription—will be submitted to the

participating patients monthly. The seventh and final questionnaire will assess patients' level of satisfaction and the clinical benefits they perceived from this interprofessional practical-experimental project.

Primary Health Care Physicians and Pharmacists

Primary health care physicians and pharmacists will also receive a final questionnaire to assess their levels of satisfaction and the benefits they perceived from this interprofessional practical-experimental project.

Data Collection Procedure and Ethical Considerations

Data collection, pooling, transmission, and evaluation processes will be done in conformity with data protection policies and have been validated by the Human Research Ethics Committee of the Canton Vaud. Data anonymization and confidentiality are guaranteed by a blinded coding process between pharmacists and the Haute école spécialisée de Suisse Occidentale, with specifically restricted access to the data. The first pooling of anonymized data is done at an administrative level by the Valais Pharmacy Association, and after a second coding it is transmitted to the RedCap system, where analysis takes place using an anonymized, standardized procedure.

All participants will receive oral and written information about the study before any data are collected. Participants' written informed consent will be required to authorize primary care physicians and pharmacists to disclose their PPI medication prescriptions to the research team and to participate in this interprofessional study and collaboration project. Participants who refuse to give consent will be excluded from the project. Participants will be free to withdraw from the study at any time during data collection, without the need to provide any justification. In the event of revocation of consent, the law provides that data may still be used as long as they are subsequently anonymized. These clauses will be written into the information and consent form and will be discussed before each patient interview. After written consent, participants will be able to use electronic or paper questionnaires. [Multimedia Appendices 1, 2, and 3](#) present the data collection procedure.

Data Analysis and Secure Storage

Data Analysis

Sociodemographic data, category distributions, and questionnaire data will be analyzed using descriptive statistics: distributions, frequencies, minimum, maximum, mean/median, SDs/interquartile ranges, and exact tests (chi-squared). Odds ratios/relative risks will be explored. Inferential statistics will be applied to analyze changes in categories and associations between sociodemographic data, categories, and questionnaires. *t* tests, analysis of variance, and repeated measurements will be applied where appropriate. An appropriate strategy will be applied to deal with missing data. The statistical level of significance will be set by considering the number of variables and the range of the databases. Data will be analyzed using the IBM Statistical Package for Social Sciences, version 25.0 (IBM Corp).

Data Storage

RedCap software will be used for data collection and the storage of sociodemographic data, participant data, and responses to the initial and final questionnaires completed by patients, pharmacists, and attending physicians. At each stage in the research, quality control will be maintained according to the standard quality criteria for quantitative research. The file linking participant identities to their identifying information will only be accessible by password to research team members (protection by RedCap). Participants' data will be stored in another file, also only accessible to participating pharmacists and research team members using a secure password. This file will only contain the identities and data analyzed in the study; these data will not contain any other information and they will be destroyed no later than 10 years after the end of data collection.

Methods to Minimize Bias

All research team members will apply the same instructions and ensure that patients, pharmacists, and attending physicians receive the same explanations and instructions. Information sheets, consent forms, and questionnaires will be pretested on 3 patients who meet the inclusion criteria. On the participants' side, one possible bias is that of *social desirability*: patients may feel obligated toward persons associated with medical authority and seek to respond to what they see as an assessment of their adherence to treatment—responding with what they think is the right or desirable answer. The research team will be very attentive and caring to insist among the participants to be free to participate or not at the study. The oral and written information transmitted to the participants will place a particular emphasis on describing the researchers' independence and nonjudgmental practices.

Results

The Primary Triple Aim outcome measures will be as follows:

- Population health: continuous health and functional status and disease burden via a monthly questionnaire filled in by patients for 6 months; behavioral/physiological factors via a final questionnaire after 6 months:
 - Fluctuation, decrease, and increase in PPI prescribing and intake by category (1, 2, and 3)
 - Measurable impact of category 3 in comparison to all 3 categories as a group

- Potential impact of the project on other aspects of health as perceived by the patient, pharmacist, and physician.
- Experience of care: via a final participant questionnaire (patients/pharmacists/doctors) and analysis of negative/positive experiences via the 6 follow-up questionnaires.
- Per capita cost: as it will be impossible to evaluate the real per capita cost in our context, this outcome will be analyzed mainly by evaluating the fluctuation or decrease in PPI intake (number of pills/dosage) by patients. The grouping of patients into different categories, according to their medical prescription, will be analyzed relative to possible bias effects on that population's overall drug intake. Perceived benefits/negative side-effects will be analyzed via questionnaire answers and extrapolated as soft factors.

Secondary outcomes will be participation rates; patient, physician, and pharmacist follow-up; and evaluations of participants' experiences, the benefits they perceived, and how they think the process could be improved.

Other Variables

Participants' sociodemographic variables will be analyzed to describe the sample's age, sex, geographic location (reference pharmacy's urban or rural location), and mother tongue.

Discussion

This project will help us to develop a deeper understanding of how Less-is-more Together and smarter-medicine strategies are perceived by patients and health care providers in their daily lives in a very specific setting. It will reveal the hindrances and facilitators to efficient cultural changes to a more sustainable health care system—factors which can be taken advantage of to scale-up the application of further Choosing Wisely approaches in Switzerland. This project uses a novel approach implying more active involvement by patients and their pharmacists in the implementation of a more responsible and interprofessional approach to prescription. The analysis of different partners' perceptions will help us to determine whether and how this reinforced interprofessional involvement should be fostered. Evaluating this practical experiment's interprofessional approach to implementing a Less-is-more Together-type strategy could lead to the development of an interprofessional example of good practice, which could be used to promote implementation of other Choosing Wisely Switzerland's initiatives.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Data collection strategy. CER-VD: Cantonal Research Ethics Committee, Vaud/Valais; HES-SO: Haute école spécialisée de Suisse occidentale; ID: identity document; PPI: proton pump inhibitors; SMV: Medical Society of Valais; UAS: University of Applied Sciences.

[PNG File, 145KB - [resprot_v8i7e13896_app1.PNG](#)]

Multimedia Appendix 2

Data collection strategy—part II. ID: identity document.

[PNG File, 104KB - [resprot_v8i7e13896_app2.PNG](#)]

Multimedia Appendix 3

Project planning—Less-is-more Together—proton pump inhibitor.

[PNG File, 29KB - [resprot_v8i7e13896_app3.PNG](#)]

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Abbreviations

ABIM: American Board of Internal Medicine

PPI: proton pump inhibitor

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Protocol

A Modified Communication and Optimal Resolution Program for Intersystem Medical Error Discovery: Protocol for an Implementation Study

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Abstract

Background: Preventable medical errors represent a major public health problem. To prevent future errors, improve disclosure, and mitigate malpractice risks, organizations have adopted strategies for transparent communication and emphasized quality improvement through peer review. These principles are incorporated into the Agency for Healthcare Research and Quality (AHRQ) Communication and Optimal Resolution (CANDOR) Toolkit, which facilitates (1) transparent communication, (2) error prevention, and (3) achieving optimal resolution with patients and families; however, how medical errors should be addressed when they are discovered between systems—intersystem medical error discovery (IMED)—remains unclear. Without mechanisms for disclosure and feedback on the part of the discovering provider, uncertainty remains as to the extent to which IMED is communicated with patients or responsible providers. Furthermore, known barriers to disclosure and reporting one's own error may not be relevant or may be replaced by other unknown barriers when considering scenarios of IMED.

Objective: This study aims to develop and test implementation of a modified CANDOR process for application to IMED scenarios.

Methods: We plan a series of studies following an implementation framework. First, we plan a participatory, consensus-building stakeholder panel process to develop the modified CANDOR process. We will then conduct a robust preimplementation analysis to identify determinants of implementation of the modified process. Using the Consolidated Framework for Implementation Research as a theoretical framework, we will assess organizational readiness by key informant interviews and individual-level behaviors by a survey. Findings from this analysis will inform the implementation toolkit that will be developed and pilot-tested at 2 cancer centers, sites where IMED is hypothesized to occur more frequently than other settings. We will measure 5 implementation outcomes (acceptability, appropriateness, reach, adoption, and feasibility) using a combination of key informant interviews and surveys over the pre- and postimplementation phases.

Results: This protocol was funded in August 2018 with support from the AHRQ. The University of Michigan Medical School Institutional Review Board has reviewed and approved the scope of activities described. As of April 2019, step 1 of aim 1 is underway, and aim 1 is projected to be completed by April 2020. Data collection is projected to begin in January 2020 for aim 2 and in August 2020 for aim 3.

Conclusions: Providing a communication and resolution strategy applicable to IMED scenarios will help address the current blind spot in the patient safety movement. This work will provide important insights into the potential utility of an implementation toolkit to improve transparent communication and optimal resolution of IMED scenarios. The natural progression of this work will be to test the toolkit more broadly, understand the feasibility and barriers of implementation on a broader scale, and pilot the implementation in new organizations.

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KEYWORDS

medical error; patient safety; disclosure; communication; feedback; ethics; implementation science

Introduction

Background

Preventable medical errors represent a major public health problem. To prevent future errors, improve disclosure, and mitigate malpractice risks, organizations have adopted strategies for early transparent communication and emphasized quality improvement through peer review [1-4]. The Agency for Healthcare Research and Quality (AHRQ) Communication and Optimal Resolution (CANDOR) process integrates these practices in a comprehensive response to medical errors, which aims to improve safety and optimize resolution for patients, providers, and health systems [4,5]. Institutions and practitioners can use the CANDOR process to respond in a timely, thorough, and just manner to unexpected events that might result in harm to patients. The major tenets of the CANDOR process are (1) transparent communication with patients and families, (2) incident reporting and safety program review, and (3) risk management and resolution programs.

However, what physicians should do after identifying an error from another system—intersystem medical error discovery (IMED)—is less clear. The literature [6-8], anecdotal experience [9], and our previous work [10,11] draw attention to scenarios where providers discover errors originating from other systems. These errors may be unknown to the patient and/or responsible provider. Although the CANDOR principles of transparent communication and optimal resolution of other physicians' errors remain possible when the physicians practice in the same system (*within system*), it is uncertain how CANDOR principles are best applied to IMED scenarios. Through the CANDOR Toolkit, AHRQ provides clear guidance on how to implement the CANDOR process within an institution, including guidelines for preimplementation assessments, gap analyses, and obtaining organizational buy-in. It includes a CANDOR event checklist and best practices for event reporting, investigation, and resolution [5]. In contrast, there are no guidelines or mechanisms for reporting and investigating errors that are discovered between systems or for providing disclosure or resolution to the patient in such scenarios.

Objective

Identification of errors between systems is particularly relevant to complex oncologic care where patients often interact with multiple systems and where specialists are highly dependent on external referrals. Solutions to IMED developed in this challenging context should be adaptable to similarly complex settings. Our preliminary work suggests cancer specialists regularly encounter IMED scenarios but lack consensus on whether or how to communicate about these errors to patients and responsible providers. Specialists struggled to provide disclosure to patients or meaningful feedback to responsible providers. Barriers to transparent communication included concern for medicolegal implications, disruptions to referral relationships, concern for the profession, and general discomfort with giving negative feedback to other physicians [10,11].

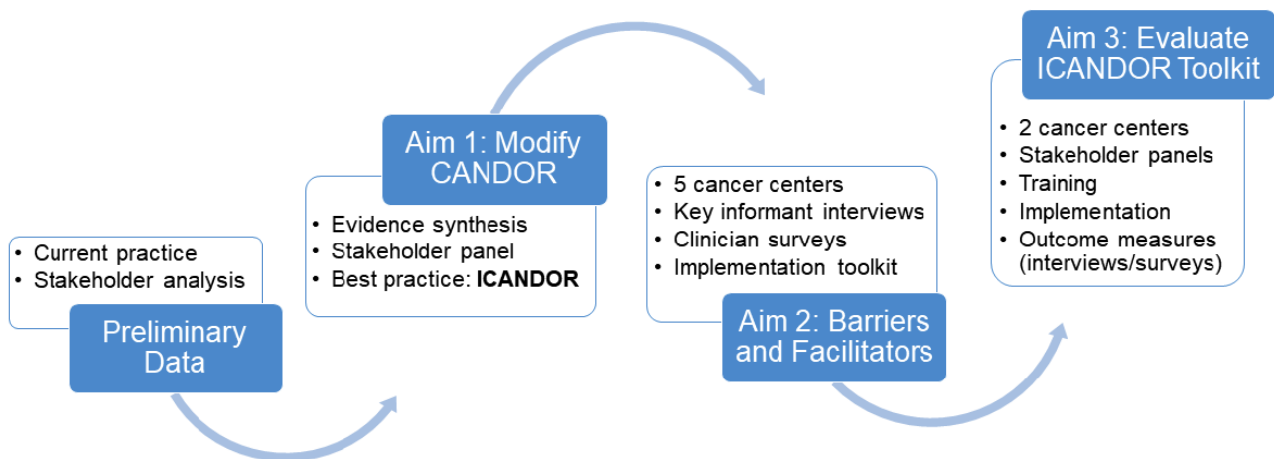
Without clear expectations or mechanisms for disclosure and feedback on the part of the discovering provider, it is uncertain how best to communicate about errors discovered between systems. Furthermore, known barriers to disclosure and reporting of one's own error may not be relevant or may be replaced by other unknown barriers when considering IMED. The objective of this study is to provide a communication and resolution strategy applicable to IMED scenarios to help address this current blind spot in the patient safety and quality improvement movement.

Methods

Overall Design

We plan a series of studies following an implementation framework [12] where we use best (aim 1) and current practice (preliminary data) to identify a practice gap. We will then conduct a robust preimplementation analysis to identify barriers and facilitators to implementation using the Consolidated Framework for Implementation Research (CFIR) [13,14] supplemented by the Theoretical Domains Framework (TDF) [15] (aim 2). Findings from aim 2 will inform the implementation toolkit that will be developed and pilot-tested in aim 3 (Figure 1).

Figure 1. Overview of studies and data flow. CANDOR: Communication and Optimal Resolution; ICANDOR: Intersystem Communication and Optimal Resolution.



Aim 1: Modify the Communication and Optimal Resolution Process for Application to Errors Discovered Between Systems

Introduction

The tenets of the CANDOR process are (1) transparent communication with patients, (2) incident reporting and safety program review, and (3) risk management and resolution. These tenets are accomplished through 5 process components: (1) event identification, (2) system activation, (3) response and disclosure, (4) event investigation, and (5) resolution. CANDOR is designed to apply *within* systems; no current process addresses communication or resolution for IMED scenarios.

Research Design

On the basis of a comprehensive stakeholder analysis and participatory, consensus-building stakeholder panel process [16-18], we will modify the CANDOR process for application to IMED scenarios. Experts will be recruited nationwide through professional contacts and will include leaders in clinical care, patient safety, bioethics, law, risk management, and hospital administration.

Step 1: Evidence Synthesis

Sources of data will include a scoping review of published ethics codes, a narrative review of legal case law relevant to feedback and reporting (completed), and a systematic review of empirical quantitative and qualitative data using previously published methodology for mixed methods meta-synthesis [19]. For the empirical qualitative data, we will use the Grading Recommendations Assessment, Development and Evaluation-Confidence in Evidence from Reviews of Qualitative Research methods for grading the evidence [20]. These reviews will collectively represent the available evidence for consideration by the stakeholder panel.

Step 2: Independent Review by Stakeholder Panel

We will create 8 to 10 IMED scenarios to which the evidence from step 1 may apply. Panelists will be provided with the scenarios as well as the evidence synthesis as a written report. They will be asked to propose modifications to the CANDOR

process based on the evidence synthesis and their expert judgment. Participants will respond anonymously.

Step 3: Face-to-Face Meetings of Stakeholder Panel—Preliminary Proposals

The study team will compile the responses, and the panelists will then be brought together in a face-to-face meeting (videoconference if necessary). The aggregate proposals will be presented for discussion. During the face-to-face meeting, we will utilize nominal group technique to encourage contributions from all stakeholders and to prioritize recommendations. Through this technique, each participant will have opportunities to share their priority proposals with the group in turn. A facilitator will record and further consolidate proposals as needed. Thereafter, the group will discuss each proposal in turn and further prioritize them using the multivoting procedure. Discussions will be audio-recorded for further analysis.

Step 4: Summary of Recommendations by Research Team

The research team will then summarize the written and audio-recorded recommendations and deliver them to the stakeholder panel in a written report. Issues of disagreement and areas requiring further elaboration will be highlighted in the report as specific questions. The stakeholders will again be asked to propose answers to the specific questions as well as modifications or revisions to the recommendations generally. Stakeholder responses will be received by email and anonymized.

Step 5: Face-to-Face Meeting of Stakeholder Panel—Iterative Review and Revisions

The study team will compile the responses, and the panelists will be brought together for a second face-to-face meeting. An iterative facilitated process will follow, through which panelists will have an opportunity to provide feedback on the draft recommendations and approve the final recommendation.

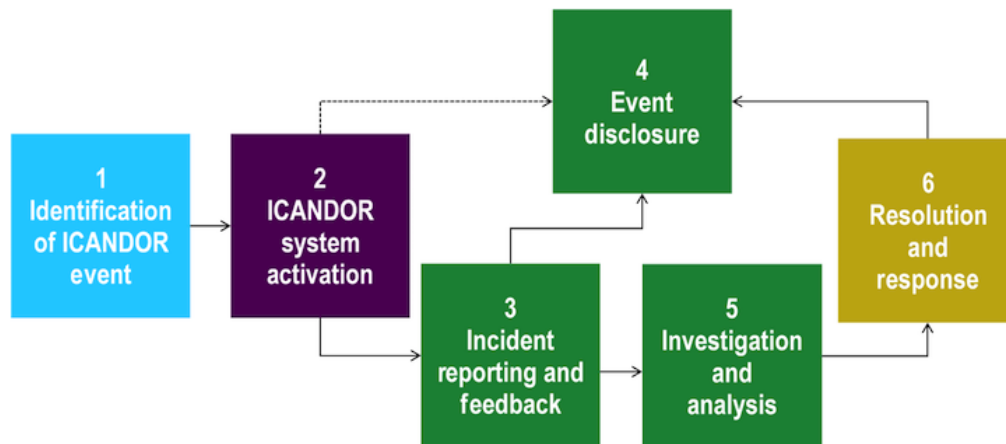
Step 6: Final Recommendation Prepared and Disseminated by the Research Team

The research team will then provide final recommendations of the stakeholder panel in a published report. The expected outcome from aim 1 will be a modified process for the

transparent communication and optimal resolution of errors identified between systems—the intersystem CANDOR process (ICANDOR) based on a comprehensive stakeholder analysis. The modified process (Figure 2, adapted from the CANDOR

Toolkit [5]) will describe ICANDOR system activation, provide recommendations for feedback and/or reporting, and establish guidelines for disclosure in these scenarios.

Figure 2. Possible modified ICANDOR process resulting from Aim 1. ICANDOR: Intersystem Communication and Optimal Resolution.



Aim 2: Understand the Barriers and Facilitators to Implementation of the Intersystem Communication and Optimal Resolution Process

Introduction

Although AHRQ provides implementation guidance for adoption of the CANDOR process, our preliminary data suggest that the barriers to responding to errors discovered between systems are different from those encountered within a system [10,11]. In this case, the implementation strategy for the CANDOR process (the CANDOR Toolkit) may be ineffective. For example, AHRQ recommends building a business case for CANDOR given the evidence that CANDOR may reduce medicolegal claims (*a facilitator of implementation*) [21-23]. Conversely, specialists express concern that disclosing another physician's error may negatively impact future referrals, thereby providing a business disincentive to ICANDOR (*a barrier to implementation*) [10]. Our goal is to develop an implementation toolkit that includes key information about the implementation constructs most salient to ICANDOR dissemination and implementation and strategies for effective ICANDOR implementation.

Research Design

We will conduct a robust preimplementation assessment to understand organizational and individual barriers and facilitators to implementing ICANDOR. We will assess organizational readiness and culture by key informant interviews and individual-level behaviors by a cancer specialist survey. We will use the CFIR [13,14] to guide data collection and analysis, supplemented by the TDF [15] for the individual-level analysis [24].

Theoretical Frameworks and Instruments

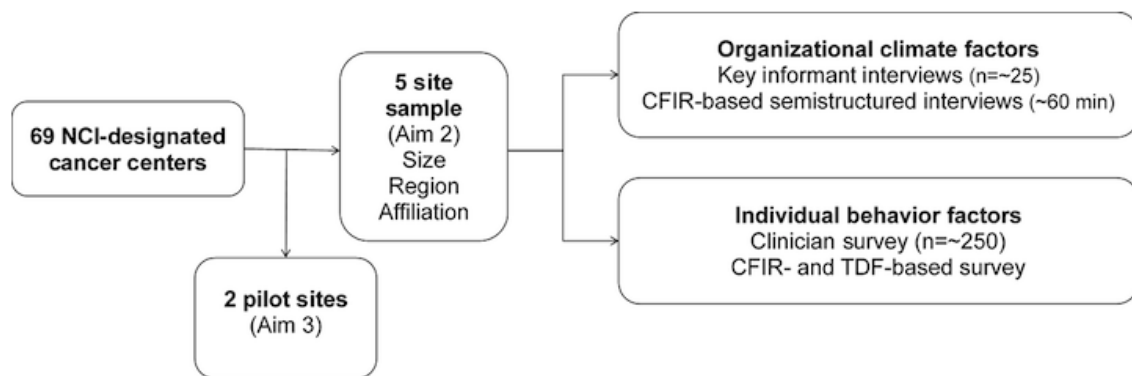
CFIR is a meta-theoretical framework that comprises 39 constructs across 5 domains consolidated from published

implementation theories to systematically assess contextual factors influencing practice change. Domains include intervention characteristics, outer setting (eg, external policies and incentives), inner setting (eg, implementation team communication), individual characteristics, and implementation process [13]. CFIR was selected because it provides a pragmatic, consistent typology applicable across multiple implementation contexts. Because CFIR focuses on organizational characteristics, we will supplement the survey with constructs from TDF to enable a thorough evaluation of individual behavior change constructs. TDF was developed for implementation research to identify influences on health professional behavior; it consolidates 33 theories of behavior change into 14 domains [15,25]. On the basis of our study and previous studies by others on error resolution [10,11,26], we will select the CFIR and TDF constructs most likely to be the potential determinants of implementation or to have sufficient variation across organizations.

Setting

We will purposively sample 5 of the 69 NCI-designated cancer centers in the United States (excluding the centers selected for pilot testing in aim 3) to maximize diversity in site characteristics (eg, size, geographic region, and affiliation with a university medical center; Figure 3). We have chosen cancer centers as the site of testing because identification of errors between facilities is particularly relevant to complex oncologic care. The screening, diagnosis, and multidisciplinary management of cancer requires patients to interface with multiple physicians and facility types with varying levels of integration [27]. In the cancer care environment, consequences of errors can be especially harmful, further complicating the willingness or responsibility for disclosure of the discovering provider [28,29]. Our preliminary work suggests cancer specialists lack consensus on whether or how to communicate about these errors to patients and responsible providers [10,11].

Figure 3. Overview of sampling strategy and study design for Aim 2. CFIR: Consolidated Framework for Implementation Research; NCI: National Cancer Institute; TDF: Theoretical Domains Framework.



Key Informant Interviews

For key informant interviews, we will contact institutional risk management offices through publicly available data center websites or professional contacts. We will introduce our research and identify and recruit key hospital personnel at each site who led CANDOR process implementation, if applicable, or are involved in patient safety and error resolution. These may be risk managers, patient safety and quality improvement personnel, legal counsel, or clinical ethicists (3-5 interviews per site). We will use snowball sampling [30] supplemented with information-rich informants to ensure representation of diverse perspectives. Interviews (60 min approximately) will be recorded, transcribed, and imported into a software that supports qualitative/mixed methods analyses. We will analyze data using framework analysis in the following steps: (1) immerse in the details of each transcript, (2) use CFIR constructs as key themes, (3) code transcripts with CFIR framework to identify recurrent subthemes, (4) summarize data in a matrix, and (5) synthesize data by comparing across cases. Preliminary analysis will be performed iteratively with interviews to assess sample size for appropriate *information power* up to a total of 25 individuals. Information power is an approach to estimate maximum sample size in qualitative studies that considers salient study characteristics affecting the amount of relevant information a sample is likely to provide. This maximum sample size takes into account the focus of the study aim, the specificity of the sample to personnel with experience in the topic, our prior experience with the quality of dialogue with hospital personnel [10,11], and the theoretical framework that will structure both the interview guide and analysis [31].

Clinician Survey

A random sample of clinicians (50 per site; medical, radiation, and surgical oncologists) will be recruited to complete the survey at each of the 5 sites (n=250). A roster of physicians and their contact information will be obtained from Web-based *Find a Physician* registries of each cancer center. A research assistant will confirm accurate mailing addresses by phone before mailing. Physicians will be recruited by letter with an attached survey and a nonconditional cash incentive [32,33]. We will use the Dillman method of survey administration [34] to achieve optimal response rates with a goal of 65% [27,35-37]. The survey will be developed to determine barriers and facilitators to ICANDOR implementation, using CFIR constructs as a guide

for selecting survey items, augmented by the TDF to fully explore individual behavior. The questionnaire will be pilot-tested for face validity, clarity, and stability over time with 15 participants representing all study sites, who will be excluded from subsequent participation. Face validity will be established by qualitative assessment via field notes with pilot respondents and other nonparticipant stakeholders. Clarity will be established by observing pilot participants completing the survey, asking them to think out loud as they are completing the survey, and identifying any items requiring further clarification. Finally, stability will be tested using test-retest methodology [38]. Likert scale responses will be dichotomized as follows: (1) likely/very likely versus not sure/unlikely/very unlikely. Summary statistics will include sample size, mean, median, SD, and range for continuous variables, and counts and percentages for categorical or ordinal variables.

Mixed Methods Analysis

Summary statistics for clinician surveys at each site will be imported to the qualitative data analysis software and linked to the qualitative analysis of key informant interviews at the site level (ie, each of the 5 sites will be analyzed as a case). This will enable mixed methods analysis by examining potential patterns in the data among the 5 sites.

Implementation Toolkit

The proposed activities will identify barriers and facilitators to implementation of the ICANDOR process across a diverse setting of cancer centers. From these data, we will generate an implementation toolkit for guiding ICANDOR implementation. We anticipate that multiple categories of implementation strategies will be necessary, and the final strategy will be a bundled approach [39]. Our proposed activities will also identify the CFIR constructs most salient to ICANDOR, providing a foundation for evaluating future implementation efforts.

Aim 3: Evaluate the Acceptability and Feasibility of a Toolkit for Intersystem Communication and Optimal Resolution Implementation

Introduction

Although toolkits are effective interventions to facilitate practice change, there is a need to rigorously study the acceptability, utility, and impact of specific toolkit components before widespread implementation.

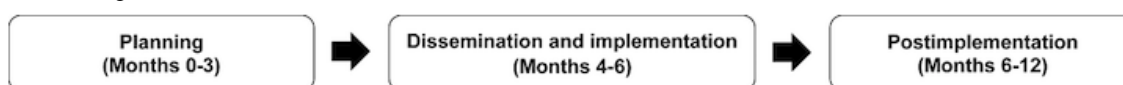
Research Design

We will use the implementation toolkit created in aim 2 to implement ICANDOR at 2 National Cancer Institute (NCI)-designated cancer centers with whom the study team has strong institutional ties. We will collaborate with study site stakeholders to select and refine tools and strategies from the toolkit and implement ICANDOR. We will then measure early implementation outcomes including acceptability, appropriateness, reach, adoption, and feasibility. The overall study period will be 12 months (Figure 4). Study sites will include 2 NCI-designated cancer centers with distinct representation of geographic region and affiliation.

In the planning phase, we will form stakeholder panels (eg, clinicians, legal experts, bioethicists, risk officers, and patients) at each site. We will present the ICANDOR Toolkit from aim

2 to the stakeholder panels and elicit feedback on site-specific barriers/facilitators and the toolkit strategies perceived as acceptable and useful. We will then use a rapid assessment approach [40] to balance rigor with timeliness in the analysis and synthesis of data, review key stakeholder recommendations, and specify final implementation interventions. At the end of the planning period, we will conduct training sessions among cancer specialists participating in 3 multidisciplinary tumor boards at each site (eg, Sarcoma, Colorectal, Thoracic, Gynecologic Oncology) in error identification between systems and ICANDOR (active dissemination), as well as the use of selected implementation strategies. We will initiate ICANDOR at the study sites (month 4). In months 4 to 12, we will collect data on implementation outcomes including adoption (month 4-6) and appropriateness, reach, acceptability, and feasibility (month 12).

Figure 4. Research design and timeline for Aim 3.



Outcome Measures

We will measure 5 implementation outcomes from the Proctor et al [41] taxonomy of outcomes—acceptability, appropriateness, reach, adoption, and feasibility (Table 1). To assess initial acceptability, appropriateness, and feasibility, we will conduct key informant interviews (n=10 at each site, or until appropriate information power is achieved [31]) in the planning phase. Following the clinician training in the dissemination and implementation phase, we will conduct short posttraining surveys to measure adoption. Finally, at month 12, we will invite all cancer specialists participating in the training

sessions (estimated n=100) and the error resolution staff (n=20) during the study period to complete surveys to reassess acceptability, appropriateness, and feasibility. To gain a greater understanding about the quantitative survey findings, we will then purposively sample 2 or 3 respondents within each stakeholder type at each site (n=30 total, or until appropriate information power is achieved [31]) with very high or very low scores to participate in semistructured interviews. We will also measure reach by determining the number of unique providers who report an ICANDOR event, triggering use of the implementation toolkit, during the study period.

Table 1. Summary of dissemination and implementation outcomes, method, and timing of measurement.

Construct	Definition	Method of measurement	Timing
Acceptability	Perception among implementation stakeholders that the toolkit is agreeable, palatable, or satisfactory	Key Informant Interviews; Clinician Survey	Planning; postimplementation
Appropriateness	Perceived fit, relevance, or compatibility of the toolkit for the particular practice setting	Key Informant Interview; Clinician Survey	Planning; postimplementation
Reach/penetration	The number of providers who report an ICANDOR ^a event divided by the number of providers who participated in the training	Reporting Data	Postimplementation
Adoption	The intention, initial decision, or action to try or employ the ICANDOR Toolkit	Clinician Survey	Posttraining
Feasibility	The extent to which the ICANDOR Toolkit can be successfully carried out	Key Informant Interviews; Clinician Survey	Planning; postimplementation

^aICANDOR: Intersystem Communication and Optimal Resolution.

Analysis

Given this study’s focus on acceptability and feasibility, our analysis will be primarily descriptive. For analysis of the quantitative data, we will calculate descriptive and bivariate statistics on survey responses (acceptability and appropriateness). We will then generate mean acceptability and appropriateness scores for each component of the implementation toolkit. For key informant interviews, all meetings will be recorded, transcribed, and analyzed using rapid

assessment. Using a joint display organized by prespecified implementation activities, we will visually merge findings from qualitative and quantitative data analysis, presenting quantitative scores with representative qualitative quotes. Monthly ICANDOR adoption rates in the 6 months after pilot implementation will be measured. We will present findings to the stakeholder panels and refine the implementation toolkit to include a detailed description of the implementation planning process, advice about toolkit use, and improved strategies and tools.

Results

This protocol was funded in August 2018 with support from the AHRQ (see [Multimedia Appendix 1](#)). The University of Michigan Medical School Institutional Review Board has reviewed and approved the scope of activities described (study ID HUM00151593). As of April 2019, step 1 of aim 1 is underway, and aim 1 is projected to be completed by April 2020. Data collection is projected to begin in January 2020 for aim 2 and in August 2020 for aim 3.

Discussion

Providing a communication and resolution strategy applicable to IMED would help address this current blind spot in the patient safety and quality improvement movement. The proposed work will generate a refined toolkit to guide ICANDOR dissemination and implementation more broadly, thereby improving response to errors discovered between systems. The natural progression of this work will be to test the toolkit more broadly, understand the feasibility and barriers of implementation on a broader scale, and pilot the implementation in new organizations.

This study has several potential limitations, which we have attempted to mitigate. We may find that the components of CANDOR are not easily modified to apply to ICANDOR events, or that new components need to be added. In this case, we will rely on the expertise of the panelists to develop new components. We may encounter some key informants or providers who are unwilling to participate. We expect this is unlikely given our success in recruiting practitioners for the published preliminary studies and for the ongoing work involving other stakeholders. In the unlikely event that study site participation is poor, we can identify additional sites of similar size, region, and affiliation. We will incentivize participation by providing a nonconditional cash incentive to interviewees and survey respondents. Finally, every setting is unique and not all successful practices can be adapted to other settings (eg, the organization's support for implementation may vary). To optimize our feasibility study, we will engage stakeholders at the study sites in selecting tools and strategies from the toolkit. Identifying microlevel strategies and tools (ie, those that are essential in specific settings or populations) is a critical area for future work.

Conflicts of Interest

RCB reports a financial relationship with Boothman Consulting Group, LLC which offers assistance to health systems utilizing Communication and Resolution Programs. The remaining authors declare no conflicts of interest.

Multimedia Appendix 1

Peer reviews from the Agency for Healthcare Research and Quality.

[\[PDF File \(Adobe PDF File\), 164KB - resprot_v8i7e13396_app1.pdf\]](#)

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Abbreviations

AHRQ: Agency for Healthcare Research and Quality
CANDOR: Communication and Optimal Resolution
CFIR: Consolidated Framework for Implementation Research
ICANDOR: Intersystem Communication and Optimal Resolution
IMED: Intersystem Medical Error Discovery
NCI: National Cancer Institute
TDF: Theoretical Domains Framework

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Protocol

Refugee Youth and Transition to Further Education, Training, and Employment in Australia: Protocol for a Mixed Methods Study

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Abstract

Background: Young people with refugee experiences are widely acknowledged as encountering multiple disadvantages that affect their school completion and retention, university entry, and subsequent employment. This paper discusses the rationale for and protocol of a mixed methods investigation focusing on improving education and employment outcomes among refugee background youth aged 15 to 24 years from three focus regions: the Middle East (Afghanistan, Iran, Iraq, Syria), South Asia (Nepal, Bhutan, Myanmar/Burma, Pakistan) and Africa (Sudan, South Sudan, Liberia, Ethiopia, Somalia, DR Congo).

Objective: The rationale of the project is to identify the facilitators and barriers to successful transition from school to further education and employment; investigate participant awareness of support systems available when faced with education and employment difficulties; redress the disadvantages encountered by refugee background youth; and bridge the gap between research, policy, and practice in relation to social inclusion and participation.

Methods: The study involves collecting survey data from 600 youth followed by individual interviews with a subset of 60 youth, their parents/primary caregivers, and their teachers. A cross-sectional survey will assess facilitators and barriers to successful transition from school to further education and employment. Individual interviews will provide context-rich data on key issues relevant to education and employment outcomes.

Results: The study began in 2016 and is due for completion by the end of 2019. The quantitative survey has been conducted with 635 participants and was closed in March 2019. The qualitative interview stage is ongoing, and the current total in April 2019 is 93 participants including educators, youth, and family members of the youth. Analysis and presentation of results will be available in 2020. Some preliminary findings will be available during the late half of 2019.

Conclusions: This project will contribute new and unique insights to knowledge in relation to key factors influencing education and employment outcomes among refugee youth. This research will enable effective planning for the needs of some of Australia's most disadvantaged and marginalized young people, leading to a sustainable improvement in the education and employability of young refugees.

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KEYWORDS

refugee; youth; education; employment; mixed-methods; Australia

Introduction

Background

A large proportion of humanitarian arrivals in Australia are children who receive their education in their new home country [1]. They may face unique challenges that place them at increased risk of poor education and employment outcomes [2-5] such as limited English language skills [6,7]; difficulty navigating the education, training, and employment systems; limited or interrupted former education; psychosocial problems associated with premigration and postmigration stressors; lack of support at school and home; and racism and discrimination [6,8-10]. Refugee intakes can diversify and increase the skill level of Australia's population [2,11] with long-term positive economic impacts for Australia [1,12]. However, the effect of multiple disadvantages on school completion and retention rates, university entry, and subsequent employment for refugee youth is widely acknowledged [2,3,5,7,13].

Australia is a multicultural nation, with 49% of all Australians either born overseas or having at least one parent born overseas [14]. Of recent migrants, 76% were born in other than English-speaking countries and 91% were aged 15 to 44 years on arrival [14]. Refugees are a growing group in the broader migrant population, with more than 800,000 arriving since 1945, or 13,750 arrivals each year [1,11,15]. Young people account for 25% of all youth aged 12 to 24 years in Australia and about 50% of Australia's humanitarian intake [11,14,16].

There is consensus that recently arrived refugee youth face a different and unique set of challenges that place them at increased risk of education and employment challenges outside the experience of youth in the general population [7,17]. Similar to migrant youth, young refugees must locate and connect themselves within a new cultural environment [18] and work through life cycle challenges (eg, identity development during adolescence) but unlike migrant youth, they must also try to find a sense of safety and security within fractured families and communities while addressing consequences of experiencing and/or witnessing past traumatic events during armed conflict, organized violence, and prolonged displacement [4]. Additionally, many refugee youths are not accessing support services that could increase their prospects for successful integration [19,20] and improved employment opportunities.

Schools have the potential to not only provide educational opportunities but, more importantly, offer a means of integration into the host society [3]. School is a prime location for refugee youth to begin building a new sense of civic identity [4,21] and belonging [7,20]. Education is crucial in establishing routines and giving a sense of normality and hope for children's futures. School can be a place of security when all other things may seem to be in confusion [22].

Although school has the potential for positive outcomes and experiences, structural, cultural, and language barriers place refugee students on an unequal footing with their

Australian-born peers. The interplay between structure, culture, and agency is a framework within which the nature of power structures and experiences of school may be interrogated [23]: the significance of a student's ethnicity, for example, is determined by a range of factors including institutional bias, school policies, or the agency of individuals to be flexible within a school's hierarchical systems [24].

Adding further pressure are parental expectations that these youth enter highly competitive professions such as medicine, engineering, and dentistry [6]. Most refugee parents suffer a loss of role and status with migration [25,26]. Many are living on welfare payments or working in unskilled, low-paid, and low-status jobs [27], which for the more educated and affluent represent a marked change from their former circumstances. For their part, many young people feel their parents do not understand how difficult it is to excel in a new and unfamiliar education and employment environment [6].

There is a recurring issue of language as a barrier to accessing health, employment, and education services [28,29]. English language challenges and limited understanding of school structure and processes may prevent many parents from helping students with studies or attending parent interviews and other school activities designed to support children in their studies [30].

People with a refugee background may be a part of a culturally identifiable group; however, it is vital to acknowledge that these groups are, in turn, made up of unique individuals with diverse contextual needs [21]. Supporting diversity with the aim of successful settlement and integration of refugees is a critical issue for host societies [4], and engaging with the labor market is pivotal to this [1,13]. The settlement of refugees is more difficult in virtually all aspects than the settlement of other migrants, and employment outcomes are considerably poorer than for other migrants [2].

Education has the potential to broaden opportunities for employment and increasing individuals' capacity to make choices about their career path. Although research has been undertaken on the educational experiences of young refugees in Australia and elsewhere [4,7,20,25,31-33], studies of actual education and employment outcomes are scarce, yet these are crucial stages through which individuals have opportunities for development into fully participating, productive Australian citizens.

Aim

The main aim of this project is to investigate education and employment outcomes among refugee youth aged 15 to 24 years from three focus regions—the Middle East (Afghanistan, Iran, Iraq, Syria), South Asia (Nepal, Bhutan, Myanmar/Burma, Pakistan) and Africa (Sudan, South Sudan, Ethiopia, Liberia, Somalia, DR Congo)—with a view to influencing education, training, and employment policy and practice.

The following objectives will be employed for meeting project aims:

- Identify facilitators and barriers to successful transition from school into further education and employment
- Map out support systems accessed by youth who are experiencing education- and employment-related difficulties
- Investigate the extent of youth and family awareness of available education, training, and employment pathways
- Bridge a gap between research, policy, and practice in relation to the social inclusion and participation of refugee youth in educational settings
- Propose evidence-based recommendations for policy and decision makers in the education, training, and employment sectors
- Respond to social justice concerns by providing new insights into potential improvements to the long-term employment opportunities of refugee youth

Theoretical Framework

In the absence of refugee youth visibility in policy and research, there is no one theoretical framework appropriate to help us address the significant educational disadvantages confronting refugee youth and their migration experiences, educational participation, adjustment, and integration. This research is innovative and important because it brings together two frameworks to generate an integrated conceptual framework (integrated immigration model) to help understand refugee youth educational participation, adjustment, and integration (cultural, social, and economic). First, the segmented assimilation model combines elements of both the assimilation and ethnic disadvantage perspectives by recognizing the diversity of settlers' experience [34]. Second, the advocacy/transformational conceptual framework, marked by the conscious inclusion of groups that are generally excluded from mainstream society, allows participants to benefit both during the research process and afterward when findings are used to bring changes in action or policy [35,36]. This theoretical lens sees action as an important outcome of research and provides methodological guidance for researchers working in the interest of social justice in culturally complex communities to improve unsatisfactory social conditions and outcomes for marginalized population groups.

The migration experience is clearly impacted by the experience and knowledge that settlers bring with them, the context into which they arrive, and the responsiveness of the host community [1]. We expect the integration pathways to be affected by these contextual factors. Our integrated approach argues that some settlers experience structural barriers that limit their access to employment and other opportunities while others experience upward mobility. Our approach also emphasizes multiple pathways to incorporation, and the policy emphasis is on identifying the contextual, structural, and cultural factors that separate successful incorporation from unsuccessful integration [1,34].

The main aim of the study is to investigate education and employment outcomes among refugee youth aged 15 to 24 years from three focus regions. Findings from the study will contribute new and unique insights and knowledge relating to key factors influencing further education and employment outcomes among refugee youth in Australia.

Methods

Selection Criteria

The survey component will target youth aged 15 to 24 years who have migrated, or whose parents have migrated, to Australia since 2006 and are studying at the time of participation. The criteria for ethnicity will be self-ascribed ethnic origin. Families with more than one child will be given the option of having up to two of their eligible youth participate in the study. The method of selection will be the birthday technique (ie, two youths with birthdays closest to the date of the interview will be selected).

Time of arrival is restricted to the last 10 years because the initial and middle stages of migration and resettlement present particular adjustment problems [37] that are the focus of this study. The interview stage will only accept consenting participants (with parental consent for those under age 18 years) who additionally consent to interviews of their caregivers and teachers.

Sample Size

We assume approximately 60,000 to 70,000 refugee youth aged 15 to 24 years are resident in Australia [15,16]. With regard to the quantitative component of this study, a sample of 600 would provide the following accuracy with 95% confidence for any question with an expected frequency response of 50%: overall ($\pm 4\%$), for each gender ($\pm 5.5\%$), for each migration region ($\pm 7\%$), and for gender within migration region ($\pm 10\%$).

The qualitative component will purposively target 60 youth (20 youth for each of the target migration regions) along with their parents/primary caregivers (60) and their teachers (60) from the larger sample allowing 10% of the entire survey group to be represented in the qualitative stage of the study.

See [Multimedia Appendix 1](#) for a report on the demographic profile of the South Australian refugee youth population in 2019.

Sampling Method

We will use a combination of convenience and snowball sampling to recruit the research participants. Convenience and snowball sampling are generally used when the desired characteristics of the sample are uncommon, when the target population is difficult to access, and when nonprobability sampling methods are not possible [38], all of which apply to refugee populations.

Recruitment

The sample of participating youth will be drawn from youth with refugee backgrounds who are studying at the time of participation. Learning institutions identified as having significant numbers of refugee students aged between 15 and 24 years will be targeted. The research package will be given to youth who express interest in participating in the project.

Additionally, groups and organizations having extensive contact with refugee populations will assist with the recruitment of initial participants who in turn will refer other potential participants to the study. A range of promotion strategies in

multiple community settings will be used to ensure the sample is as representative as possible. The project will be widely promoted through multicultural service providers, refugee community leaders, schools, refugee community events, and ethnic community radio/media using brochures, flyers, letters, and a Call for Volunteers sheet.

Youth will be recruited for individual interviews through an Expression of Interest form they receive after completing the survey. Parents or caregivers of those participants who complete an interview will also be interviewed. Teachers will be recruited from among staff where youth participants are studying.

Study Design and Data Collection

A survey of 600 refugee youth (with approximately 200 from each focus region) will form a major foundation of the study. A survey will be developed, and detailed pilot testing will be undertaken to ensure that the instrument is able to produce meaningful and robust results.

The qualitative component will purposively target 60 youth from the larger sample. These youths, their parents/caregivers, and their teachers will be individually interviewed. Interview questions will be constructed from survey data, investigating key challenges and successes at school, transitional issues, knowledge of the Australian education system including educational pathways, and family influences on education-based decision making.

Interviews and surveys will be completed at multiple venues at the convenience of participants. Venues will include the Multicultural Youth South Australia (MYSA) and Australian Migrant Resource Centre (AMRC) premises, interview or counseling rooms at other organizational premises, schools, participants' homes, or public libraries.

Selection and Training of Bilingual Workers

A group of bilingual youth workers will deliver the research package and administer the survey. This will enable enhanced communication so nothing is missed in interpretation. The bilingual youth workers will receive training and a comprehensive instruction manual providing background research information, promotional strategies, participant eligibility criteria, an explanation of the research questions, detailed instructions for their administration, and important ethical considerations.

Translation of Study Materials

Study materials will be translated, as required, into the target languages by translators accredited by the National Accreditation Authority for Translators and Interpreters and back-translated by an independent bilingual professional from each of the target communities with knowledge of concepts. A panel of language and content experts will examine the adequacy of the original translation and will advise on use of correct terms to ensure translation conveys the meaning and the exact concepts are maintained. The survey will be pretested with three youth from each of the target communities, and revised if necessary before being administered to the target groups. The cover letter, information page, and consent form will also be recorded as audio (in the target languages) for parents/caregivers who are illiterate in their own language.

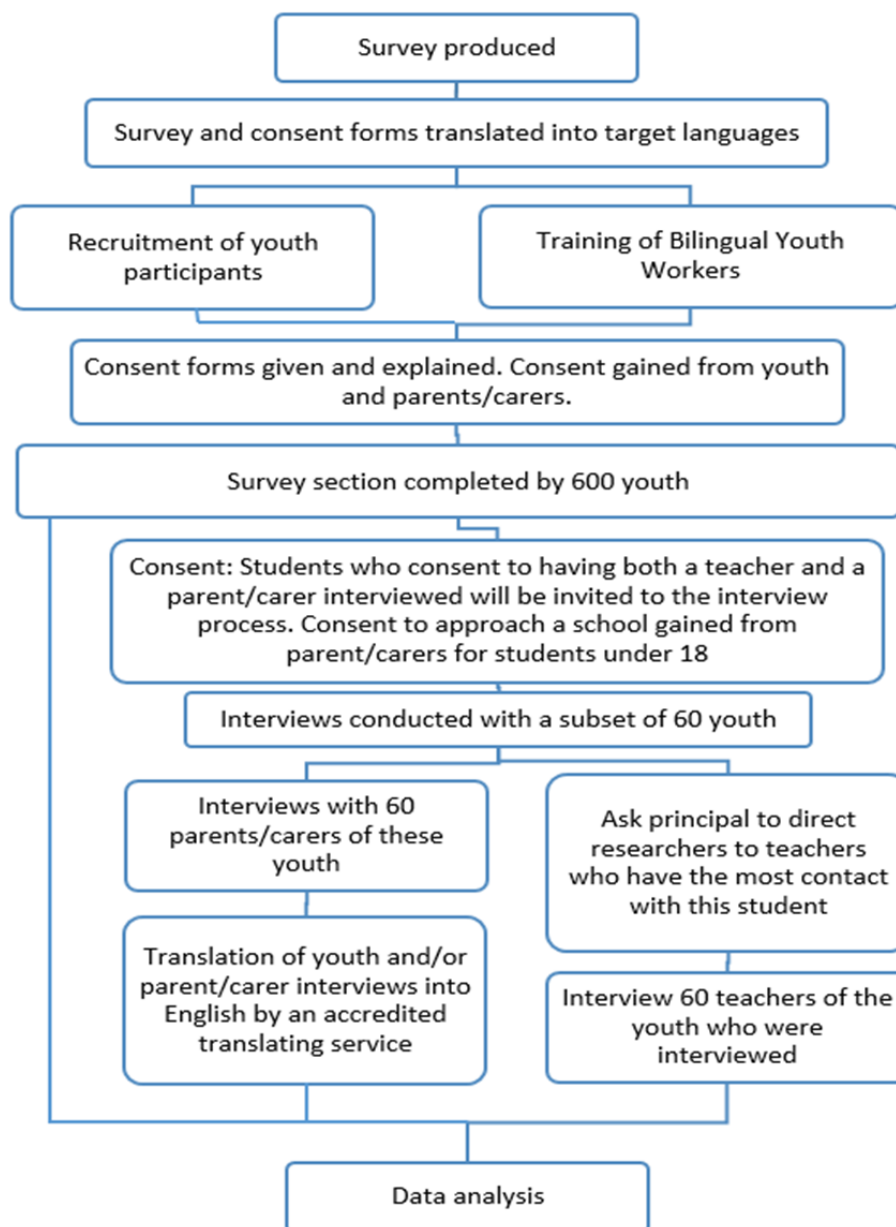
Ethical Considerations

In line with our collaborative approach, a reference group consisting of ethnic community representatives and external senior researchers with transcultural research expertise will be established to ensure the research is carried out in partnership with the communities in a culturally appropriate manner and the results are relevant to the community. Bilingual youth workers will ensure clear understanding of the survey questions, and interpreters will be available at all times for youth or their families to clarify concepts or terms when necessary.

All researchers and bilingual youth workers who work with youth will have a National Criminal History Record Check and Screening Assessment, which is a requirement for people working with children in Australia. Individual contact details of participants will be recorded in a password-protected file kept separately from survey and interview data. Digital copies of the interview recordings will also be kept separately from de-identified transcriptions and translations.

Prior to any data collection, detailed information will be given to participants (and parents/caregivers for those aged under 18 years) and appropriate consent will be sought and gained for each stage of the study. Participants will be informed that they may withdraw at any time without any consequence and any related data will be excluded from the study. An option to be referred to appropriate counseling services will be offered to participants who may become distressed from the research experience. See [Figure 1](#) for the study protocol.

Figure 1. Study protocol.



Results

Data Collection

This study is due for completion by the end of 2019. It began in 2016, and data collection commenced in 2017. The quantitative survey component of the study currently includes 635 participants and was closed in March 2019. The remaining qualitative data collection is currently in progress, with an in-progress total of 93 interview participants including educators, youth, and family members of the youth. Preliminary analysis of quantitative data is currently underway and is expected to be reported in 2019-2020. Similarly, qualitative data will be analyzed once the data set is complete and is expected to be presented in 2019-2020.

Statistical Analysis and Data Management

With respect to quantitative data analysis, standard statistical techniques will be used. The response rate will be presented followed by a comparison of the demographics of the respondents with that for refugee youth as a whole in South Australia. Descriptive statistics will be presented with counts and percentages for categorical variables and means and standard deviations (or nonparametric equivalents) for continuous measures. Confidence intervals will be provided for main results. Tables will be provided for cross-tabulations by gender, migration region, and gender by migration region. Chi-square tests will be undertaken for comparisons of categorical variables by gender and migration region and analysis of variance undertaken for continuous variables. Time since arrival in Australia will be used as a covariate in all analysis where this is appropriate. However, these analyses will be undertaken in the spirit of hypothesis generation rather than

hypothesis testing and levels of significance interpreted in this light. Regression models may also be employed for exploratory analysis purposes.

With respect to qualitative data analysis, the interviews will be recorded as audio and transcribed verbatim [9]. The data will be prepared, organized, and analyzed using a thematic approach following the principles and procedures suggested by Krueger and Casey [39]. The data will be presented in the form of detailed description using case illustrations, paraphrases, and direct quotations from the identified themes.

Discussion

Summary

This project seeks to provide benefits for refugee youth during and after the research process. It is hoped that benefits will also accrue to the broader refugee community as a result of the researchers' advocacy activities by disseminating the findings to policy makers, services planners, and others strategically placed to take action and make changes on behalf of refugee youth populations. In keeping with the advocacy interest in ensuring that the people affected by an issue are enabled to take action on their own behalf [35], the knowledge generated through the research will be made available to refugee communities, multicultural agencies, organizations, and youth advocacy bodies.

Building on earlier studies [1,6,12,40], this project incorporates new areas for investigation and involves collaboration between researchers from the University of South Australia, the University of Adelaide, and industry partners MYSA and AMRC, the two leading settlement agencies for refugee youth and families in South Australia.

The successful settlement of refugee youth as fully participating Australian citizens is desirable both for our society and for the individuals concerned as it directly affects their contribution to the nation at large [1,2,7]. Until recently, the literature on migration and education outcomes has failed to take account the experiences of refugees as distinct from those of other migrants [7,41]. Education policy makers have focused mainly on migrant and multicultural education. These exclusions from academic research and public policy provide a context for targeted policies and frameworks. Attention needs to be given to the education and training needs of refugee youth who are at high risk in a complex transition process [7,19,41].

The transition from school to employment is not always linear; rather, young people may take a pathway that leads to partial employment or further education before successfully embarking on a career path. Effective transitions require individual self-efficacy and motivation combined with resources such as

family or social connections, educational qualifications, vocational training, and knowledge. A relative weakness in one of these areas can be made up for with a strength elsewhere, but a combination of poor resources and a lack of individual agency results in a likelihood of more negative transition outcomes [42]. Smooth transitions can therefore be facilitated by improving access to education and training and by building individuals' belief in their skills, abilities, and capability to make informed choices regarding the future.

As people with a refugee background access and participate in education and employment, the likelihood of their successful integration into the larger community increases [20,43]. With effective delivery, education can not only support well-being and connection for young people [44] but it is also a means to employment through the provision of vocational skill development, support of young people's maturity, and establishment of opportunities for professional intervention [21].

This research addresses an issue of significant economic and social concern. There is enormous potential for refugees' economic, social, and civic contribution, and it is crucial that finely tuned policies work to realize that potential [1,12].

Conclusion

This project will contribute new and unique insights to knowledge in relation to key factors influencing education and employment outcomes among refugee youth. It will bridge identified gaps in the knowledge of researchers and government policy makers who, as part of their focus on employment, are concerned to support research partnerships that will result in improved employment outcomes for disadvantaged groups such as refugees [1,7].

There are very few studies focusing on this key transitional phase between school and further education or employment, particularly with the inclusion of both generation 1 and generation 1.5 (youth born overseas who arrived in Australia as adolescents or children). This project will be the first of its kind undertaken in Australia and will contribute new insights resulting in significant improvements to the long-term employment opportunities of refugee youth. Factors that help and hinder young refugees in achieving their desired education, training, and employment goals will be identified. Findings will assist agencies and professionals within these sectors to identify and plan strategic support, and existing approaches will be assessed to further increase the capacity of refugee youth to achieve their desired employment goals. This research will enable effective planning for the needs of some of Australia's most disadvantaged and marginalized young people, leading to a sustainable improvement in the education and employability of young refugees.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Demographic Profile of South Australian Refugee Youth Population 2019.

[[PDF File \(Adobe PDF File\), 7MB - resprot_v8i7e12632_app1.pdf](#)]

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Abbreviations

AMRC: Australian Migrant Resource Centre

MYSA: Multicultural Youth South Australia

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Protocol

Impact of Early Medical Treatment for Transgender Youth: Protocol for the Longitudinal, Observational Trans Youth Care Study

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Abstract

Background: Transgender children and adolescents (ie, those who experience incongruence between assigned sex at birth and internal gender identity) are poorly understood and an understudied population in the United States. Since 2008, medical care for transgender youth has generally followed guidelines developed by professional consensus, given the paucity of empirical research, particularly in the US setting.

Objective: The objective of this research was to provide evidence-based data to inform clinical care for transgender youth. The study aims (1) to evaluate the impact of gonadotropin-releasing hormone agonists administered for puberty suppression on mental health, psychological well-being, and metabolic and physiologic parameters including bone health in a cohort of children and adolescents (Tanner stages 2-4) with gender dysphoria, comparing baseline and follow-up assessments, and (2) to determine the impact of gender-affirming hormones (eg, estradiol and testosterone) administered for phenotypic gender transition on mental health, psychological well-being, and metabolic and physiologic parameters in a cohort of adolescents with gender dysphoria, comparing baseline and follow-up assessments.

Methods: The study uses a longitudinal observational design to examine the outcomes of existing medical treatment protocols for gender dysphoria in two distinct cohorts: youth initiating puberty suppression and youth pursuing a phenotypic gender transition. Data on routine anthropometric and physiologic parameters are collected through chart abstraction, questionnaires, and research interviews in the 24-month study period. Audio computer-assisted self-interview and individual interview survey instruments are used to collect demographic, mental health, psychosocial, and behavioral data from parents and youth in the blocker cohort and only from youth in the gender-affirming hormone cohort at baseline and 6, 12, 18, and 24 months.

Results: Participant recruitment commenced in July 2016, and enrollment was completed in September 2018. A total of 90 participants were enrolled in the blocker cohort and 301 participants were enrolled in the gender-affirming hormone cohort. Findings based on baseline data are expected to be submitted for publication in 2019.

Conclusions: This longitudinal, observational study is collecting critical data on the existing models of care for transgender youth that have been used in clinical settings for close to a decade, although with limited empirical research to support them. This research is a direct response to the Institute of Medicine report calling for such studies as well as the needs of clinicians and patients. Results from this study have the potential to significantly impact the medical and mental health services provided to transgender youth by making available rigorous scientific evidence on the impact and safety of early treatment based on the sexual development stage. Ultimately, we aim to understand if early medical intervention reduces the health disparities well known to disproportionately affect transgender individuals across their lifespan.

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KEYWORDS

transgender youth; gender dysphoria; puberty blockers; gender affirming hormones

Introduction

Background

“Transgender” is a broad term used to describe individuals whose gender self-identification or expression transgresses established gender norms associated with their assigned sex at birth. Specifically, it is the state of one’s gender identity not aligning with one’s assigned sex at birth [1]. The identities and behaviors of transgender individuals are socially and medically stigmatized, resulting in a grossly underserved population at high risk for significant morbidity and mortality. Transgender people often experience gender dysphoria resulting from the incongruence between their assigned sex at birth and their gender identity. The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) outlines the criteria for the diagnosis of gender dysphoria in adolescents and adults as the presence of a marked incongruence between one’s experienced/expressed gender and assigned gender, lasting for at least 6 months, as manifested by at least two of the following: (1) a marked incongruence between one’s experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics); (2) a strong desire to be rid of one’s primary and/or secondary sex characteristics because of a marked incongruence with one’s experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics); (3) a strong desire for the primary and/or secondary sex characteristics of the other gender (or a gender different from that assigned at birth); (4) a strong desire to be of the other gender (or a gender different from that assigned at birth); (5) a strong desire to be treated as the other gender (or a gender different from that assigned at birth); and (6) a strong conviction that one has the typical feelings and reactions of the other gender (or a gender different from that assigned at birth). Finally, the individual must also experience clinically significant distress or impairment in social, occupational, or other important areas of functioning [2].

Transgender children and adolescents are a poorly understood and a distinctly understudied population in the United States. The limited available data suggest that transgender youth who are gender dysphoric are at an increased risk for anxiety, depression, suicide, and substance use compared to their peers [3-6]. The development of undesired secondary sex characteristics during puberty often intensifies the distress

associated with gender incongruence and increases the risk for these conditions. Current clinical practice guidelines aim to decrease gender dysphoria and ameliorate potential negative health outcomes. Pharmacologic treatment recommendations vary depending on the age and developmental stage of youth with gender dysphoria. For youth in the earliest stages of pubertal development (Tanner stages 2-3; [Multimedia Appendix 1](#) [7]), treatment with a gonadotropin-releasing hormone agonist (GnRHa) is recommended to suppress endogenous puberty and avoid the development of undesired secondary sex characteristics. Among adolescents in the later stages of pubertal development (Tanner stages 4-5), treatment with testosterone or estrogen is recommended to induce the desired masculine or feminine features [8,9]. Although these guidelines have informed care at academic and community centers across the United States, they are based on very limited data. Furthermore, there is minimal available data examining the long-term physiologic and metabolic consequences of gender-affirming hormone treatment in youth. This represents a critical gap in knowledge that has significant implications for clinical practice across the United States.

Research about transgender youth has historically focused on the disproportionate morbidity and mortality among transgender individuals in comparison to the population at large. An Institute of Medicine (IOM) report released in May 2011, entitled “The Health of Lesbian, Gay, Bisexual, and Transgender People,” noted that the existing body of scientific evidence documenting health and well-being of transgender individuals is sparse. The report explicitly called for National Institutes of Health-supported research on transgender health needs, including the development of evidence-based data for providing transgender-specific health care to address gender dysphoria and rigorous research aimed at understanding the health implications of hormone use and other transgender-specific issues. In addition, the IOM report called for longitudinal and cohort studies that incorporate a life course perspective to examine the specific experiences of transgender individuals across different chronological ages [10].

The “Dutch Model”

Over the past 30 years, a team of specialists in the Netherlands at the *Amsterdam Center of Expertise on Gender Dysphoria* observed that transgender individuals who underwent hormonal gender transition at younger ages assimilated more easily into their “new gender” roles because of greater concordance

between their physical appearance and gender [11]. Additionally, many transgender youth going through an undesired endogenous puberty experience distress, commonly resulting in negative emotional, academic, and family functioning [11,12]. Gooren's lifetime follow-up of 3500 adults treated with hormones revealed increased mortality even with the best of care, due to causes that were overwhelmingly psychosocial (suicide, substance abuse, homelessness, etc) [13]. Based on these clinical observations, Dutch clinician-/investigator-initiated early interventions for transgender youth to suppress undesired puberty with GnRHa have historically been used as the primary strategy for suppression of puberty in children experiencing central precocious puberty [14]. Early results from the first 70 gender dysphoric youth undergoing puberty suppression with GnRHa in the Netherlands showed a decrease in behavioral and emotional problems [15].

In 2006, this "Dutch Model" was published outlining this new approach to the care of transgender youth. Adolescents aged 12 years and older with gender dysphoria are administered GnRHa to minimize further development of undesired secondary sexual characteristics. To induce feminization or masculinization, appropriate gender-affirming hormones (estrogen or testosterone, respectively) are added to the regimen when youth reach the age of 16 years. A recent follow-up study from the Dutch team showed alleviation of gender dysphoria and steady improvement of psychological functioning among 55 transgender young adults whose medical gender transition consisted of puberty suppression, followed by gender-affirming hormones and eventually, gender-affirmation surgery [16].

One important limitation of the Dutch model is the chronological age criteria stating that youth with gender dysphoria need to be at least 12 years of age before initiating suppression of puberty and at least 16 years of age before initiating gender-affirming sex-steroid treatment. It is well documented that many children in the United States are already well into their puberty at the age of 12 years [17,18]. In 2013, Biro et al reported that across three major metropolitan areas in the United States, the median age at onset of stage 2 of breast development was 8.8, 9.3, 9.7, and 9.7 years for African American, Hispanic, white non-Hispanic, and Asian participants, respectively [19]. Use of criteria based on chronological age rather than sexual developmental stage decreases early intervention potential and may overlook key windows of opportunity to decrease the risk for negative mental health outcomes. Only a few studies describe the physiological and psychosocial impact of this treatment protocol for puberty suppression in transgender youth [15,16]. There are a handful of studies that have acknowledged the importance of family support in the psychological health and well-being of youth with gender dysphoria [20-22]; however, there is a significant paucity of data examining the experience of parents/caregivers of youth with gender dysphoria. Many youth seeking services for gender dysphoria related to phenotypic transition will access care at or after the age of majority, as they lack parental consent necessary for initiating medical treatment. For youth who are undergoing puberty suppression in early puberty, the chronological age dictates the necessity of parent/guardian consent and thus provides an opportunity to collect information about their experiences in

this study. Finally, the recommendations from the Dutch model are based on data collected from a homogenous population of white, European youth living in relatively supportive environments and are not necessarily generalizable to multiethnic transgender youth in the United States, particularly given the ethnic differences in the timing of pubertal development [19].

The Endocrine Society Clinical Practice Guidelines

In 2009, using the best available evidence, but largely based on expert opinion, the Endocrine Society incorporated the Dutch model into the clinical guidelines "Endocrine Treatment of Transsexual Persons," which includes recommendations for the treatment of transgender youth [9]. Using the Dutch model as a springboard, the Endocrine Society recommended starting treatment with GnRHa for puberty suppression based on sexual development (Tanner staging) rather than chronological age. These "developmental stage, not age" guidelines are based on sexual development at the time of entry into care. The first iteration of the guidelines recommended puberty-blocking medications for youth with gender dysphoria at the beginning stages of puberty (Tanner stage 2 or 3), followed by appropriate gender-affirming hormone therapy at around the age of 16 years. The most recent version of the guidelines, published in 2017, outline compelling considerations for earlier gender-affirming hormone initiation, including potential adverse effects on height and bone mineral density and potential harm to mental health (emotional and social isolation) if initiation of secondary sex characteristics is delayed until the person has reached 16 years of age [8]. However, there are only minimal data supporting earlier use of gender-affirming hormones in transgender adolescents. Since the introduction of these guidelines, no data have been reported in the United States on the physiologic and mental health impact, safety, or tolerability of puberty-suppressing medical interventions with GnRHa for transgender youth, particularly children younger than 12 years of age, leaving a gap in evidence for this practice. Furthermore, the impact of GnRHa on the bone health of transgender children, specifically in those younger than 12 years, remains unknown.

For those patients initiating clinical care in later puberty, gender-affirming hormones are prescribed without GnRHa as a monotherapy, a protocol commonly used in both adolescents and adults. Studies in adult transgender populations have reported on the physiologic impact of gender-affirming hormones [13,23,24], but only a handful have detailed the physiologic impact of puberty blockers and/or gender-affirming hormone administration in transgender adolescents [25,26].

Although the Endocrine Society Clinical Practice Guidelines are widely adopted by providers around the United States and worldwide, there are no formal empirical studies of related clinical outcomes in transgender children and adolescents.

The Network

The study described here began with the creation of a unique network of four university-affiliated gender clinics across the United States. The Network's first project—the Transyouth Care Study—was designed to recruit two developmental cohorts of multiethnic transgender youth and conduct a multisite,

observational study examining the safety of hormonal interventions and the physiological and psychosocial outcomes associated with these treatments. All four sites (ie, Children's Hospital Los Angeles/University of Southern California, Boston Children's Hospital/Harvard University, Lurie Children's Hospital of Chicago/Northwestern University, and the Benioff Children's Hospital/University of California San Francisco) employ similar models of care that include a multidisciplinary team of medical and mental health professionals and are considered the national leaders in the care of transgender children and adolescents.

The Center for Transyouth Health and Development at Children's Hospital Los Angeles promotes healthy futures for transgender and gender diverse youth by providing mental health and medical services, research, training, and capacity building that are developmentally informed, affirmative, compassionate, and holistic. The Center has been providing services for gender diverse and transgender youth since the 1990s and currently includes 1500 youth in active care. Staffed by professionals in the fields of Adolescent Medicine, psychology, social work, psychiatry, researchers, and peer navigators, the Center provides individualized care plans for each patient.

The Gender Development Program at Ann & Robert H Lurie Children's Hospital of Chicago provides outpatient services aimed at supporting the physical, mental, and social health of patients and their families as youth progress through gender identity development. Their specialists in pediatric and adolescent gender development recognize that when it comes to providing effective care, "no one size fits all." Therefore, their goal is to keep families most informed of treatment options and to support them with medical and behavioral health care.

The University of California San Francisco (UCSF) Child and Adolescent Gender Center (CAGC) serves as the Pediatric/Adolescent clinical arm of the widely recognized UCSF Center of Excellence for Transgender Health. The CAGC, housed in the Division of Pediatric Endocrinology at UCSF Benioff Children's Hospital, provides multidisciplinary care to gender nonconforming/transgender youth and adolescents, attracting patients from northern California and beyond. Since the first transgender adolescent patient was seen 10 years ago, the CAGC has served over 950 patients, and its research and outreach activities are funded by grants from the National Institutes of Health and the San Francisco Department of Public Health.

Results from these four sites will likely be generalizable to youth with gender dysphoria residing in urban areas, and while all four sites provide services for some families and youth from surrounding rural areas, the majority of participants are from urban areas. Additionally, it is of critical value to acknowledge that participants recruited from specialized gender centers are likely to experience a specific set of circumstances that may positively impact their capacity to cope with some of the challenges of gender dysphoria. For example, youth who are minors must have parental consent to engage in medical interventions related to gender dysphoria. Parental consent carries an implicit level of parental support, a known factor in the mental health outcomes of youth with gender dysphoria.

The data gathered from these cohorts will not be generalizable to youths with gender dysphoria who have no access to services, such as those with little or no parental support, precariously housed, in foster care without intervention advocacy, or geographically located in an area without transgender youth services.

Specific Aims

The aims of this study are as follows:

- To investigate the impact of medical treatments for gender dysphoria in two developmentally distinct and multiethnic cohorts of transgender youth recruited from four academic sites across the United States via a network of Gender Centers dedicated to their care;
- To evaluate the impact of GnRHa administered for puberty suppression on mental health, psychological well-being, and physiologic parameters including bone health and to document the safety of GnRHa in a cohort of children and adolescents with Tanner stages 2-4 and gender dysphoria, comparing baseline and follow-up assessments; and
- To evaluate the impact of gender-affirming hormones administered for phenotypic gender transition on mental health, psychological well-being, and metabolic/physiologic parameters and to document the safety of gender-affirming hormones in a cohort of adolescents with gender dysphoria, comparing baseline and follow-up assessments.

Methods

Study Design

This longitudinal, observational multisite study aims to better understand the impact of medical treatments for gender dysphoria in youth who are initiating puberty suppression or pursuing a phenotypic gender transition with gender-affirming hormones. Participants are being studied prospectively over a 24-month period from either the initiation of GnRHa or gender-affirming hormones. Day 0 for this study is the initial administration of GnRHa (blocker cohort) or the initiation of gender-affirming hormones (gender-affirming hormone cohort). The baseline assessments may be up to 3 months prior to GnRHa or gender-affirming hormone initiation.

This study was approved by the Institutional Review Boards at the Ann & Robert H Lurie Children's Hospital of Chicago, Boston Children's Hospital, Children's Hospital Los Angeles, and the University of California San Francisco.

Study Population and Recruitment

A total of 90 youth and their parents/caretakers/legal guardians were enrolled in the blocker cohort. In the cohort initiating gender-affirming hormones, 301 participants were enrolled. Youth and parents were recruited from patients seeking care (hormonal intervention to either suppress the progression of puberty with GnRHa or begin phenotypic gender transition with gender-affirming hormones) at any of the four sites.

To be considered eligible for enrollment in the *blocker cohort*, youth must have met the following criteria: presence of gender dysphoria as determined by a clinician; Tanner stage 2, 3, or 4 of sexual development; appropriateness to undergo puberty

suppression with GnRHa; age of 8-16 years; ability to read and understand English; and receiving or planning to receive clinical services at a study site clinic. The exclusion criteria were prior utilization of GnRHs, precocious puberty (assigned males at birth younger than 9 years or assigned females at birth younger than 8 years), pre-existing osteoporosis, presence of serious psychiatric symptoms (eg, active hallucinations and thought disorder), or appearing visibly distraught (eg, suicidal, homicidal, and exhibiting violent behavior) at the time of consent or the baseline study evaluation.

To be considered eligible for enrollment in the *gender-affirming hormone cohort*, participants must have met all the following criteria: presence of gender dysphoria as determined by a clinician, appropriateness for initiating phenotypic gender transition with gender-affirming hormones by the team, age of 8-20 years, ability to read and understand English, and receiving or planning to receive services at a study site clinic. The exclusion criteria were prior utilization of gender-affirming hormones, previously or currently enrolled in the blocker cohort, presence of serious psychiatric symptoms (eg, active hallucinations and thought disorder), appearing visibly distraught (eg, suicidal, homicidal, or exhibiting violent behavior) at the time of consent or the baseline study evaluation, or intoxicated or under the influence of alcohol or other substances that would impair the ability to provide true informed consent or understand and answer the questions.

Regarding age, the minimum age in the inclusion criteria for the gender-affirming hormone cohort was decreased from 13 years (as stated in the original grant proposal) to 8 years in order to ensure that potential participants who might be eligible for hormones based on their Tanner stage would not be excluded due to age alone. Additionally, considerations were made for youth who were found to have very low bone density in the screening, which occurs with youths initiating blockers. Only 7 youths under the age of 13 years at the time of enrollment were enrolled into the cross-sex hormone cohort.

Participants are provided a US \$100 gift card after completion of the baseline, 12-month, and 24-month visits (these are longer visits that include the Mini International Neuropsychiatric Inventory for Children and Adolescents [MINI] diagnostic interview) and a US \$50 gift card after completing the 6- and 18-month visits.

Data Collection and Measures

Audio computer-assisted self-interviewing (ACASI) survey instruments are used to collect demographic, mental health, psychosocial, behavioral, and physiologic data from parents/caretakers and youths in the blocker cohort and youth only in the gender-affirming hormone cohort. Measures that address the study aims are described below. Survey instruments collect data from four domains: demographic, transgender-specific experiences including gender dysphoria, mental health, and additional psychosocial information including quality of life and relationships with parents and peers. These data are collected at baseline and 6, 12, 18, and 24 months. The ACASI takes approximately 1-1.5 hours to complete. Questions pertaining to suicidality are particularly sensitive; therefore, to protect participants experiencing active suicidal ideation, these

items are flagged in the ACASI and the study coordinator facilitating the study visit is immediately notified. This provides an opportunity for staff to check in with participants, direct them to onsite mental health professionals for assessment, and determine whether the study visit should be continued or postponed. An additional check-in with participants occurs at the end of each study visit to address any concerns regarding suicidality.

Mental health diagnoses are assessed at baseline and 12 and 24 months by the MINI Kid or the MINI for participants aged 17 years and older [27]. Parent participation in the MINI Kid for the blocker cohort is optional.

For the blocker cohort, the Child Behavior Checklist (CBCL) will also be completed by participants' parents/caregivers. For the gender-affirming hormone cohort, behavioral and emotional problems will be assessed by the Youth Self-Report (YSR) module of the CBCL at baseline, 12 months, and 24 months. The CBCL and YSR assign scores for internalizing, externalizing, and total problems based on the DSM-IV guidelines [28]. The MINI Kid or MINI and the CBCL or YSR are completed after the ACASI on the same day or during a second visit within 2 weeks of the first research visit. The following constructs were administered:

Blocker Cohort

Specific ACASI measures for parent/caregiver were demographics and their own religiosity/spirituality and stress. Measures for their child were transgender-specific experiences, anxiety, trauma symptoms, autism, suicidality, depression, social relationships, negative affect, general life satisfaction, and stress/self-efficacy ([Multimedia Appendices 2 and 3](#)).

Gender-Affirming Hormone Cohort

The measures included demographics, religiosity/spirituality, gender dysphoria, mental health and trauma assessments, depression, suicidality, gender minority stress, resilience autism symptoms, suicidality, quality of life, body esteem, body image, parental support, negative affect, psychological well-being, social relationships, stress, self-efficacy, quality of life, life change events, and behavioral risk ([Multimedia Appendix 4](#)).

Anthropometric and Physiologic Data for Both Cohorts

Data on anthropometric and physiologic parameters will be routinely collected through chart abstraction, questionnaires, and interviews throughout the study period. Items include lab results, height, weight, blood pressure, diagnoses, prescription medications, Tanner stage, physiologic changes, and bone mineral density as well as dietary calcium intake and weight-bearing exercise (blocker cohort only; [Multimedia Appendix 5](#)).

Statistical Analysis

Primary Objective: Effects of Hormonal Interventions on Mental Health and Psychological Well-Being

Hypotheses under the primary objective will be tested in each cohort using repeated measures multivariate analysis of variance (MANOVA) to assess the trajectories of continuous mental health outcomes and psychological well-being over time within

each cohort. The MANOVA approach will preserve statistical power to detect significant effects among this set of related continuous outcomes without the inflated Type I error rates associated with a series of individual analysis of variance (ANOVA) or regression analyses. The MANOVA analyses will investigate the changes over time in gender dysphoria, depression, anxiety, trauma symptoms, self-injury, suicidality, body esteem, and quality of life. The model will incorporate time (ie, measurement time points: baseline, 6-month, 12-month, 18-month or 24-month) as a within-participants factor. Asserted gender, age, ethnicity, and other sociodemographic variables may additionally be entered as possible covariates (ie, analysis of covariates) to improve statistical power in order to detect significant time effects. However, we do not propose any *a priori* hypotheses about demographic effects on these outcomes, and any demographic variables that do not contribute significantly to the model will be removed from the analysis to preserve power and increase model parsimony.

In keeping with conventional practice, analysis will first proceed with a review of the Box test for the equality of covariance matrices [29]. Violations of this assumption would require the use of the Pillai trace statistic [30], as opposed to the Wilks lambda statistic, to determine multivariate statistical significance. If, as hypothesized, the within-participant time variable demonstrates significant multivariate effects, the follow-up univariate results will be inspected as appropriate. The assumption of sphericity via the Mauchly test [31] will be checked for each measured outcome; if sphericity is violated, the Huyhn-Feldt correction for degrees of freedom will be applied to that outcome [32]. Finally, for outcomes showing significant time effects, linear and quadratic contrasts will be checked for significance, and marginal means will be computed and plotted to create a visual display of significant trajectories. An *a priori* *P* value of .05 will be applied as the criterion for statistical significance in all analyses.

Secondary Objective: Safety of Hormonal Interventions

Unlike the mental health and psychological well-being measures, the question of interest for metabolic and physiological parameters is not whether there are significant fluctuations over time (which may or may not be meaningful), but rather whether initiation of hormonal interventions pushes any physiological indicator into a clinically unsafe range, that is, above or below the safety cutoff values predetermined from previous literature and clinical guidelines. Safety will be assessed cross-sectionally with one-sided one-sample *t* tests comparing cohort mean scores to the cutoff value. We hypothesize that the cohort means will be significantly lower than the cutoff score. We will use the Benjamini-Hochberg procedure to account for inflated family-wise alpha due to multiple comparisons at each time point [33].

Additionally, ranges of raw scores from all patient labs will be computed at each time point as part of the preliminary data cleaning and descriptive analysis phase. This will provide an immediate assessment of whether the indicator value for any individual patient has crossed the safety threshold for that indicator as data are collected at each time point. In the event that any participant experiences an individual increase in

laboratory values above or below the threshold, medication adjustments will be made to protect the well-being of the patient according to the discretion of the medical provider at the site where they are receiving care regardless of the whole-cohort significance test results for that time point.

Bone Density in the Blocker Cohort and Gender-Affirming Hormone Cohort With Previous Gonadotropin-Releasing Hormone Agonist Experience at Puberty

We will use repeated measures ANOVA to estimate trajectories of raw and age-matched bone density scores over time in the blocker cohort and the gender-affirming cohort who previously utilized GnRHa to delay pubertal development. Gender and sociodemographic variables may be entered as possible covariates, linear and quadratic contrasts will be assessed, and marginal means will be computed and plotted to create a visual display of trajectories for both outcomes. We hypothesize that for raw scores, the linear term will not differ significantly from zero, indicating net stability in bone density over time (ie, no loss of bone density). However, for age-matched z-scores, the linear term may be negative, as youth receiving GnRHa fail to add bone density at a rate comparable to their age-matched peers.

Exploratory Objective: Risk Behavior in Youth Initiating Gender-Affirming Hormones

We will conduct an exploratory assessment of sexual risk and substance use behavior in the gender-affirming hormone cohort, using repeated measures MANOVA to model trajectories of these risk behaviors over time. Gender and sociodemographic variables may be entered as possible covariates. Given that sexual risk and substance use behaviors increase during adolescence in normative samples, we do not specify *a priori* hypotheses regarding the impact of hormone treatment on these risk behaviors in our transgender population; however, linear and quadratic contrasts will be assessed. Significant positive terms (indicating increased risk over time) would be indicative of a typical adolescent risk trajectory, whereas significant negative terms (indicating decreasing engagement in risky behaviors) or nonsignificant time effects (suggesting no net change in risk) would instead support a “treatment-as-prevention” explanation. Again, the Box test will be reviewed for equality of covariance matrices [29], and the multivariate test statistic will be determined accordingly. Sphericity will be assessed via the Mauchly test with the Huyhn-Feldt correction applied as needed [31,32].

Additional Analytic Considerations: Site Clustering Effects

Although the observational study is conducted at four sites nationwide, we do not anticipate substantial site effects. To verify this, a group identifier for each participant will be included in the merged analytic dataset, and the intraclass correlation for each outcome will be calculated before conducting multivariate analyses. If, as anticipated, no significant variance is carried at the group level, we will reduce the model to a traditional one-level model. If significant

group-level variance emerges, dummy codes to control site-specific variance will be used to enhance statistical power.

Results

At the close of study enrollment in September 2018, 301 participants were enrolled from all four sites in the gender-affirming hormone cohort (125% of the target) and 90 participants and a parent/caregiver/legal guardian were enrolled in the puberty blocker cohort (102% of the target). We are in the process of conducting the 6, 12, 18, and 24-month visits with the study participants. To date, our follow-up retention rates among participants eligible for each study visit are as follows: 91% for the 6-month visit, 87% for the 12-month visit, 81% for the 18-month visit, and 88% for the 24-month visit.

Initial data from youth enrolled in the blocker cohort across all study sites ($n=90$) demonstrate that the age of participants ranges from 8 to 16 years at enrollment, with a mean age of 11 (SD 1.5) years. Slightly more than half (51%) of all blocker cohort participants were assigned male at birth, and 49% were assigned female at birth. In addition, 78% of blocker cohort participants self-identified as white individuals; 20%, as Hispanic or Latino individuals; 13%, as multirace individuals; and 3%, as black/African American individuals. While the majority identified as white individuals, this sample is significantly more ethnically diverse than previous cohorts described undergoing puberty suppression. All blocker cohort participants report current enrollment in some form of schooling, ranging from 3rd grade to 11th grade.

Participants in the gender-affirming hormone cohort range in age from 11 to 20 years at enrollment, with a mean age of 16 (SD 1.9) years. About two-thirds of gender-affirming hormone participants (67%) were assigned female at birth and 33% were assigned male at birth. Over half (63%) of gender-affirming hormone participants self-identified as white; 22%, as Hispanic or Latino; 5%, as Asian; 4%, as black/African American; 1%, as American Indian or Alaska Native; and 3%, as multirace. The majority (91%) of gender-affirming hormone participants reported that they were students, with approximately 16% in 8th or lower grades, and 65% were currently in high school. As the first enrolled participants did not complete their year 2 visit

until July 2018, no impact data are available to report on the study objectives, aims, and hypotheses.

Discussion

The lack of data supporting medical interventions for transgender youth, combined with a shortage of providers knowledgeable of the complex psychosocial risk factors facing these young people, contributes to a health disparity and public health crisis of considerable magnitude.

This longitudinal, observational study is collecting critical data on the existing models of care for transgender youth that have been commonly used in clinical settings for close to a decade, although with very limited empirical research to support them. The gap in existing knowledge about the impact of these practices leaves providers and caretakers uncertain about moving forward with the recommended medical interventions for transgender youth seeking phenotypic transition. This research is a direct response to the IOM report calling for such studies as well as the needs of clinicians and patients. Results from this study have the potential to significantly impact the medical and mental health services provided to transgender youth in the United States by making available rigorous scientific evidence outlining the impact and safety of early treatment based on sexual development stage. Additionally, data from this study will help in understanding the impact of the recommended treatment protocols among a diverse, multiethnic cohort of transgender youth more representative of the US population.

The findings from this research have the capacity to substantially expand treatment across the country by providing rigorous evidence to demonstrate the benefits of early treatment and to ultimately decrease the existing health disparities for transgender youth.

Future studies should focus on sexual health (including HIV prevention and treatment for transgender youth), the developmental trajectories and medical needs of nonbinary youth, and long-term potential health risks that may arise over the lifespan from early interventions. Finally, the long-term follow-up regarding attributes including adjustment, satisfaction, happiness, educational, and employment attainment and function are critical to understanding the benefit of early access to medical care for these vulnerable youth.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Tanner stages.

[[PDF File \(Adobe PDF File\), 38KB - resprot_v8i7e14434_app1.pdf](#)]

Multimedia Appendix 2

Blocker cohort - youth survey measures.

[[PDF File \(Adobe PDF File\), 58KB](#) - [resprot_v8i7e14434_app2.pdf](#)]

Multimedia Appendix 3

Blocker cohort - parent survey measures.

[[PDF File \(Adobe PDF File\), 58KB](#) - [resprot_v8i7e14434_app3.pdf](#)]

Multimedia Appendix 4

Gender-affirming hormone cohort survey measures.

[[PDF File \(Adobe PDF File\), 73KB](#) - [resprot_v8i7e14434_app4.pdf](#)]

Multimedia Appendix 5

Anthropometric and physiologic data for both cohorts.

[[PDF File \(Adobe PDF File\), 49KB](#) - [resprot_v8i7e14434_app5.pdf](#)]

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Abbreviations

- ACASI:** audio computer-assisted self-interviewing
- ANOVA:** analysis of variance
- CAGC:** Child and Adolescent Gender Center
- CBCL:** Child Behavior Checklist
- DSM:** Diagnostic and Statistical Manual of Mental Disorders
- GeMS:** Gender Management Service

GnRH: gonadotropin-releasing hormone
GnRHa: gonadotropin-releasing hormone agonist
MANOVA: multivariate analysis of variance
UCSF: University of California San Francisco
YSR: Youth Self-Report

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Protocol

Key Worker–Mediated Enhancement of Physical Health in First Episode Psychosis: Protocol For a Feasibility Study in Primary Care

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Abstract

Background: Studies have demonstrated that, for patients with psychosis, a majority of the decline in health status and functioning emerges during the first few years after the onset of illness. This knowledge led to the development of specialized early intervention services (EISs) targeting patients experiencing their first episode of psychosis. The central component of EISs is often assertive case management delivered by a multidisciplinary team, where an appointed key worker is responsible for coordinating treatment and delivering various psychosocial interventions to service users.

Objective: This paper outlines the protocol for a feasibility study examining how key workers may enhance physical health by supporting integration between primary and secondary care.

Methods: Semistructured interviews were conducted with key stakeholder groups (General Practitioners and health care professionals working in mental health services). The interviews informed the development of the complex intervention involving a longitudinal pre-post intervention in 8 general practices in 2 regions in Ireland (one urban and one rural). Patients with first episode psychosis (FEP) will be identified from clinical records at general practices and mental health services.

Results: Baseline and follow-up data (at 6 months) will be collected, examining measures of feasibility, acceptability, and intervention effect size.

Conclusions: Study findings will inform future practice by examining feasibility of key workers enhancing physical health through improved interaction between primary and secondary care. By identifying issues involved in enhancing recruitment and retention, as well as the likely effect size, the study will inform a future definitive intervention.

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KEYWORDS

psychosis; review; health; primary care; secondary care

Introduction

Background

Psychosis is a clinical syndrome that affects several domains, including affective, cognitive, motivational, sensory, and social functioning. Psychosis can manifest in a variety of symptoms including positive symptoms (eg, delusions and hallucinations), negative symptoms (eg, reductions in motivation, volition, and emotion experience or expression), declines in cognitive and social functioning, and disorganized speech and behavior [1]. Psychosis often manifests as a symptom of psychotic-spectrum disorders, which include schizophrenia-spectrum disorders (eg, schizophrenia and schizoaffective disorder) and affective disorders with psychotic features (eg, bipolar disorder with psychotic features) [2]. Psychotic-spectrum disorders are associated with severe difficulties in psychiatric, physical, and functional well-being. Each year it is estimated that 1500 people develop a first episode of psychosis in Ireland. The implications of this issue for population health are considerable. Psychosis usually develops in late adolescence or early adulthood, a critical phase of our life cycle in terms of personal, academic, and economic development. In addition, the personal, familial, and societal costs of psychosis are considerable [3-7].

It has been widely documented that individuals living with psychotic-spectrum disorders have high mortality rates [8,9], and patients with severe mental health disorders, such as psychosis, have a life expectancy that is 10 to 25 years lower than age-matched peers in the general population [8,10-16]. This is partly due to higher rates of suicide, which has been found to be up to 12 times greater in this group than the general population [17,18]. However, suicide accounts for only a fraction of this reduced life expectancy, and the majority is due to the higher rates of cardiovascular, pulmonary, and infectious diseases found in this population [17,19]. There is now clear evidence that weight gain, cardiovascular risk, and metabolic disturbance commonly appear early in the course of emerging psychosis and are potentially modifiable [20]. Psychosis is associated with unhealthy lifestyle choices such as high rates of alcohol, drug and tobacco use, poor nutrition, and low activity levels [21-28]. Heavy smoking is 2 to 6 times more common among people with schizophrenia. Obesity exists in 45% to 55% of people with schizophrenia, diabetes in 10% to 15%, and hypertension in 19% to 58% [29-31]. Individuals with severe mental illness receive poorer medical care for their physical health problems than do members of the general population [11,32]. These factors result in poorer health outcomes and mortality in people with psychosis [33,34].

In the Early Intervention in Psychosis (EIP) model of care, First Episode Psychosis (FEP) is defined as “psychotic symptoms that have lasted at least a week (ie, hallucinations and/or delusions with/without evidence of thought disorder for at least seven consecutive days) leading to distress or disruption to functioning” [35] and that continues throughout the entire

critical period [36]. The critical period is defined as the first 5 years for a subset of people [35]. For all others, there is international consensus that treatment should continue for at least 2 years [37].

The first few years of psychotic-spectrum disorders are likely to be a *critical period* in which the provision of targeted, phase-specific intervention could dramatically improve the usual course of psychotic-spectrum disorders [38]. Research has demonstrated that a majority of the decline in health status occurs in the first few years following the onset of psychosis [39]. Furthermore, individuals earlier in the course of a psychotic disorder may be more responsive to both pharmacological and psychosocial treatments than those with a more long-standing illness.

In recent years, an international consensus has identified that most people who develop psychosis are unwell for a considerable period of time before seeking help [4,32,40,41]. This time period is called the *duration of untreated psychosis* and it is crucial because the longer individuals with psychosis remain undiagnosed and untreated, the greater the opportunity for adverse physical, psychological, and social outcomes. Reducing the duration of untreated psychosis and ensuring people receive treatment that is specific to the early phase of the illness are associated with improved physical and social outcomes. Therefore, early detection and optimal early treatment in people experiencing their first episode of psychosis have been emphasized as a best practice in FEP literature in recent years [42]. Pioneering work in Melbourne that established *Early Intervention* teams to work with individuals during a first episode of psychosis demonstrated considerable benefits in terms of health gain and satisfaction to the family and economically to the state [43-45] and this model of care has been replicated worldwide [46-48]. These services are characterized by holistic, multimodal, and phase-specific treatment of patients with FEP, typically centred around assertive case management with access to a comprehensive range of pharmacological and psychosocial interventions [49].

Primary care has a key role in the care of patients who experience FEP, and effective links between secondary and primary care have been a key feature of Ireland's FEP Early Intervention Services (EISs) [50,51]. EISs seek to enhance the outcome trajectories of psychotic-spectrum disorders [38,52,53] by focusing on early detection of new cases [54,55], shortening delays to effective treatment [54,56-58] and providing comprehensive and timely treatment to patients with FEP throughout the entire critical period [58,59]. Early intervention programs generally engage in some form of assertive community treatment [60-62], which attempts to treat patients in the community instead of making use of inpatient services [63]. Therefore, the presence of a primary care point of contact between service users and mental health services is an important factor for many EISs. Key workers have been identified as a key strategy to support patient engagement with mental health

services and this is especially the case for patients with psychosis [64,65]. Furthermore, Ireland's Health Services Executive, specifically the Clinical Programme (Early Intervention for First Episode Psychosis [EIP]) has identified EIP key workers as a key mechanism to enhance links between primary and secondary care and to improve physical health (Early Intervention Services for Psychosis, Submission to the National Clinical Programme HSE by Early Intervention Working Group of the College of Psychiatrists of Ireland, 2015).

Key workers can be from a range of mental health clinical backgrounds but need to be of a certain level of seniority. They must also be adequately trained and maintain competencies in early intervention, skills including assessment of psychosis, relapse prevention, and family psychoeducation and assessment of suicide or violence risk [66]. Key workers can serve as the consistent point of contact between the service user (and family or carers), the EISs, and other agencies involved, provide basic psychosocial interventions, and ensure the organization of individual care plans and service transfers for their patients. EIP key workers have an important role in enhancing initial diagnosis and subsequent treatment for FEP. Increased liaison between primary and secondary care improves the clinical effectiveness and cost-effectiveness of detection of people with or at high risk of developing FEP [67]. Although EISs provide formal structured professional support for service users, the role of EIP key workers from *assessment and engagement* through to the *long-term successful delivery of effective treatments* is also crucial [68]. There is increasing consensus that EIP key workers for those suffering from psychosis are seen as important health care *resources* [69]. With a general consensus that integrated approaches to health care are likely to enhance outcomes, and in the case of patients experiencing FEP, a recognition of the potential of EIP key workers to promote this goal, this is an ideal context in which to examine how EIP key workers can enhance the capacity of primary and secondary care to collaborate to enhance physical health outcomes for people who experience an FEP. This question has not been addressed internationally and such knowledge is needed to inform service development, and especially integrated care, thus reducing the global burden of chronic disease among people with severe enduring mental illness.

Objective

This study aims to inform health policy in Ireland and internationally by conducting a mixed-methods study examining

how key workers might enhance integration between primary and secondary care to improve outcomes for patients with FEP. Outcomes of interest include general and mental health outcomes, substance use disorders, and chronic illness and multimorbidity prevalence. We will examine the feasibility, acceptability, and likely efficacy of a key worker-led intervention in a *real-world* clinical setting, thereby informing future definitive interventions in the area.

Methods

This project design was informed by the *MRC Framework for the Design and Evaluation of Complex Interventions to Improve Health* [70], which suggests the phased development of health interventions. The study design involved a mixed methodology in primary and secondary care in Ireland, with 2 sequential phases.

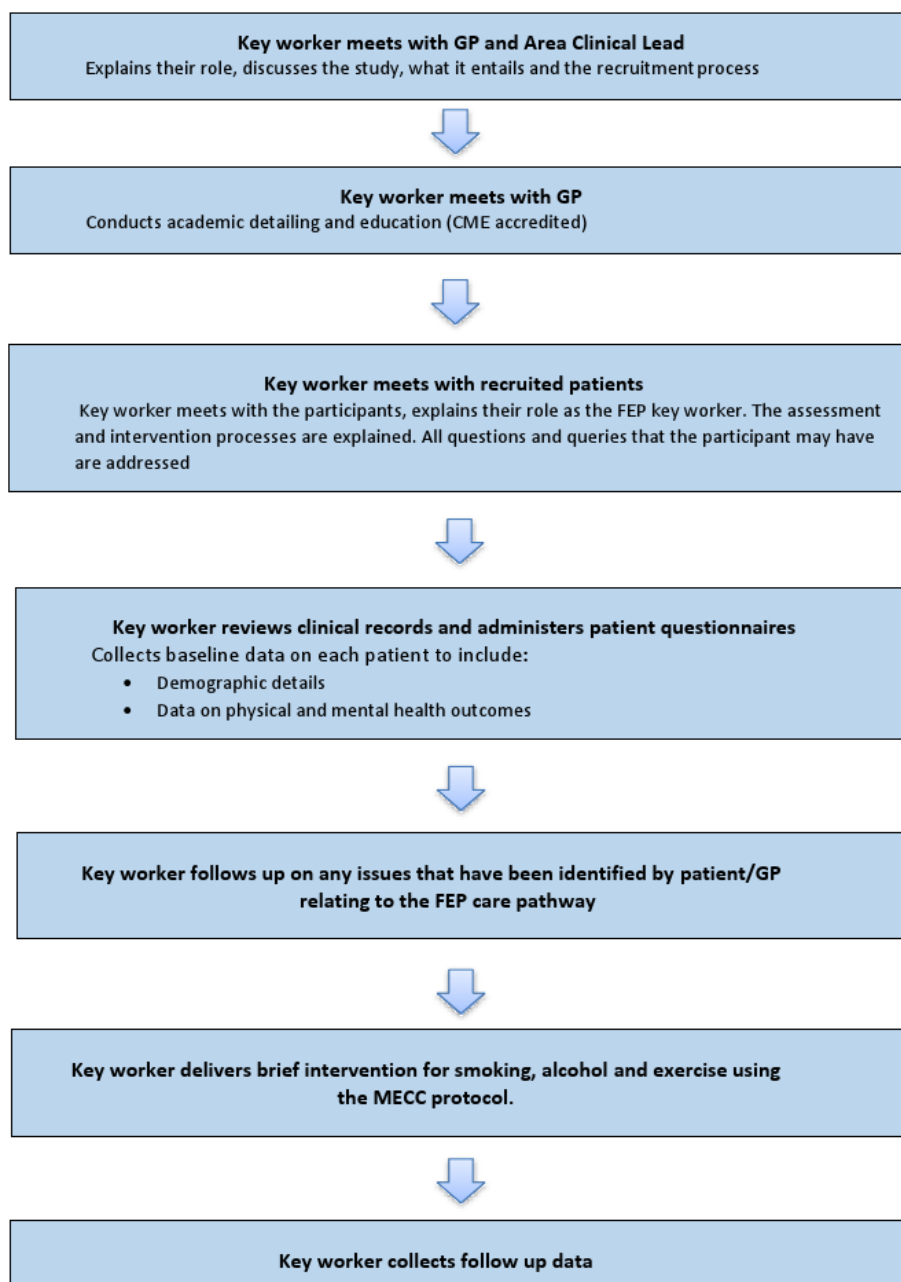
Study Design and Setting

A longitudinal pre-post intervention in 8 general practices in 2 regions in Ireland (one urban and one rural), in which patients with FEP, will be identified from clinical records in general practice (using a previously developed software tool [71]) and in mental health services. Baseline and follow-up data (at 6 months) will be collected on a number of measures of patients' physical and mental health.

Intervention Development and Design

Semistructured interviews will be conducted with GPs and health care professionals, such as psychiatrists and nurses, working in mental health services (n=16) to inform the *complex intervention* which will consist of the following:

- Academic detailing.
- Education and training of GPs.
- Key worker:
 - To optimize (bidirectional) communication between primary and secondary care with regard to physical health issues requiring follow-up.
 - To deliver brief interventions for problem alcohol use/tobacco smoking.
 - To identify community-based health agencies (eg, primary care team members, nongovernmental organizations, and third sector) who can assist with preventative health interventions (see [Figure 1](#)).

Figure 1. Key worker intervention.

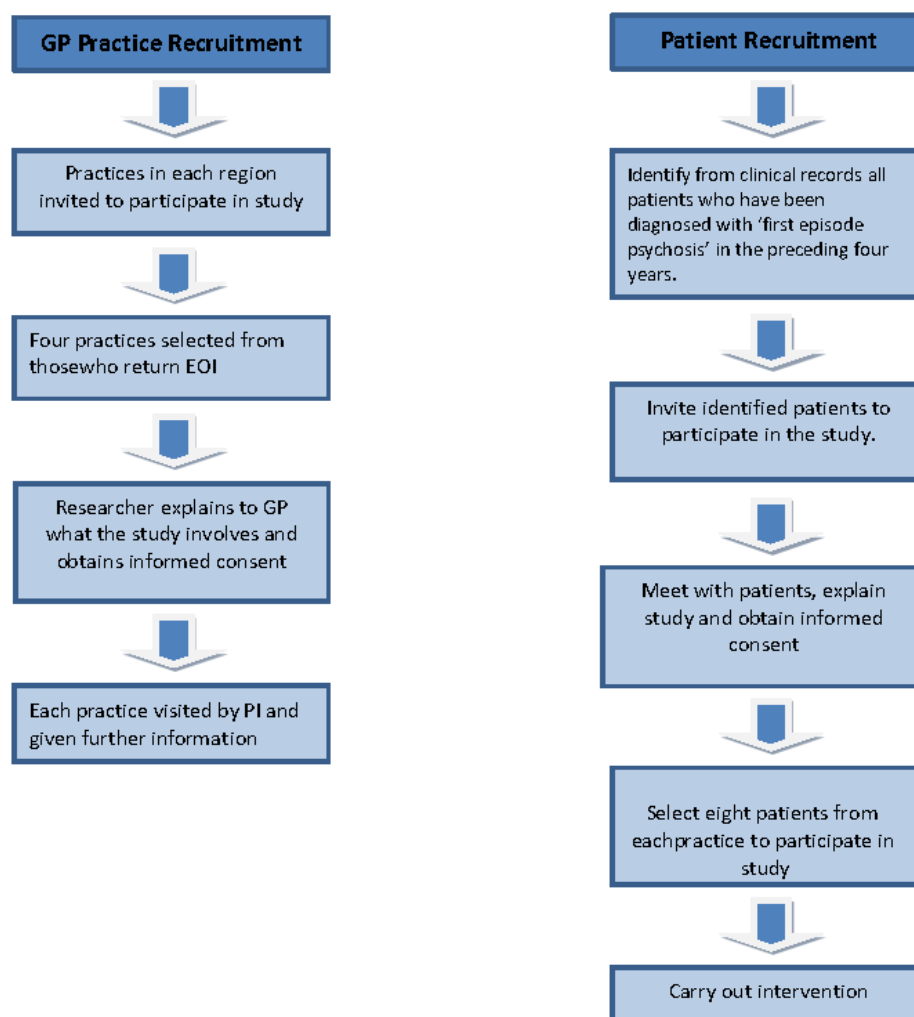
Approach to Sampling and Recruitment

The clinical lead in each of Ireland's mental health service catchment areas will be invited to participate, and expressions of interest will be sought to participate in this feasibility study. From these expressions of interest, one urban and one rural service will be identified.

At both sites, all general practices will be eligible to participate in the study. From those who express an interest in participating, 4 practices will be selected using stratified sampling, to be representative in terms of practice size and location. Sampled GPs will be contacted about their participation, given further information on the study (eg, what their involvement will entail), and consulted about patient recruitment. The research team will telephone those not replying. Each practice will be visited by

the principal investigator/lead researcher and provided with information about the research program.

At each participating practice, all patients who have been diagnosed with *FEP* in the preceding 4 years will be identified from clinical records (at the general practice or at the mental health service) and invited to participate in the study. Potential participants will be given written information on the study. Those interested in participating will be invited to meet a researcher who will be at the practice during the recruitment period. At this meeting, interested patients will be given further information on the study and will have an opportunity to ask the researcher questions. If they consent to participate, patients will be asked to sign a consent form. In total, 8 participants will be selected to participate from each practice (see [Figure 2](#)).

Figure 2. CONSORT diagram—practice and patient recruitment.

Sample Size

Semistructured interviews will be conducted with 16 health care professionals working in mental health services ($n=16$) to inform the *complex intervention*. Although it is difficult to predict the number of participants required to reach data saturation, our previous qualitative work [72,73] has indicated that 12 to 16 verbatim are required.

The goal of this feasibility study is to estimate rates of recruitment, consent, retention and response, methodological procedures, and issues. In addition, estimation of the parameters of likely primary outcome measures would allow the sample size of a definitive trial to be determined. With an average of 2 patients presenting to a GP with an FEP each year [74], that is, 8 per 4 years, and 8 practices in total across the 2 sites, we consider the sample size will be sufficient to estimate the actual recruitment and retention rates for a sample of patients recruited in primary care and provide data on acceptability of study processes and outcome measures which will inform a future definitive trial.

Data Collection

At baseline, demographic details and data on physical and mental health outcomes will be collected by reviewing clinical records and by participants completing study instruments at

recruitment (baseline) and 3 months post intervention. Baseline and follow-up data will be collected on the following:

- Mental disorders, using Primary Care Evaluation of Mental Disorders/Patient Health Questionnaire [75].
- Substance use disorders (Alcohol, Smoking, Substance Involvement Screening Test) [76].
- General health status (SF-12) [77].
- Chronic illness and general medical morbidity (ie, clinical records review using a structured instrument previously developed by our group for morbidity surveys among problem drug users attending general practice [78].)
- Cardiometabolic risk, using body composition, blood pressure, and blood samples.

Qualitative Evaluation

To explore study participants' experience of the intervention, 6 to 8 health care professionals in participating practices and 6 to 8 patients will be interviewed in depth on the question *your experience of and satisfaction with the complex intervention, how can primary/secondary care work collaboratively to enhance physical health for patients with FEP*. Interviews will be conducted with a semistructured questionnaire (with open questions), in person or by telephone, as preferred by the participant. The conversation will be recorded digitally, and answers to the structured questions will be recorded. Each

interview will be transcribed verbatim, following which the transcript will be reviewed by the researchers for accuracy.

Data Analysis

At baseline and follow-up, descriptive statistics will be estimated with regard to key feasibility variables, that is, as follows:

- Practice recruitment rate—percentage of invited practices who express an interest in participating.
- Patient recruitment rate—percentage of invited patients who participate.
- Prevalence of cardiovascular disease, diabetes, and tobacco and substance use.
- Practice/patient retention rates.

The IBM SPSS version 20 statistical package will be used for statistical analysis.

Qualitative Data Analysis

Thematic analysis will be used to analyze qualitative data. This approach has many benefits for studies such as this which are interpretive in nature, as it is a “method for identifying, analyzing and reporting patterns (themes) within data” [79]. The process of thematic analysis is concerned with the basic to advanced encoding of data. The codes are subsequently developed to themes. This flexible approach can also be seen in how themes identified at one level can help the researcher describe their observations and at a more advanced level allow the researcher to interpret aspects of the phenomenon under study [79]. The qualitative research software NVivo version 8 will be used to facilitate the coding of these data. The analysis will follow a *5-Step Analysis* approach whereby data are reviewed, examined, coded, and themes generated and defined [79]. To achieve validity in the coding/analysis of data, 2 reviewers will code data independently and inter-rater reliability measures will be computed based on this coding. Coding consistency will be maintained throughout the coding process and will be reviewed by regular meetings between researchers and the principal investigator. The findings will be compared with other study findings (validity and credibility). The researchers will present the findings to participants to determine if the study findings reflect their experience of the topic under study (member checking). Illustrative quotes will be used to emphasize points made by the participants.

Ethical Considerations

Ethical considerations and safeguards include the following:

- Informed consent and consenting capacity: all potential participants (GPs and patients) will be given written information on the study and the model of care being proposed and will be asked to provide written consent that they are happy to participate and that nonparticipation will not compromise their usual care. Participation in the study will be on a voluntary basis. No inducements to participate will be offered.
- Confidentiality: Any data/personal details that could potentially reveal the identity of individuals will be removed. Only anonymized, deidentified information will leave the practice of origin. To allow follow-up, an alphanumeric code will be assigned to each participant's

data; a database will be maintained on a password-protected database. The list will be kept separately from patient data but will indicate the medical record number of each participant and the alphanumeric code. All research data will be stored on a password-protected desktop computer at the host organization. Study participants will be invited to give permission to have their name, address, and contact details held by the research team to facilitate their receiving a synopsis of the study findings on publication and to be contacted for follow-up data collection. All data will be stored securely at the host institution.

- Clinical governance does no harm: it is possible that participating in the study may raise health-related issues for participants and may identify a health issue that requires clinical intervention. Therefore, all participants will be advised to speak with their doctor if participating in the study has raised any such issues. Furthermore, only patients who health care professionals deem able to participate will be asked to take part.
- General Data Protection Regulation (GDPR): GDPR compliance will be adhered to in terms of the following:
 - Data privacy rights—participants will have the right to request information about their data throughout the research process.
 - Transfer of data—participants will be informed about the circumstances under which their data may be transferred and safety measures which will be taken to protect the data (eg, data are encoded).
 - Retention of data—patients will be informed how long their data will be stored.

Application will be made to the Health Service Executive, Irish College of General Practitioners (GPs) and University College Dublin Research Ethics Committees.

Results

The study findings have the potential to provide important information on how key workers might enhance collaboration between primary and secondary care to improve outcomes for patients with FEP.

Discussion

Strengths and Limitations

This study is the first study to examine how key workers might enhance collaboration between primary and secondary care to improve outcomes for patients with FEP. It will provide important information to enhance scientific understanding of the role of key workers in improving health outcomes for patients with FEP. It will provide key information to inform health policy and service development in Ireland and internationally. However, it may be difficult to extrapolate these results among a high-risk population because of the specificity of the symptomatology in the early phases. This study has the potential to make an important impact on patient care and will provide high-quality evidence to help inform health care professionals on the importance of key workers for FEP patients. The intervention is scalable and, therefore, if found to be feasible

and acceptable, it can be readily implemented elsewhere and used to guide policy and service development internationally.

Possible limitations of the study include potential issues of bias and lack of generalizability that may arise from the recruitment process, owing to the likelihood that health care professionals who are more interested in research and innovation will choose to participate. As qualitative data analysis is open to interpretation, there are also potential issues of bias that may arise from data analysis. The use of multiple researchers during the qualitative analysis phase will attempt to reduce this possibility. Despite these potential limitations, this study will provide important information regarding the role of key workers

in improving collaboration between primary and secondary care to improve health outcomes for patients with FEP.

Conclusions

At the end of this study, the feasibility of a clinical intervention, informed by international best practices and local barriers, will be evaluated among a high-risk population. This feasibility study will inform clinical practice by providing initial indications as to how key workers might enhance collaboration between primary and secondary care to improve outcomes for patients with FEP. It will also inform future research on the topic by providing key parameters for the design of a future randomized controlled trial.

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Conflicts of Interest

None declared.

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Abbreviations

- EIP:** Early Intervention in Psychosis
- EISs:** early intervention services
- FEP:** First Episode Psychosis
- GDPR:** General Data Protection Regulation
- GP:** General Practitioner

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Protocol

Clinical Outcomes of Pneumonia and Other Comorbidities in Children Aged 2-59 Months in Lilongwe, Malawi: Protocol for the Prospective Observational Study “Innovative Treatments in Pneumonia”

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Abstract

Background: Pneumonia is the leading infectious cause of death worldwide among children below 5 years of age. Clinical trials are conducted to determine optimal treatment; however, these trials often exclude children with comorbidities and severe illness.

Conclusions: Given the paucity of data from Africa, African-based research is necessary to establish optimal management of childhood pneumonia in malaria-endemic settings in the region. An expanded evidence base that includes children with pneumonia and other comorbidities, who are at high risk for mortality or have other complications and are therefore typically excluded from childhood pneumonia clinical trials, can contribute to future iterations of the World Health Organization Integrated Management of Childhood Illness guidelines.

Methods: The study enrolled 1000 children with pneumonia presenting to the outpatient departments of Kamuzu Central or Bwaila District Hospitals in Lilongwe, Malawi, who were excluded from concurrent randomized controlled clinical trials investigating fast breathing and chest indrawing pneumonia and who met the inclusion criteria for this prospective observational study. Each child received standard care for their illnesses per Malawian guidelines and hospital protocol and was prospectively followed up with scheduled study visits on days 1, 2 (if hospitalized), 6, 14 (in person), and 30 (by phone). Our primary objectives are to describe the clinical outcomes of children who meet the inclusion criteria for this study and to investigate whether the percentages of children cured at day 14 among those with either fast breathing or chest indrawing pneumonia and comorbidities such as severe malaria, anemia, severe acute malnutrition, or HIV are lower than those in children without these comorbidities in the standard care groups in concurrent clinical trials. This study was approved by the Western Institutional Review Board, Malawi College of Medicine Research and Ethics Committee, and the Malawi Pharmacy, Medicines and Poisons Board.

Objective: This prospective observational study aimed to assess the clinical outcomes of children aged 2-59 months with both pneumonia and other comorbidities in a malaria-endemic region of Malawi.

Results: The Innovative Treatments in Pneumonia project was funded by the Bill and Melinda Gates Foundation (OPP1105080) in April 2014. Enrollment in this study began in 2016, and the primary results are expected in 2019.

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KEYWORDS

childhood pneumonia; comorbidities; outcomes; Africa

Introduction

Pneumonia is the leading infectious cause of childhood mortality worldwide. As part of the Innovative Treatments in Pneumonia (ITIP) project conducted in Lilongwe, Malawi, two randomized controlled clinical trials are evaluating the optimal duration of treatment with amoxicillin for fast breathing (ITIP1) and chest indrawing (ITIP2) childhood pneumonia [1]. Clinical trials evaluating the treatment for pneumonia often exclude children with comorbidities who are at high risk for mortality or have other complications. Pneumonia with comorbidities is common, and many factors determine whether contact with an etiologic agent will result in a severe episode of pneumonia and whether the episode will be fatal [2-6]. These factors can be related to the child (eg, age, sex, and underlying diseases), disease (eg, type of infection), environment, family and its socioeconomic status, or health system and type of care [7]. A systematic review and meta-analysis of risk factors for mortality from acute lower respiratory infections in children under the age of 5 years in low- and middle-income countries found that chronic underlying diseases (odds ratio [OR] 4.76, 95% CI 3.27-6.93), HIV/AIDS (OR 4.68, 95% CI 3.72-5.90), and severe malnutrition (OR 4.27, 95% CI 3.47-5.25) were associated with mortality due to acute lower respiratory infections [7]. In an effort to generate data on pneumonia treatment outcomes among high-risk African children after introduction of the *Haemophilus influenzae* type b and *Streptococcus pneumoniae* conjugate vaccines and to better interpret the results of the concurrent clinical trials, a prospective observational study (ITIP3) to assess the clinical outcomes of children aged 2-59 months with both pneumonia and other comorbidities was conducted. Given the paucity of data from Africa, African-based research is necessary to establish optimal treatment regimens for childhood pneumonia in the region.

Methods

Ethical Approval

The study was approved by the Western Institutional Review Board in the state of Washington, USA; the Malawi College of Medicine Research and Ethics Committee, Blantyre, Malawi; and the Malawi Pharmacy, Medicines and Poisons Board.

Written informed consent was obtained by trained study staff from all eligible children's caregivers prior to enrollment.

Study Design and Settings

The primary objective of this prospective, observational study is to determine the clinical outcomes of children aged 2-59 months with pneumonia and other comorbidities in Lilongwe, Malawi, who were excluded from ITIP1 and ITIP2 pneumonia treatment clinical trials and meet the inclusion criteria for ITIP3. We will also investigate whether the percentages of children cured on day 14 from diagnosis among those with either fast breathing or chest indrawing pneumonia and comorbidities such as severe malaria, anemia, severe acute malnutrition, or HIV are lower than those without these comorbidities in the standard care groups in the concurrent clinical trials. The primary aim of the ITIP1 and ITIP2 clinical trials is to provide evidence for the optimal duration of treatment of children with fast breathing or chest indrawing childhood pneumonia (but without other major comorbidities) with amoxicillin dispersible tablets. These two randomized controlled clinical trials are conducted with immunocompetent children aged 2-59 months residing in a malaria-endemic region of Malawi. Children enrolled in the clinical trials are followed for 14 days, with ITIP1 follow-up assessments conducted on days 2, 3, 4, and 14 and ITIP2 follow-up assessments conducted on days 2, 4, 6, and 14. The prospective observational study ITIP3 enrolls children with pneumonia who are excluded from the two clinical trials because of other comorbidities in an effort to provide additional valuable evidence on standard care and outcomes for children with pneumonia in Malawi who are most at risk for mortality or have other complications. An observational design was chosen to follow the clinical outcomes of high-risk children with pneumonia who are typically excluded from clinical trials. This study is conducted at the outpatient and inpatient departments of Kamuzu Central Hospital (KCH) and the outpatient department of Bwaila District Hospital (BDH) in Lilongwe, Malawi (Figure 1). The 750-bed government facility KCH is the primary referral hospital for the central region of Malawi, serving a population of approximately 5 million people. BDH is the district hospital for Lilongwe with no inpatient facilities for children. Children requiring inpatient care are referred to KCH.

Figure 1. Map of the study area in Lilongwe, Malawi. KCH: Kamuzu; BDH: Bwaila District Hospital.



Study Participants

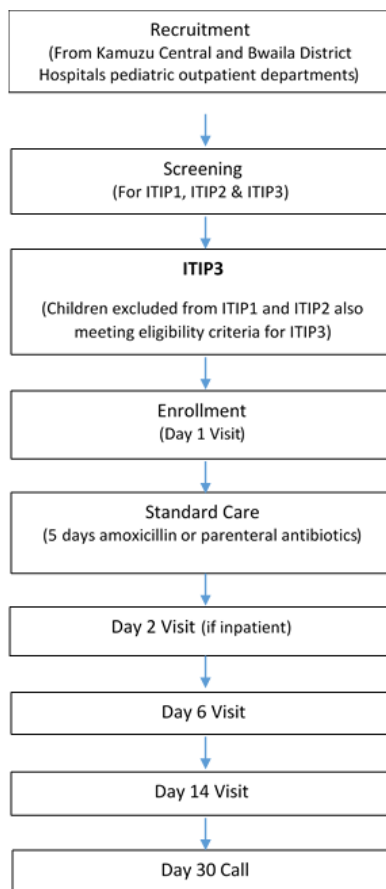
Children aged 2-59 months with cough or difficulty breathing were recruited by trained hospital staff during routine intake and screening procedures in the hospitals' outpatient departments and referred to the study staff for information on the study, written informed consent, and additional screening to determine enrollment eligibility (Figure 2). Screening procedures included assigning a participant an identification number; collecting demographic and contact information and medical history; and assessing eligibility criteria with a targeted physical examination, malaria rapid diagnostic testing, HIV rapid antibody testing, hemoglobin testing, and bronchodilator response testing (if wheezing).

Caregivers of eligible children meeting the case definition (Textbox 1) of fast breathing or chest indrawing pneumonia, who do not meet the eligibility criteria for ITIP1 and ITP2

clinical trials and meet the eligibility criteria for ITIP3 (Textbox 2) were invited to participate by providing written informed consent for enrollment. Final eligibility determination for enrollment depended on the results of the medical history, clinical examination, laboratory testing, appropriate understanding of the study (comprehension assessment checklist), and completion of the enrollment consent process.

Clinical cure was defined as (1) the absence of fast breathing, chest indrawing, severe respiratory distress, hypoxemia, World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) general danger signs, and fever; (2) cure from pneumonia but failure to complete the initial antibiotic treatment regimen; and (3) cure from pneumonia and completion of the initial antibiotic treatment regimen. In contrast, those who showed a deterioration in their condition or were stable (not improving or deteriorating, prognosis unclear) were not considered to be clinically cured.

Figure 2. Schedule of enrollment and follow-up assessment. ITIP1: Innovative Treatments in Pneumonia 1, randomized controlled clinical trial evaluating the optimal duration of treatment with amoxicillin for fast breathing pneumonia; ITIP2: Innovative Treatments in Pneumonia 2, randomized controlled clinical trial evaluating the optimal duration of treatment with amoxicillin for chest indrawing pneumonia; ITIP3: Innovative Treatments in Pneumonia 3, prospective observational study.



Textbox 1. Study definitions.

Study definitions

- Fast breathing pneumonia: Cough less than 14 days or difficulty breathing AND fast breathing for age
- Chest indrawing pneumonia: Cough less than 14 days or difficulty breathing AND visible indrawing of the chest wall with or without fast breathing for age
- Fast breathing for age: Respiratory rate >50 breaths per minute (for children aged 2 to <12 months of age) or >40 breaths per minute (for children aged >12 months of age)
- Very fast breathing for age: >70 breaths per minute (for children aged 2 to <12 months of age) or >60 breaths per minute (for children aged >12 months of age)
- Severe respiratory distress: Grunting, nasal flaring, and/or head nodding
- Hypoxemia: Arterial oxyhemoglobin saturation < 90% in room air, as assessed noninvasively by a pulse oximeter
- World Health Organization Integrated Management of Childhood Illness general danger signs: Lethargy or unconsciousness, convulsions, vomiting everything, and inability to drink or breastfeed
- Severe acute malnutrition: Weight for height/length < -3 SD, mid-upper arm circumference < 11.5 cm, or peripheral edema
- Severe malaria: Positive malaria rapid diagnostic test with any World Health Organization Integrated Management of Childhood Illness general danger sign, stiff neck, abnormal bleeding, clinical jaundice, or hemoglobinuria
- HIV exposure: Children <24 months of age with an HIV-infected mother
- Serious adverse event: Adverse event that
 - Results in death
 - Is life threatening
 - Requires inpatient hospitalization or prolongation of existing hospitalization
 - Results in persistent or significant disability/incapacity
 - Is a medical event, based on appropriate medical judgment, that may jeopardize the health of the participating child or require medical or surgical intervention to prevent one of the outcomes listed

Textbox 2. Eligibility criteria.

Inclusion criteria:

- 2-59 months of age
- Cough < 14 days or difficulty breathing
- Excluded from enrollment in ITIP1 and ITIP2 clinical trials due to the presence of any of the following:
 - Severe respiratory distress
 - Hypoxemia
 - Hemoglobin level < 8.0 g/dL, if positive malaria rapid diagnostic test
 - Severe acute malnutrition
 - Severe malaria
 - HIV seropositivity or HIV exposure
- Ability and willingness of child's caregiver to provide informed consent and to be available for follow-up for the planned duration of the study, including accepting a home visit if he/she fails to return for a scheduled study follow-up visit

Exclusion criteria:

- Stridor when calm
- Possible tuberculosis (coughing for more than 14 days)
- Hemoglobin level < 8.0 g/dL, if negative malaria rapid diagnostic test
- Known allergy to penicillin or amoxicillin
- Receipt of an antibiotic treatment in the 48 hours prior to the study
- Living outside the study area
- Any medical or psychosocial condition or circumstance that, in the opinion of the investigators, would interfere with the conduct of the study or for which study participation might jeopardize the child's health
- Participation in a clinical study of an investigational product within 12 weeks prior to enrollment or planning to begin participation during this study
- Prior participation in ITIP1, ITIP2, or ITIP3 during a previous pneumonia diagnosis

Study Procedures

All study procedures are conducted according to the protocol provided in [Multimedia Appendix 1](#) (version 4.0; May 26, 2017). On day 1, after study screening was complete and enrollment informed consent was obtained, the study staff performed the following procedures for enrollment: conducting physical examination, obtaining vaccination history, and collecting additional sociodemographic information. Recruitment, screening, and enrollment occur at the outpatient departments of KCH or BDH, with BDH enrollees transferred to KCH for continued evaluation, observation, and admission, if needed. Hospital observation or admission and follow-up occur solely at KCH.

Each enrolled child receives standard care for their illnesses per Malawian guidelines and KCH protocol and is prospectively followed up by the study staff with scheduled study visits on days 1, 2 (if hospitalized), 6, 14 (in person), and 30 (by phone). All visits occur on the calendar day on which they are initially scheduled or within 24 hours, with the exception of the day 14 visit and the day 30 phone call. The day 14 visit can occur either 2 days before or after day 14, and the day 30 phone call can occur either 2 days before or 14 days after day 30 and still be considered completed within the visit windows. During

follow-up visits, the study staff review participants' medical history since the last study visit and perform a physical examination. In case of a no-show at the scheduled follow-up visits, children are followed up with home visits by the study staff. If a phone call on day 30 is not possible due to no phone in the home, the study staff conducts a home visit to obtain the day 30 outcome information.

Sample Size

The primary objectives of ITIP3 are to describe the clinical outcomes of children who meet the inclusion criteria for ITIP3 and to investigate whether the percentages of children cured on day 14 among those with either fast breathing or chest indrawing pneumonia and comorbidities such as severe malaria, anemia, severe acute malnutrition, or HIV are lower than those without these comorbidities in the standard of care groups in the concurrent clinical trials. For hypothesis testing, we focused on four high-frequency and high-mortality comorbidities (ie, severe malaria, anemia, severe acute malnutrition, and HIV infection or exposure) within ITIP3. We estimate that the study can enroll 1000 children during the time it is concurrently conducted with the ITIP1 and ITIP2 clinical trials, and we estimate the effect sizes for the primary outcome comparisons for which we have 80% power. We also assume that 1000 children can be enrolled in each of the standard care groups in ITIP1 and ITIP2. With

available data from KCH and Malawi, we estimate the prevalence of severe pneumonia to be 10%-24%, severe malaria to be 15%-20%, severe acute malnutrition to be 4%-7%, and HIV seropositivity to be 5%-10%. Based on the estimated treatment failure rates for ITIP1 and ITIP2, we conservatively estimate that clinical cure will be observed in 90%-95% of children in ITIP1 and 85%-90% in ITIP2. We estimate the effect sizes we would be able to see for various comparisons between ITIP3 and ITIP1 or ITIP2, along with different estimated prevalence rates (Table 1). For example, comparing the clinical cure among children with HIV infection or exposure in ITIP3

and those in the standard of care group in ITIP2, if the prevalence of HIV infection or exposure is 10% in ITIP3, we will have 80% power to detect an absolute difference in proportions of 9.9% if at least 90% of the children in ITIP2 are cured and 80.1% of the children with HIV infection or exposure in ITIP3 are cured. Note that the absolute observable difference is largest for severe acute malnutrition, as that outcome is expected to have the lowest prevalence among the outcomes of interest. Nonetheless, we considered all the estimated effect sizes to be clinically relevant.

Table 1. Observable effect sizes for comparisons of Innovative Treatments in Pneumonia (ITIP) 3^a with ITIP1^b or ITIP2^{c,d}. N (ITIP1 or ITIP2) = 1000.

Exposure of interest, prevalence of exposure (ITIP3), and N (ITIP3) ^e	Absolute observable difference, %	Prevalence of clinical cure (ITIP1 or ITIP2), %	Prevalence of clinical cure (ITIP3), %
Severe malaria			
20%			
200	5.5	95	89.5
200	7.2	90	82.8
200	8.3	85	76.7
15%			
150	6.3	95	88.7
150	8.1	90	81.9
150	9.4	85	75.6
Anemia			
10%			
100	7.6	95	87.4
100	9.9	90	80.1
100	11.1%	85	73.6
7.5%			
75	8.8	95	86.2
75	11.3	90	78.7
75	13.1	85	72.0
HIV infection or exposure			
10%			
100	7.6	95	87.4
100	9.9	90	80.1
100	11.4	85	73.6
5%			
50	10.9	95	84.1
50	13.9	90	81.3
50	15.9	85	69.1
Severe acute malnutrition			
7%			
70	9.1	95	85.9
70	11.7	90	78.3
70	13.5	85	71.5
4%			
40	12.2	95	82.8
40	15.6	90	74.4
40	17.8	85	67.2

^aProspective observational study.

^bRandomized controlled clinical trial evaluating the optimal duration of treatment with amoxicillin for fast breathing pneumonia.

^cAlpha value set to 5% and power set to 80%.

^dRandomized controlled clinical trial evaluating the optimal duration of treatment with amoxicillin for chest indrawing pneumonia.

^eAssuming similar values for fast breathing pneumonia and chest indrawing pneumonia to be able to compare the ITIP1 and ITIP2 cohorts.

Data Collection and Quality Assurance

All study data are collected by clinical study staff using designated source documents or paper-based case report forms (Multimedia Appendix 2), which are then entered into electronic databases. Clinical research data are maintained through a combination of a secure electronic data management system and physical files with restricted access to ensure confidentiality. Data related to the study endpoints will be extracted from the electronic databases for statistical analyses. Two distinct study databases are maintained: the primary study database with study visit data and a database with participating children's personally identifiable information. The database with identifiable information is maintained separately by the study site, while the designated contract research organization (CRO) maintains the primary study database. To ensure accuracy and completeness, data are routinely reviewed by the site quality control and assurance team as well as the coinvestigators who monitor the site and perform quality assurance reviews, audits, and evaluation of the study safety and progress. Standard Good Clinical Practice (GCP) is followed to ensure accurate, reliable, and consistent data collection.

Data Management

Primary data management activities, which include data entry and validation, data coding and cleaning, database quality control, disaster recovery plans, preparation and submission of compliance reports, and preparation of final study database, are undertaken by the designated CRO. The on-site study data manager oversees data-related procedures at the study site and is supervised by the CRO data management staff. Data management activities are performed using Clindex Clinical Trial and Data Management software, developed by Fortress Medical Systems (Hopkins, MN). All data management activities are in compliance with the International Council on Harmonization (ICH) GCP E6 (R2), a regulatory sponsoring organization, and institutional requirements for the protection of children and confidentiality of personal and health information.

Outcomes

The primary endpoint is whether children treated for pneumonia are cured 14 days from diagnosis. Secondary endpoints are treatment regimens in ITIP3; treatment responses of children in ITIP3 in comparison to those in the standard care groups in ITIP1 and ITIP2 as measured by vital signs, oxygen saturation, laboratory test results, length of hospital stay; proportion of children who are rehospitalized or die; and proportion of children in ITIP3 who are clinically cured by day 14 (characteristics such as gender, age, weight, mid-upper arm circumference, HIV status, malaria, and vaccination status were considered).

Statistical Analysis

Generalized linear models with robust standard error will be used to compare the percentages (absolute risk differences) of children who are clinically cured by day 14 among ITIP3 children who have severe malaria (or are anemic or present with severe acute malnutrition, or are HIV positive or exposed) and children in the standard care groups in ITIP1 or ITIP2.

Two-sided tests will be performed, with an alpha value of 0.05. No adjustments will be made for multiple comparisons because of the observational and exploratory nature of this study. If loss to follow-up is higher than 5%, multiple imputations will be considered for sensitivity analyses. The imputations will be performed separately for each cohort using multiple (n=20) hot deck imputations and the child's age and gender and educational status of the caregiver. Multiple imputation estimates will be combined using the approach by Rubin [8]. Similar linear or generalized linear models will be used for secondary outcome analyses. Where appropriate, we will adjust for gender, age, weight, mid-upper arm circumference, HIV status, malaria, and vaccination status.

Ethics and Dissemination

Ethical Approval and Consent

The study is performed in accordance with the ICH GCP and the Declaration of Helsinki 2008. The study was approved by the Western Institutional Review Board, Washington, USA; the Malawi College of Medicine Research and Ethics Committee, Blantyre, Malawi; and the Malawi Pharmacy, Medicines and Poisons Board. Written informed consent was obtained by trained study staff from at least one of the caregivers of each eligible child prior to enrollment.

Possible Risks

There are few potential risks to study participation, given that it is observational in nature and there is no study intervention. Caregivers may feel compelled to enroll in the study in order to receive care for their child within a research setting, which may be perceived to be of a higher quality than the standard care. In order to minimize the risk of coercion, study staff do not recruit participants directly. Instead, hospital clinicians inform caregivers about the study and refer only those who are interested. During the informed consent process, study staff emphasize that the child will receive medical care whether or not he/she is enrolled in the study. Another possible risk involves blood specimen sampling at screening, which can cause pain and bruising at or around the blood draw site. To mitigate this risk, all study staff who collect specimens from children in the study are trained in the appropriate procedures and supervised accordingly. Participation in the study has the potential to compromise care for hospitalized children if study procedures are prioritized above urgent clinical care for acute infections. In order to minimize the possibility that participation in this trial interferes with medical management, KCH staff undertake the clinical management of hospitalized children in accordance with standard procedures. Furthermore, recognizing that some children may not come back for the follow-up visits, our trained study staff locate children who miss their follow-up appointments and conduct these visits in their home.

Dissemination

We plan to disseminate the study results in peer-reviewed journals and international conferences, targeting those involved in the clinical care of children in low-resource settings as well as those who develop and advise on policies and guidelines in those settings. This trial is registered with ClinicalTrials.gov (NCT02960919).

Results

The ITIP project was funded by the Bill and Melinda Gates Foundation (OPP1105080) in April 2014. ITIP3 enrollment started in 2016, and the primary results are expected in 2019.

Discussion

The following discussion outlines our efforts to safely and efficiently conduct a prospective observational study with the goal of providing informative and generalizable results that are applicable to real-world, nonstudy settings in African low- and middle-income countries.

Efforts Toward Generalizable Results and Addition to the Literature

The study was specifically developed and pragmatically designed with inclusion and exclusion criteria to allow generalizable results. Children enrolled in this study are diagnosed with pneumonia based on the WHO IMCI clinical guidance. Although microbiological and radiological diagnosis may add improved specificity to the clinical diagnosis of pneumonia, the majority of low-resource settings do not have access to this testing, and children are typically diagnosed based on clinical criteria alone. Children with pneumonia and severe illness or underlying comorbidities are intentionally included to provide additional evidence regarding standard care and outcomes for children with pneumonia and to generate data on the generalizability of the concurrent fast breathing and chest indrawing pneumonia clinical trials. Previous investigations on the management of childhood pneumonia with comorbidities in Malawi examined data prior to scale-up of the *Haemophilus influenzae* type b (Hib) vaccine and relied on clinical diagnosis of comorbidities (eg, malaria and anemia) instead of laboratory test results [9]. Similar studies in other African countries such as Tanzania have been limited by small sample sizes [10], while another larger study in Kenya only focused on mortality risk factors for children with nonsevere pneumonia [11]. Data from ITIP3 may help bridge the gap in data and provide insight regarding the course of childhood pneumonia in this region of Africa.

Efforts Toward Rigorous Protocol Implementation

Dedicated trained study staff follow-up children enrolled in the study to assure the protocol and standard operating procedures are followed, data are collected without error, and the highest level of safety is provided. Standardized training, supervision, oversight, and testing are undertaken to ensure quality, consistency, and harmonization in study procedures and implementation. Regular site monitoring visits by Save the Children are conducted to assess compliance with human subjects and other research regulations and guidelines, adherence to the study protocol and procedures, quality and accuracy of data collected, and quality of care and child safety.

Limitations and Bias

A limitation to this study and a potential source of bias is loss to follow-up. To minimize loss to follow-up, caregivers are provided clear follow-up instructions as well as called the afternoon before their visits to remind them to visit the following day. A travel stipend for all follow-up visits is provided. In addition, children are followed up with home visits upon a missed visit. An additional limitation related to follow-up is that children in this observational study are followed up less frequently and have different assessment time points than those who are enrolled in the two clinical trials for fast breathing pneumonia and chest indrawing pneumonia. The three study protocols also have differences in the eligibility criteria and treatment regimens. These differences, in addition to the different follow-up schedules, will present some challenges for analyses and interpretation of results. Where possible, we will attempt to adjust for baseline characteristics (not in the causal pathway) as well as perform sensitivity analyses. Nevertheless, the potential for unmeasured confounders cannot necessarily be overcome or assessed. Other limitations to this study are the clinical diagnosis of pneumonia, rather than a microbiological or radiological diagnosis, and the limited follow-up duration of 30 days. All study staff receive rigorous training in the WHO IMCI classification of pneumonia; however, no microbiological or radiological tests are routinely undertaken unless clinically indicated. Of note, this was a pragmatic design decision, as in standard clinical care in this setting, microbiological or radiological tests are not typically undertaken unless clinically indicated. In addition, it is possible that we are missing longer-term consequences after treatment, given the limited follow-up period of 30 days.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

ITIP3 protocol.

[[PDF File \(Adobe PDF File\), 569KB - resprot_v8i7e13377_app1.pdf](#)]

Multimedia Appendix 2

ITIP1 and ITIP2 follow-up visit schedule.

[[PDF File \(Adobe PDF File\), 39KB - resprot_v8i7e13377_app2.pdf](#)]

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Abbreviations

BDH: Bwaila District Hospital
CRO: contract research organization
GCP: good clinical practice
Hib: Haemophilus influenzae type b
ICH: International Council on Harmonisation
ITIP: Innovative Treatments in Pneumonia
IMCI: integrated management of childhood illness
KCH: Kamuzu Central Hospital
MUAC: mid-upper arm circumference
OR: odds ratio
WHO: World Health Organization

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Protocol

Cerebrospinal Fluid Markers of Synaptic Injury and Functional Connectivity in Alzheimer Disease: Protocol for a Cross-Sectional Study

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Abstract

Background: Synaptic loss is the best surrogate for cognitive decline in Alzheimer disease (AD) and is more closely associated with cognitive function than amyloid or tau pathologies. Neurogranin (Ng) and synaptosome-associated protein-25 (SNAP-25) have demonstrated utility as cerebrospinal fluid (CSF) markers of synaptic injury in presymptomatic and symptomatic AD. While these synaptic markers have been shown to correlate with cognitive impairment and whole brain or regional atrophy in previous studies of AD, to our knowledge, the relationship between fluid markers of synaptic injury and functional brain imaging has not been previously investigated.

Objective: The main objective of this study is to examine the relationship between CSF markers of synaptic injury (Ng and SNAP-25) and functional connectivity (FC) in the default mode and semantic memory networks in individuals with mild cognitive impairment (MCI) and mild dementia due to AD (Clinical Dementia Rating [CDR] 0.5-1) and cognitively normal controls (CDR 0), adjusting for age, gender, and the apolipoprotein E4 (APOE4) genotype. Secondary objectives include investigating the associations between CSF markers of amyloid and tau pathology (CSF tau, p-tau181, and A β 42) and FC in the default mode and semantic memory networks in AD (CDR 0.5-1) and controls (CDR 0), adjusting for age, gender, and the APOE4 genotype.

Methods: This is a cross-sectional study of individuals with MCI or mild dementia due to AD (CDR 0.5-1; n=20), and cognitively normal controls (CDR 0; n=20). Participants will undergo detailed clinical and neuropsychological assessments, CSF biomarker assessments (CSF Ng, SNAP-25, tau, p-tau181, and A β 42 levels) and functional magnetic resonance imaging assessments, using a Siemens 3.0 Tesla Prisma scanner, during resting state and during the performance of a semantic memory task. All study procedures will be completed within 4 months of enrollment. Partial correlation analyses will examine associations of CSF biomarker measures with FC in the default mode and semantic memory networks in AD and controls.

Results: This study was funded by the Chronic Brain Injury Discovery Themes of the Ohio State University College of Medicine. Study enrollment began in April 2018. Study procedures and data analysis are currently underway. Results are expected by December 2019.

Conclusions: Findings from this study will further support the utility of CSF Ng and SNAP-25 as markers of synaptic injury by examining their associations with functional alterations in cortical networks affected by early AD pathology.

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KEYWORDS

Alzheimer disease; aging; functional imaging; synaptic injury; cerebrospinal fluid

Introduction

Background

Amyloid plaques and neurofibrillary tangles are the two main pathological hallmarks of Alzheimer disease (AD) [1]. While amyloid and tau deposition begins a decade or more prior to the first signs of memory loss, it is only after significant neuronal and synaptic loss has occurred in vulnerable brain regions that the first signs of cognitive impairment appear [2]. Pathological studies of AD and proposed models of disease progression suggest that synaptic loss is the best surrogate for cognitive decline in AD [3,4] as it appears to be more closely associated with cognitive outcomes than the degree of amyloid plaques, neurofibrillary tangles, or gliosis in AD brains [5].

Neurogranin (Ng) and synaptosome-associated protein-25 (SNAP-25) have recently been identified as potential cerebrospinal fluid (CSF) biomarkers of synaptic injury in AD [6,7]. Ng and SNAP-25 are synaptic proteins which are abundantly and preferentially expressed in the presynaptic (SNAP-25) or postsynaptic (Ng) membranes and are widely distributed in the human brain [8,9]. Ng is a neuron-specific [8] calmodulin-binding postsynaptic protein [10] which is abundantly expressed in neuronal dendritic spines. Several studies have implicated Ng in activity-dependent synaptic plasticity, memory, and learning [10-14]. Ng enhances synaptic function [8] and facilitates long-term potentiation by regulating the availability of calmodulin at synaptic sites [15-17]. SNAP-25 is a widely distributed presynaptic protein which is involved in docking and fusion of synaptic vesicles, a process essential for exocytosis [18]. SNAP-25 has also been implicated in axonal outgrowth and neurite elongation [19].

Studies by our group and others have shown that CSF Ng [7,20] and SNAP-25 [9,21] levels are elevated in AD compared to controls. Elevated CSF levels of synaptic proteins in AD likely reflect the release of abundant synaptic constituents into the extracellular space in the setting of neurodegeneration [7]. We have previously shown that CSF Ng levels strongly correlate with CSF levels of tau and tau phosphorylated at threonine 181 (p-tau181), whole brain and regional atrophy, and rates of cognitive decline in a large, well-characterized cohort of cognitively normal individuals and individuals with presymptomatic and early symptomatic AD. These individuals were enrolled in studies of aging and dementia at the Knight Washington University Alzheimer's Disease Research Center and followed longitudinally for 2-3 years [7]. Furthermore, we have shown that CSF Ng levels correlate with cortical amyloid deposition in presymptomatic AD [7]. Importantly, in the previous cohort, CSF Ng offered a predictive value for future cognitive impairment in cognitively normal individuals over a 2-3 year follow-up period that was comparable to other biomarkers of AD pathology (CSF tau, p-tau181, and A β 42). CSF Ng also complemented the collective ability of these markers to predict AD pathology in cognitively normal elderly individuals (ie, presymptomatic AD). Data from our group [22] and others [9,21], suggest that CSF SNAP-25 offers value as a diagnostic and predictive marker in early AD, and correlates with other CSF biomarkers of AD pathology. Together, these

findings support the value of CSF Ng and SNAP-25 as CSF surrogates of synaptic injury in AD.

Functional magnetic resonance imaging (fMRI) studies have identified networks of cortical regions which demonstrate highly synchronized activity during the resting state or during the performance of specific cognitive tasks [23,24]. The default mode network (DMN), which includes the posterior cingulate, precuneus, medial temporal, medial prefrontal, and inferior parietal regions, is active during rest and shows reduced activity during cognitive tasks [25,26]. Reduced functional connectivity (FC) within the DMN has been shown in early AD, including mild cognitive impairment (MCI) due to AD [24,27,28].

Semantic memory refers to the recall of general facts and knowledge that are not contextually specific (eg, making a categorical or attributional judgment to a presented item) [29]. The neural correlates of semantic memory include a left lateralized network of cortical regions, including the posterior cingulate, precuneus, parahippocampal gyrus, posterior inferior parietal, middle temporal, fusiform, dorsomedial prefrontal, ventromedial prefrontal, and inferior frontal cortices [30,31]. Previous studies have shown the utility of the Famous Name Discrimination Task (FNDDT) in evaluating FC within the semantic memory network in older adults, including those with early AD [32].

To our knowledge, no studies have investigated the utility of CSF Ng or SNAP-25 as surrogates of synaptic injury in functional imaging studies of healthy aging and AD. In this study, we propose to investigate associations between CSF Ng or SNAP-25 levels and FC measures in the default mode and semantic memory networks in cognitively normal older adults and those with early symptomatic AD, including MCI (Clinical Dementia Rating [CDR] 0.5) and mild dementia (CDR 1) due to AD. Findings from this study will support the utility of CSF Ng and SNAP-25 as fluid surrogates of synaptic injury in AD by evaluating their associations with functional imaging as an in vivo marker of synaptic integrity. CSF biomarkers that reflect functional alterations in neural networks targeted by early AD pathology (ie, default mode and semantic memory networks) will offer valuable tools to monitor disease progression and response to disease modifying therapies in clinical trials of AD therapeutics, independently of changes to amyloid or tau pathology, and will supplement information provided by cognitive and imaging outcome measures.

Study Objectives

Primary Objectives

The first primary objective of the study is to investigate correlations between CSF biomarkers of synaptic injury (Ng and SNAP-25) and FC in the DMN using resting state fMRI (adjusting for age, gender, and the apolipoprotein E4 [APOE4] genotype) in AD (CDR 0.5-1) and controls (CDR 0). The second primary objective is to examine correlations between CSF biomarkers of synaptic injury and FC in the semantic memory network on task activated fMRI during the performance of the FNDDT (adjusting for age, gender, and the APOE4 genotype) in AD and controls.

Secondary Objectives

This study has three secondary objectives. The first is to investigate potential correlations between established AD biomarkers (CSF tau, p-tau181, and A β 42) and FC in the DMN using resting state fMRI (adjusting for age, gender, and the APOE4 genotype) in AD and controls. The second is to examine the possible correlations between established AD biomarkers and FC in the semantic memory network on task activated fMRI during the performance of the FNDT (adjusting for age, gender, and the APOE4 genotype) in AD and controls. Lastly, the third objective is to compare correlations of novel (CSF Ng and SNAP-25) and established AD biomarkers (either individually or in different combinations) with FC in the default mode and semantic memory networks in AD and controls.

Methods

Overview

This will be a cross-sectional study of individuals with MCI due to AD or mild AD dementia (CDR 0.5-1; n=20), and cognitively normal controls (CDR 0; n=20). All participants will undergo a detailed clinical and neuropsychological assessment during the first visit, one lumbar puncture (LP) during the second visit, and one structural and functional MRI assessment during the third visit (Table 1). Functional MRI data will be acquired during resting state and performance of a semantic memory task (ie, FNDT). Cognitive, CSF, and MRI assessments will be completed within 4 months of enrollment. Resting state and task activated fMRI scans will be conducted in the same setting to minimize effects of environmental factors on fMRI parameters.

Participants

Participants will be recruited from the community and the Cognitive Neurology Clinic of the Ohio State University Wexner Medical Center. This study will include n=20 cognitively normal

individuals (CDR 0), and n=20 individuals with a clinical diagnosis of single-domain or multi-domain amnesic MCI due to AD (CDR 0.5) or mild AD dementia (CDR 1). As some participants who enroll in the study may later elect to withdraw their participation (ie, drop out) or may be lost to follow-up, we anticipate the need to enroll a total of 50 participants (CDR 0, n=25; and CDR 0.5-1, n=25) to maintain adequate statistical power for the study.

Inclusion Criteria

Participants included in the study will be: 1) 60 years of age or older, with a clinical diagnosis of amnesic MCI due to AD or mild AD dementia, or with normal cognition (See Criteria for Diagnostic Classification); 2) will have no significant medical or surgical comorbidities; 3) will have no contraindications to LP or MRI (see [Multimedia Appendix 1](#)); and 4) will have adequate visual and auditory acuity for testing. In addition, participants must have a responsible study partner who either lives with them or is in regular contact with them for at least 10 hours per week.

Exclusion Criteria

Criteria which exclude participants from the study include: 1) MCI due to AD or mild AD dementia being treated with cholinesterase-inhibitors (CHEI) or memantine within 3 months of study enrollment, or with a dosage of these medications that has been adjusted in the 3 months prior to enrollment; 2) any past history of ischemic or hemorrhagic strokes; 3) traumatic brain injury (including concussions); 4) imaging evidence of significant cerebrovascular disease or structural brain lesions (eg, tumor, demyelinating disorders, or infection); 5) an active mood or psychiatric disorder; 6) active daily alcohol use; (7) past or current history of alcohol abuse or dependence; or 8) active, daily or frequent (≥ 2 times/week) use of benzodiazepines, barbiturates, anticholinergics, antihistamines, sedatives, sleep aids, or antiepileptic medications in the 3 months prior to study enrollment.

Table 1. Study overview and procedures.

Study visit	Evaluations and procedures to be completed	Estimated visit duration
1	<ul style="list-style-type: none"> A detailed clinical history, including a detailed review of the history of present illness, past medical, surgical, social, and family history, medications, and allergies from study participants and their study partners A detailed physical and neurological exam A detailed neuropsychological assessment which includes evaluation of verbal and nonverbal memory, language, attention, processing speed, executive and visuospatial functions in addition to behavioral and functional assessments Blood sample collection for APOE4^a genotyping and screening coagulation parameters A detailed review of eligibility criteria for the LP^b and MRI^c assessments (see Multimedia Appendix 1) 	3-4 hours
2	<ul style="list-style-type: none"> Lumbar puncture (collection of 20-25 ml of cerebrospinal fluid) 	60-90 minutes
3	<ul style="list-style-type: none"> MRI during resting state and performance of a semantic memory task (ie, Famous Name Discrimination Task) 	90 minutes

^aAPOE4: apolipoprotein E.

^bLP: lumbar puncture.

^cMRI: magnetic resonance imaging.

Eligible participants who have been on stable doses of CHEI and/or memantine for ≥ 3 months at the time of enrollment, and who meet the other eligibility criteria for the study, will be included. Eligible study participants will be instructed to avoid the use of alcohol, benzodiazepines, over-the-counter sleep aids, antihistamines, and anticholinergic medications for at least 2 weeks prior to the time of their enrollment and for the whole duration of the study.

Written informed consent will be obtained from all participants or their legally authorized representatives when appropriate. Additionally, written informed assent will be obtained from all participants with mild AD dementia (CDR 1).

Criteria for Diagnostic Classification

The clinical diagnosis of amnesic MCI due to AD will be made according to standard clinical criteria as described by the National Institute on Aging and Alzheimer's Association (NIA-AA) Working Group [33]. Clinical diagnoses will be supported by CSF biomarker data for tau, p-tau181, and A β 42 (ie, the CSF biomarker phenotype of AD including elevated CSF tau or p-tau181, and low CSF A β 42 levels) at the time of data analysis. This includes evaluation for other systemic or neurological disorders which could significantly contribute to cognitive impairment, and inclusion of results from ancillary structural imaging (brain computed tomography [CT] or structural MRI), neuropsychological testing, and ^{18}F -fludeoxy-glucose positron emission tomography (FDG-PET) imaging (when available) into the diagnostic scheme [33].

The diagnosis of amnesic MCI will be based on impairment in episodic memory with or without impairment in other cognitive domains (ie, multi-domain and single-domain amnesic MCI, respectively), which is 1-1.5 SDs of age-, gender-, and education-matched norms, and is not associated with significant functional decline [33]. In most centers, a diagnosis of amnesic MCI due to AD is equivalent to a CDR of 0.5.

The clinical diagnosis of dementia due to AD will be made according to standard clinical criteria as described by the NIA-AA Working Group [34] and supported by CSF biomarker data for tau, p-tau181, and A β 42. This will include evaluation for other disorders which could significantly contribute to cognitive impairment, and will also include results from ancillary structural imaging, neuropsychological testing, and FDG-PET imaging (when available) [34].

In individuals who meet standard criteria for dementia due to AD, the CDR will be used to determine the severity of dementia. A CDR designation of 1, 2, and 3 denotes mild, moderate, and severe AD dementia, respectively [35].

Normal cognition will be defined as cognitive performance on detailed neuropsychological assessments that falls within 1 SD of age-, gender-, and education-matched norms in all cognitive domains, and no subjective report of cognitive decline from an individual's baseline (ie, CDR 0). CSF biomarker data will be used to differentiate cognitively normal controls who have no biomarker evidence of AD pathology (ie, those with normal CSF tau, p-tau181 and A β 42 levels: CSF tau < 350 pg/ml, p-tau181 < 50 pg/ml, and A β 42 > 500 pg/ml) from cognitively

normal controls who have biomarker evidence of AD pathology (ie, those with the CSF biomarker phenotype of AD: CSF tau ≥ 350 pg/ml, p-tau181 ≥ 50 pg/ml, and A β 42 ≤ 500 pg/ml) at the time of data analysis. These cutoff values are based on the CSF biomarker levels that provided the highest diagnostic accuracy (ie, combination of sensitivity and specificity as measured by the area under the curve [AUC] for the receiver operating characteristic [ROC] curves) in differentiating individuals with a clinical diagnosis of AD from cognitively normal controls in previous longitudinal studies of healthy aging and dementia at the Washington University's Knight Alzheimer's Disease Research Center [36].

Clinical Assessments

Clinical assessments will be performed by neurologists and nurse practitioners in the Cognitive Neurology clinic of the Ohio State University. Clinical assessments will include a detailed review of the history of present illness, past medical, surgical, social, and family history, medications, allergies, and a detailed physical and neurological exam.

Neuropsychological Assessments

Neuropsychological assessments will be performed by experienced neuropsychometricians, and will include the following tests [37]: (1) Associate learning subtest of the Wechsler memory scale-IV [WMS-IV] [38]; (2) WMS-IV Logical Memory (I and II) [38]; (3) Hopkins Verbal Learning Test-Revised [39]; (4) Information subtest from the Wechsler adult intelligence scale-IV [WAIS-IV] [40]; (5) Boston naming test (short version) [41]; (6) animal fluency test [42]; (7) WMS-IV mental control (symbol span) [38]; (8) digit span forward and digit span backward (WAIS-IV) [40]; (9) letter fluency for F and S [43]; (10) block design (WAIS-IV) [40]; (11) digit symbol substitution tests [44]; (12) trail making tests A and B [45]; (13) the CDR [46]; (14) the Mini Mental Status Examination (MMSE) [47]; (15) the Self-Administered Gerocognitive Examination (SAGE) [48]; (16) the Geriatric Depression Scale (GDS) [49]; (17) the behavioral component of the Neuropsychiatric Inventory (NPI) [50]; and (18) the Functional Activity Questionnaire [51].

Plasma Collection and Apolipoprotein E Genotyping

A total of 10 ml of blood will be obtained from each participant, collected in EDTA tubes, aliquoted, and frozen at -80°C . APOE genotyping will be performed using real-time PCR (polymerase chain reaction) on an Applied Biosystems 7900HT Real-Time PCR machine using the TaqMan SNP (single nucleotide polymorphism) Genotyping Assay (Applied Biosystems) for rs429358 and rs7412 as described [52].

Lumbar Puncture

Each participant will undergo one LP within 4 months of the clinical and neuropsychological assessments. A total of 20-25 ml will be obtained from each participant in the lateral decubitus position under sterile conditions, collected in sterile polypropylene tubes, centrifuged, aliquoted and placed on dry ice. CSF aliquots will be stored at -80°C , then thawed and centrifuged prior to analysis. CSF analyses of tau, p-tau181, and A β 42 levels will be performed using the Innostest enzyme-linked immunoassay (Fujirebio, formerly Innogenetics)

as described [7]. CSF analyses for Ng and SNAP-25 levels will be performed using a single molecule counting chemiluminescence assay (Erenna, Singulex) as described [7,53].

Magnetic Resonance Imaging

Structural Magnetic Resonance Imaging

Structural MRI data will be collected using a Siemens 3.0 Tesla Prisma scanner (Siemens, Erlangen, Germany). One to four T₁-weighted sagittal magnetization-prepared rapid gradient-echo (MP-RAGE) scans will be acquired from each participant. Image processing will be performed as described [54,55]. High resolution, three-dimensional anatomic images will be acquired using the MP-RAGE sequence (TE [echo time]=2.45 milliseconds [ms]; TR [time to repetition]=2500 ms; inversion time=1060 ms; flip angle=8 degrees; slice thickness=1.0 mm; field of view [FOV]=256 mm; matrix size=256 × 256; and a resolution of 1 × 1 × 1 mm). Foam padding will be used to reduce head movement within the coil.

Whole brain volume will be obtained using freely available Freesurfer 5.0 software [56,57], with segmentation classifying each voxel of the MRI image as CSF, gray matter, or white matter. Normalized whole brain volumes (nWBVs) will be computed as the proportion of all voxels occupied by gray and white matter (equivalent to 100% minus the percentage of CSF) voxels, yielding a unit that represents the proportion of estimated total intracranial volume (ICV).

Functional Magnetic Resonance Imaging

Whole brain resting state and task activated fMRI will be conducted on a Siemens 3.0 Tesla Prisma scanner equipped with a 32-channel head array coil. Echo planar images will be collected using a pulse sequence (TE=28 ms; flip angle=60 degrees; FOV=240 mm; and matrix size=72 x 80). Forty-five contiguous axial 3-mm-thick slices will be selected to provide coverage of the entire brain (voxel size=3 × 3 × 3 mm). The TR will be 1 second.

Functional images will be preprocessed and registered using fMRI of the Brain Software Library techniques [58]. Data will be preprocessed according to a standard functional analysis pipeline employing motion correction, spatial smoothing using an *a priori* determined full width half maximum Gaussian smoothing kernel, high-pass temporal filtering at 0.01 hertz (Hz) to remove any low frequency noise from scanner drift or participant-related artifacts, brain extraction, and nonlinear spatial registration to optimize individual anatomical localization. FC within the DMN and semantic memory networks will be examined using a region of interest (ie, seed) model. Following the pipeline employed in previous studies [59-61], we will choose the left and right precuneus as seeds for the DMN and the semantic memory networks to create voxel-wise partial correlation maps, representing a correlation between the timeseries of the seed and that of every voxel in the brain. These individual level maps will then be forwarded separately to higher-level analyses, whereby intersubject variability will be treated as a random variable. These higher-level analyses will compare differences in FC of the DMN and the semantic memory networks between individuals

with MCI or mild dementia due to AD (CDR 0.5-1) and cognitively normal controls (CDR 0). All maps will be thresholded at $z=2.33$ ($P<.01$) and a cluster threshold of $P<.05$ to correct for multiple comparisons. For each participant, the functional imaging data will first be registered to the participant's high-resolution MP-RAGE, followed by registration to the Montreal Neurological Institute template [62]. Nonlinear transformations will be employed for all registrations to account for the significant heterogeneity in brain structure observed in clinical populations.

Semantic Memory Task

The task activated fMRI will be obtained during performance of the FNMT, a semantic memory task which consists of the presentation of 30 highly recognizable famous names and 30 unfamiliar names. Accuracy and reaction time will be recorded. The use of a semantic memory task offers several advantages over episodic memory tasks in MCI and mild AD dementia. In contrast to episodic memory tasks, which may be impaired with healthy aging, semantic memory tasks remain relatively intact in healthy elderly individuals but are impaired in the presence of AD pathology [32]. Furthermore, semantic memory tasks are easier and less frustrating for the elderly to perform, thereby allowing for more accuracy in interpreting test results by eliminating confounding effects of increased mental effort on fMRI signal. The FNMT has been successfully applied in previous fMRI studies of MCI and AD dementia [32].

Statistical Analysis

Student's *t* tests, chi-square (χ^2) analyses, and analysis of covariance (ANCOVA) will examine differences in demographic, clinical, neuropsychological, CSF biomarker, and FC measures between the study groups (SPSSv15, SPSS, IL). Partial correlation analyses and linear regression models will examine associations between CSF biomarker levels and FC measures, adjusting for age, gender, and the APOE4 genotype (SPSSv15, SPSS, IL). Bootstrap analyses will compare correlations between CSF biomarker measures (individually or as combinations of markers, using principal components analysis) and FC in the DMN and semantic memory networks in AD and controls (R Statistical Software).

Outcome Measures

The main outcome measures of the study include CSF biomarker measurements (CSF Ng, SNAP-25, tau, p-tau181, and A β 42 levels in pg/ml) and functional imaging measures including FC of the left and right precuneus seeds (ie, correlation between the timeseries of each of the left and right precuneus seeds and that of every voxel in the brain represented by voxel-wise partial correlation maps) during resting state and the performance of the semantic memory task (ie, FNMT). Analyses will be adjusted for covariates including age, gender, and the APOE4 genotype.

Results

A total of 35 potential participants underwent initial screening for the study. Of those, 22 participants met the eligibility criteria and were subsequently enrolled in the study. Three participants were lost to follow-up during the study period. Therefore, a

total of 19 participants (n=12 cognitively normal controls and n=7 participants with a clinical diagnosis of MCI/mild dementia due to AD) are currently enrolled in this study. Participant enrollment and study procedures are currently underway.

Discussion

The main purpose of this study is to examine cross-sectional associations between CSF markers of synaptic injury (Ng and SNAP-25) and FC in the default mode and semantic memory networks using 3T-functional MRI in early symptomatic AD (MCI and mild dementia due to AD; CDR 0.5 and 1, respectively; n=20) and cognitively normal controls (CDR 0; n=20). To our knowledge, this is the first study to investigate associations between CSF markers of synaptic injury and FC in early symptomatic AD and healthy controls. We have previously demonstrated correlations of CSF Ng levels with whole brain and regional atrophy in AD [7], however, we are not aware of any studies which have investigated correlations between CSF Ng or SNAP-25 levels and functional imaging measures in AD or healthy aging. Furthermore, this will be the first study to examine associations between CSF biomarkers of AD pathology (including CSF markers of synaptic injury) and FC during the performance of a semantic memory task (ie, FNNT) which can be reliably performed by individuals with early symptomatic AD (CDR 0.5-1).

We hypothesize that higher CSF Ng and SNAP-25 levels (ie, reflective of more severe synaptic injury) will be associated with lower FC of the left and right precuneus seeds during

resting state and the performance of the FNNT in individuals with MCI and mild AD dementia. Conversely, we hypothesize that no significant correlations between CSF Ng and SNAP-25 levels and FC of the left and right precuneus seeds will be observed during resting state or the performance of the FNNT in cognitively normal controls.

The identification of CSF biomarkers that reflect functional alterations in neural networks affected by early AD pathology (ie, default mode and semantic memory networks) will shed light on the potential utility of synaptic proteins as CSF surrogates of functional connectivity within neural networks and provide useful information regarding their value as potential outcome measures or stratification tools in clinical trials of AD therapeutics. CSF markers of synaptic injury may provide valuable tools to monitor disease progression, target engagement, and response to disease modifying therapies which target different pathological substrates of AD independently of changes to amyloid or tau pathology. Imaging methods that utilize amyloid binding ligands do not reliably reflect soluble A β species, which contribute significantly to synaptic damage and cognitive impairment in AD. Therefore, synaptic markers may offer useful measures for disease outcomes and therapeutic response at an earlier stage, and to a better degree, than CSF or imaging markers of amyloid or tau pathology. Importantly, this study will provide insight into the molecular mechanisms that underly the radiologic correlates of neural activity in different stages of disease and will improve our understanding of the dynamic interface between CSF and imaging surrogates of synaptic activity in the presence and absence of AD pathology.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Checklist for magnetic resonance imaging and lumbar puncture contraindications.

[\[DOCX File, 16KB - resprot_v8i7e14302_app1.docx \]](#)

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Abbreviations

- AD:** Alzheimer disease
- ANCOVA:** analysis of covariance
- APOE:** apolipoprotein E
- AUC:** area under the curve
- CBC:** complete blood count
- CDR:** Clinical Dementia Rating
- CHEI:** cholinesterase-inhibitors
- CSF:** cerebrospinal fluid
- CT:** computed tomography
- DMN:** default mode network
- FC:** functional connectivity
- FDG-PET:** 18F-fludeoxy-glucose positron emission tomography
- fMRI:** functional magnetic resonance imaging
- FNDT:** Famous Name Discrimination Task
- FOV:** field of view
- GDS:** Geriatric Depression Scale
- Hz:** hertz
- ICV:** intracranial volume
- INR:** international normalized ratio
- LP:** lumbar puncture
- MCI:** mild cognitive impairment
- MMSE:** Mini Mental Status Examination
- MP-RAGE:** magnetization-prepared rapid gradient-echo

MRI: magnetic resonance imaging
Ng: neurogranin
NIA-AA: National Institute on Aging and Alzheimer's Association
NPI: Neuropsychiatric Inventory
nWBV: normalized whole brain volume
PCR: polymerase chain reaction
PT: prothrombin time
p-tau181: tau phosphorylated at threonine 181
PTT: partial thromboplastin time
ROC: receiver operating characteristic
SAGE: Self-Administered Gerocognitive Examination
SNAP-25: synaptosome-associated protein-25
SNP: single nucleotide polymorphism
TE: echo time
TR: time to repetition
WAIS-IV: Wechsler adult intelligence scale-IV
WMS-IV: Wechsler memory scale-IV

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Protocol

Design of Improved Intertrochanteric Fracture Treatment (DRIFT) Study: Protocol for Biomechanical Testing and Finite Element Analysis of Stable and Unstable Intertrochanteric Fractures Treated With Intramedullary Nailing or Dynamic Compression Screw

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Abstract

Background: Intertrochanteric hip fractures rank in the top 10 of all impairments worldwide in terms of loss in disability-adjusted years for people aged older than 60 years. The type of surgery is usually carried out with dynamic hip screw (DHS) devices or cephalomedullary nails (CMN). Cut-out of the hip screw is considered the most frequent mechanical failure for all implants with an estimated incidence ranging from 2% to 16.5%; this entails both enhancing our understanding of the prognostic factors of cut-out and improving all aspects of intertrochanteric fracture treatment.

Objective: The Design of Improved Intertrochanteric Fracture Treatment (DRIFT) study's main objective is to provide intertrochanteric fracture treatment expertise, requirements and specifications, clinical relevance, and validation to improve treatment outcomes by developing a universal algorithm for designing patient- and fracture-oriented treatment. The hypothesis to be tested is that a more valgus reduction angle and implants of higher angles will lead to a more favorable biomechanical environment for fracture healing—that is, higher compressive loads at the fracture site with lower shear loads at the hip screw femoral head interface. A new implant with enhanced biomechanical and technical characteristics will be designed and fabricated; in addition, an integrated design and optimization platform based on computer-aided design tools and topology optimization modules will be developed.

Methods: To test this hypothesis, a biomechanical study comprising experimental loading of synthetic femora (Sawbones Inc) and finite element analysis (FEA) will be conducted. Detailed FEA of existing implants (DHS and CMN) implemented in different clinical cases under walking conditions will be performed to derive the stress and strain fields developed at the implant-bone system and identify critical scenarios that could lead to failure of therapy. These models would be validated against instrumented mechanical tests using strain gages and a digital image correlation process.

Results: After testing, geometric drawbacks of existing implants will be fully recognized, and geometric characteristics will be correlated with critical failure scenarios. The last step would be the numeric design, computer-aided design (using FEA codes and design packages), and optimization of the new proposed implant with regard to improved biomechanical surgical technique and enhanced mechanical performance that will reduce the possibility for critical failure scenarios.

Conclusions: The optimization of the biomechanical behavior of the fracture-osteosynthesis model by the application of the ideal reduction angle and implant is expected to have a positive effect to the rate of mechanical failure and, subsequently, the healing rates, morbidity, and mortality in this fragile patient group.

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KEYWORDS

trochanteric fractures; cut-out; biomechanical testing; finite element analysis; new implant design

Introduction

Background

Hip fractures rank in the top 10 of impairments worldwide in terms of loss in disability-adjusted years for people aged older than 60 years [1]. The absolute number of hip fracture hospitalizations in the United States is estimated to approach 289,000 in 2030 [2], and the global number of hip fractures is expected to increase from 1.26 million in 1990 to 4.5 million by the year 2050 [3]. The estimated cost of treatment in the United States was approximately \$10.3 to \$15.2 billion per year in 1990 [4] and \$17 billion in 2002 [5]. In a recent study [6], the incidence of fractures of the hip in Northern Ireland rose from 54 in 100,000 in 2000 to 86 in 100,000 in 2015; the authors predict an increase to 128 in 100,000 in 2030 if this trend continues. In the United Kingdom, there is an ongoing age-standardized decrease in the rate of hip fractures of 0.5% per year, but it is estimated that the annual incidence will double in the next 25 years [7]. The consequences of hip fractures in elderly individuals are significant in terms of lives lost and associated negative impacts on hip fracture patients' functioning and quality of life. Even with an integrated, multidisciplinary model for the treatment of hip fragility fractures (90% of operations performed within 48 hours), the in-hospital mortality rate was 2.4% and the overall mortality at 1 year from the intervention 18.7%; full mobility status or a low impairment of mobility was reached in 32.1% of patients [8].

The vast majority of intertrochanteric fractures require surgical repair to withstand the early mobilization and weight bearing required to prevent complications due to prolonged bed rest and aid in fracture healing. The type of surgery is generally based on fracture pattern and patient characteristics and is usually performed with dynamic hip screw (DHS) devices or cephalomedullary nails—proximal femoral nails, proximal femoral nail—antirotation nails, gamma nails, or other implants [9-11]. Since the 1960s, the DHS has become the standard implant for surgical treatment of intertrochanteric fractures as it allows controlled fracture compression [12,13]. Despite additional modifications, such as trochanteric support plates and antirotational screws, unstable fractures are less successfully treated by this method [9,14]. Cephalomedullary nails can provide better lateral wall support in more complex fracture patterns, but cut-out of the hip screw has been described as the most frequent mechanical failure for all implants [15-20].

Cut-out is defined as “the collapse of the neck-shaft angle into varus, leading to extrusion of the screw from the femoral head” [15,16]. Several studies have shown that the incidence of cut-out

for different compression hip screws and cephalomedullary nails ranges from 0 to 16.5% [12,15-21] and, in older studies [22-25], even up to 20%. Recent developments including plates, antirotational screws, and cement-augmented fixation techniques indicate that the problem of fixation failure is still unresolved [26-27]. This complication is a multifactorial event affected by a number of variables including patient age and sex, bone quality, fracture pattern, quality of reduction, implant design, and meticulous surgical technique [17,18]. In a recent study by Bojan et al [28], the primary cut-out rate of a gamma nail in 3066 consecutive patients was 1.85% and was strongly associated with unstable fractures involving the trochanteric or cervical regions or both as well as nonanatomical reduction or nonoptimal screw position, which are the only two factors that can be controlled by the surgeon. We therefore believe that further elucidation of the effect of surgical technique on the biomechanical behavior of the fracture after fixation is required, especially concerning the effect of the implant angle, positioning, and reduction angle.

Study Hypothesis and Aims

The main objective of the Design of Improved Intertrochanteric Fracture Treatment (DRIFT) study is to provide pertrochanteric fracture treatment expertise, requirements and specifications, clinical relevance, and validation to improve intertrochanteric fracture treatment outcomes by designing, fabricating, and verifying an implant with optimized biomechanical performance and surgical technique and develop a universal algorithm for designing patient- and fracture-oriented treatment. The specific technical objectives are as follows:

- Improve the understanding of the factors associated with mechanical failure and the impact of design features of implants currently in use on the biomechanical behavior of the implant-bone interface, provided by orthopedic departments.
- Create numerical methods for the prediction of failure of the bone-implant system under static and fatigue loading conditions. Mechanical tests representing exact geometries of the bone-implant system and applying realistic static and fatigue loading conditions will be designed and executed for the verification of the proposed designs.
- Develop an algorithm for designing patient- and fracture-oriented surgical treatment based on existing and novel implants aiming to minimize mechanical failure incidences.
- Design and fabricate a new implant with enhanced biomechanical and technical characteristics. An integrated design and optimization platform based on computer-aided

design tools and topology optimization modules will be developed.

To test these hypotheses, a biomechanical study comprising experimental loading and finite element analysis (FEA) will be conducted.

Methods

Ethical Approval

As this is a biomechanical study, no institutional board approval is necessary.

Biomechanical Testing

The experimental part of the study will be undertaken in the Material Testing Laboratory at the National Technical University of Athens.

Femoral Preparation

A minimum of fifteen synthetic femora (Sawbones Inc) of medium size and normal (135°) neck shaft angle will be used. All femurs will contain a polyurethane foam filling of 12.5 pounds per cubic foot density to stimulate the material properties of osteoporotic cancellous bone. Concurrently, the digital image files (Initial Graphics Exchange Specification and Solidworks formats) of these femurs will be procured to ensure accurate modeling of the complex femoral geometry and minimal discrepancies between the experimental data and the subsequent FEA models [29-31].

The implants tested in the experimental study will be the Gamma3 nail cephalomedullary system (Stryker) and the DHS plate-hip screw system (Depuy-Synthes). There will be 2 Sawbones for each implant and fracture configuration, namely 2 Sawbones for stable fractures with gamma nail and another two for each of the following configurations: unstable fracture statically locked with normal tip to apex distance (TAD), unstable fracture statically locked with increased TAD, unstable fracture dynamically locked with normal TAD, and unstable fracture unlocked with normal TAD; likewise with the DHS, there will be testing of stable fracture and unstable fracture with two Sawbones in each category. An additional intact femur will be used to standardize the process and facilitate the FEA model validation; thus, a total of fifteen Sawbones will be used. The implants that will be used in the biomechanical testing would be the Gamma3 nail (180 mm length, 11 mm diameter, and 130° angle, titanium) and DHS (135° , 4-hole plate, steel). Although recent biomechanical data have shown equivalence of 2- and 4-hole plates, clinical data such as the study from Baird et al [32] suggest a possible higher rate of failure in unstable fractures with the 2-hole plate. As the study will involve unstable fractures, we decided to use the 4-hole side plate to reduce confounding factors. Despite the commercial availability

of titanium plates for the DHS system, the vast majority of implants used are used with stainless steel plates, which is reflected in our choice of material. The choice of a short nail rather than a long one is reflecting the common practice in the fracture types studied, given that we are not going to study reverse obliquity subtypes or subtrochanteric fractures, where long nails have a clear advantage over short nails.

The instrumentation will be performed by GK in a standardized fashion on intact (prior to fracture creation) Sawbones under image intensifier to ensure a uniform implant position and TAD of the hip screw, which will be in the range of 10 to 20 mm (Figure 1). The Sawbones will then be uninstrumented, and the fractures will be created with the aid of a cutting guide to ensure identical fracture lines. Stable fractures will be created with a fracture line running 47° from the horizontal level exiting above the lesser trochanter, while the unstable fractures will have a wedge of bone removed contained the lesser trochanter. The Sawbones will then be reinstrumented and prepared for testing. A resin mold has been created that covers the distal femoral condyles and permits sufficient stabilization of the distal femur. The femur-resin mold block will be further stabilized by the use of a stainless-steel orthogonal holder and positioned at neutral position in the sagittal plane and 11° of adduction. Strain gauges will be applied on specific points of interest, namely the distal fragment including the calcar area and the distal fixation points, and a layer of matte white paint will be applied followed by black dots, thus creating a random speckle pattern (Figure 2).

Loading Configuration

The femurs will be fixed distally in resin in a steel block with neutral flexion-extension and 11° of adduction to simulate single leg stance [17]. The load will be transmitted by means of a steel plate to allow for rotation and translation as the distal femur is fixed. As the abductor insertion can be part of the fracture, the abductor pull will not be simulated to minimize confounding factors and excess motion at the fracture site. The position that will be studied is the single leg stance in the nonconsolidated fracture status [33].

Mechanical testing will be undertaken in an MTS Insight 10 kN load frame (Testworks 4, MTS Systems Corp), and data will be retrieved with the aid of KFG Series strain gages (Kyowa Electronic Instruments Co Ltd) and a 3D image correlation system (3D-DIC, LIMESS Messtechnik und Software GmbH). The loading will include a 200 nt preload and relaxation followed by static loading until 2000 nt, which simulates the loads experienced by a hip during single leg stance (Figure 3). The implants will not be loaded to failure as static failure is not as clinically relevant as fatigue failure, which happens at submaximal loads after a high number of cycles.

Figure 1. Instrumented Sawbone with Gamma3 nail.



Figure 2. Instrumented stable intertrochanteric fracture with digital image correlation paint and strain gauges.



Figure 3. Loading configuration in unstable trochanteric fracture.



Digital Image Correlation

The setup for digital image correlation entails two digital cameras placed so as to record the femoral head, neck, and proximal cortex from different angles [30]. All femurs will have a random but unique speckled pattern painted on them. As the load will be applied and deformation of the patterns will occur, they will be recorded throughout the loading process and consequently analyzed with the aid of specialized software (Aramis Professional, GOM). The differences between the patterns will allow the detailed mapping of the strain fields on the cortical bone.

Statistical Analysis

Statistical analysis will be performed using SPSS Statistics version 23 (IBM Corp). A Shapiro-Wilk test will be used to test for normality of distribution of the main results (ie, stress and construct stiffness). Homogeneity of variances between the groups will be checked with a Levene test. Significant differences between the 2 groups will be checked with paired samples *t* tests. Level of significance will be set to $P=.05$ for all statistical tests.

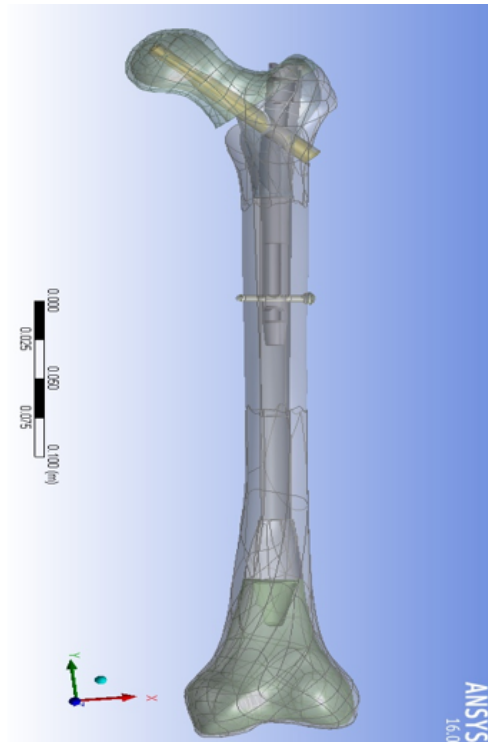
Finite Element Analysis

The loading setting will be originally validated with the loading of an intact femur and comparison of the FEA of an intact femur. Consequently, FEA will be undertaken for stable and unstable fractures treated with DHS and gamma nail and a minimum of two experiments per scenario tested experimentally.

The FEA will be conducted using Ansys 16.0 (Ansys Inc). The femoral model to be used will be identical to the Sawbones as provided by Sawbones (digital models of the purchased Sawbones). The implants to be used will be designed by the use of 3D scanning and manual design using Solidworks 2016 (Dassault Systemes). Threads will not be used in the analysis to reduce computing requirements and the risk of abnormally high peak stresses on the thread tips. The optimal type of element as well as element size and meshing refinements will be decided based on convergence studies. However, at areas of great interest, such as the bone overlying the tip of the hip screw and the fracture area, small element sizes of under 2 mm will be used to optimize the accuracy of the results.

The finite element (FE) model validation will be based on the experimental findings and will be done on two stages. First the intact Sawbone will be used to adjust for material properties attributed to cortical and cancellous bone and element size. Next the instrumented stable fractures will be used to refine meshing and element size and types, and finally the unstable fracture models will be used for fine-tuning of the FEA (Figure 4). After validation of the models, a series of fracture and reduction scenarios will be run to test our hypothesis. The effect of variable reduction angles and implant angles on the stresses incurring at the area of bone overlying the tip of the hip screw, the medial cancellous bone, and the implant and distal fixation sites will be analyzed. Additionally, the effect of distal locking static, dynamic, or no locking will be studied as well as the effect of various TAD and neck-shaft angle combinations (Textbox 1).

Figure 4. Unstable fracture finite element analysis model instrumented with Gamma3 (130/180/11).



Textbox 1. Fracture-osteosynthesis scenarios to be studied.

Unstable fractures treated with dynamic hip screw (DHS)

- Varus reduction, 130 plate, tip to apex distance (TAD)<25
- Varus reduction, 130 plate, TAD>25
- Varus reduction, 135 plate, TAD<25
- Varus reduction, 135 plate, TAD>25
- Varus reduction, 145 plate, TAD<25
- Varus reduction, 145 plate, TAD>25
- Anatomic reduction, 130 plate, TAD<25
- Anatomic reduction, 130 plate, TAD>25
- Anatomic reduction, 135 plate, TAD<25
- Anatomic reduction, 135 plate, TAD>25
- Anatomic reduction, 145 plate, TAD<25
- Anatomic reduction, 145 plate, TAD>25
- Valgus reduction, 130 plate, TAD<25
- Valgus reduction, 130 plate, TAD>25
- Valgus reduction, 135 plate, TAD<25
- Valgus reduction, 135 plate, TAD>25
- Valgus reduction, 145 plate, TAD<25
- Valgus reduction, 145 plate, TAD>25

Unstable fractures treated with gamma nail

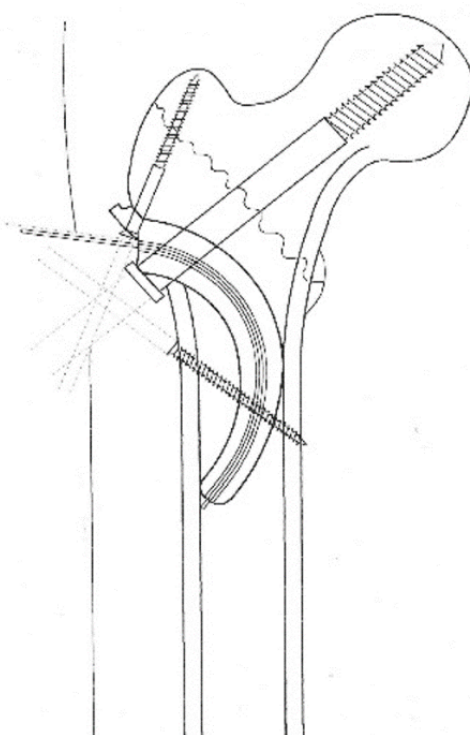
- Varus reduction, 120 nail, TAD<25, static locking
- Varus reduction, 120 nail, TAD>25, static locking
- Varus reduction, 125 nail, TAD<25, static locking
- Varus reduction, 125 nail, TAD>25, static locking
- Varus reduction, 130 nail, TAD<25, static locking
- Varus reduction, 130 nail, TAD>25, static locking
- Varus reduction, 120 nail, TAD<25, dynamic locking
- Varus reduction, 120 nail, TAD>25, dynamic locking
- Varus reduction, 125 nail, TAD<25, dynamic locking
- Varus reduction, 125 nail, TAD>25, dynamic locking
- Varus reduction, 130 nail, TAD<25, dynamic locking
- Varus reduction, 130 nail, TAD>25, dynamic locking
- Varus reduction, 120 nail, TAD<25, unlocked
- Varus reduction, 120 nail, TAD>25, unlocked
- Varus reduction, 125 nail, TAD<25, unlocked
- Varus reduction, 125 nail, TAD>25, unlocked
- Varus reduction, 130 nail, TAD<25, unlocked
- Varus reduction, 130 nail, TAD>25, unlocked
- Anatomic reduction, 120 nail, TAD<25, static locking
- Anatomic reduction, 120 nail, TAD>25, static locking
- Anatomic reduction, 125 nail, TAD<25, static locking
- Anatomic reduction, 125 nail, TAD>25, static locking

- Anatomic reduction, 130 nail, TAD<25, static locking
- Anatomic reduction, 130 nail, TAD>25, static locking
- Anatomic reduction, 120 nail, TAD<25, dynamic locking
- Anatomic reduction, 120 nail, TAD>25, dynamic locking
- Anatomic reduction, 125 nail, TAD<25, dynamic locking
- Anatomic reduction, 125 nail, TAD>25, dynamic locking
- Anatomic reduction, 130 nail, TAD<25, dynamic locking
- Anatomic reduction, 130 nail, TAD>25, dynamic locking
- Anatomic reduction, 120 nail, TAD<25, unlocked
- Anatomic reduction, 120 nail, TAD>25, unlocked
- Anatomic reduction, 125 nail, TAD<25, unlocked
- Anatomic reduction, 125 nail, TAD>25, unlocked
- Anatomic reduction, 130 nail, TAD<25, unlocked
- Anatomic reduction, 130 nail, TAD>25, unlocked
- Valgus reduction, 120 nail, TAD<25, static locking
- Valgus reduction, 120 nail, TAD>25, static locking
- Valgus reduction, 125 nail, TAD<25, static locking
- Valgus reduction, 125 nail, TAD>25, static locking
- Valgus reduction, 130 nail, TAD<25, static locking
- Valgus reduction, 130 nail, TAD>25, static locking
- Valgus reduction, 120 nail, TAD<25, dynamic locking
- Valgus reduction, 120 nail, TAD>25, dynamic locking
- Valgus reduction, 125 nail, TAD<25, dynamic locking
- Valgus reduction, 125 nail, TAD>25, dynamic locking
- Valgus reduction, 130 nail, TAD<25, dynamic locking
- Valgus reduction, 130 nail, TAD>25, dynamic locking
- Valgus reduction, 120 nail, TAD<25, unlocked
- Valgus reduction, 120 nail, TAD>25, unlocked
- Valgus reduction, 125 nail, TAD<25, unlocked
- Valgus reduction, 125 nail, TAD>25, unlocked
- Valgus reduction, 130 nail, TAD<25, unlocked
- Valgus reduction, 130 nail, TAD>25, unlocked

Design of the New Implant (Hybrid Nail)

The new hybrid nail combines properties of both techniques. Using a small entry point beneath the greater trochanter, a semicircular solid nail of different length and diameter is

introduced inside the medullary canal and impacted in the cortex, thus avoiding distal locking. The latter can be used if extra stability is needed. From the same entry point, the sliding hip screw can be inserted as well as a small trochanteric screw for unstable fracture patterns (Figure 5).

Figure 5. The proposed hybrid nail.

Results

The DRIFT study will test the hypothesis that a valgus reduction is mechanically favorable in all fracture configurations, quantify the mechanical effect, and determine the optimal postreduction implant/bone geometry.

DRIFT also aims to quantify the mechanical effects of calcar and lateral wall integrity and would define the necessity to address them. DRIFT will study the effect of other variables on TAD and its cut-off point, with a working hypothesis that TAD is not independent from fracture characteristics, reduction angle, and screw position.

Also, DRIFT will test and quantify the effect of eccentric screw positioning on fracture-implant mechanics on a multiplanar gait-based model and will test the hypothesis on FEA models aiming to prove that distal locking is not necessary in most cases of stable fracture types.

In DRIFT, finally, the stress and strain fields, which will be derived by the FE method, will be used to predict failure of existing tools under static loading conditions. Moreover, the design optimization modules that appear in the existing commercial FE codes will be used for the numerical design of the novel implant with respect to its mechanical performance.

Discussion

Summary

Despite extensive literature on the various prognostic factors of mechanical failure in the osteosynthesis of pertrochanteric fractures, the effect of reduction angle has been understudied and the implant angle has not received significant attention. The main prognostic factor recognized is the TAD where a value of

over 25 mm is being considered an independent predictive factor for failure. In a recent study from Bojan et al [28], the typical cut-out complication was represented by an unstable fracture type involving the trochanteric or cervical regions or both as well as nonanatomical reduction or nonoptimal screw position. The authors suggested that in order to reduce the risk of a cut-out it is important to achieve both anatomical reduction and optimal lag screw position as these are the only two factors that can be controlled by the surgeon. In general, the factors affecting optimal treatment of trochanteric fractures can be divided in two categories: fracture pattern (varus or valgus reduction, lesser trochanter integrity, and lateral wall integrity) and optimal implant positioning (TAD, position of lag screw, and distal locking).

Fracture Pattern

Valgus/Varus Reduction

A higher postreduction neck shaft angle intuitively results in a greater fracture compression force vector and a subsequently lower ratio of force causing shear at the screw-bone interface. Parker [34] originally suggested valgus reduction to prevent cut-out. Despite biomechanical data [35,36] suggesting that a valgus postreduction angle would facilitate initiation of hip screw sliding in fractures treated by both sliding hip screw and intramedullary devices and therefore increase interfragmentary compression, this has not been confirmed in vivo by most relevant studies. In their randomized prospective clinical study, Pajarinen et al [14] noticed a postoperative decrease in the neck-shaft angle of operatively treated unstable pertrochanteric femoral fractures. A reduction in slight valgus was advocated for the unstable fractures to normalize the posthealing anatomic outcome. Recently, a retrospective study by Andruskow et al [37] in 235 patients found a trend that did not reach statistical significance ($P=.19$) for patients with a postoperative valgus

neck-shaft angle of 5° to 10° to have a smaller chance of developing a cut-out. On the other hand, Pervez et al [38] compared 23 cases of cut-out with 77 cases of uneventful fracture healing and suggested that a varus reduction results in an increased incidence of cut-out.

Lesser Trochanter (Calcar) Integrity

The integrity of the lesser trochanter has been implicated as a potential prognostic factor of cut-out. Eberle et al [39] showed that the lack of calcar support effectively makes the implant a load-bearing device, placing more stresses on the implant in their biomechanical study using an FE model. Bojan et al [28] retrospectively reviewed 3066 cases of pertrochanteric fractures treated with trochanteric nails and found a statistically significant increase in the incidence of cut-out among patients with unstable complex fractures. The restoration of the posteromedial calcar fragments is considered a key point to achieve stable fracture fixation; on the contrary, failure to address calcar integrity can lead to higher mechanical failure rates as has been shown in two clinical studies using sliding hip screws [40,41].

Lateral Wall Integrity

Gotfried [42] retrospectively analyzed 24 patients with mechanical failure of a sliding hip screw intertrochanteric fracture fixation due to excessive fracture collapse. There was a fracture of the lateral wall in all cases, and this was associated with an increased risk for mechanical failure. In fact, loss of lateral wall integrity is considered a relative contraindication for the use of a sliding hip screw device. To tackle these challenging fractures, Gupta et al [43], in a series of 74 patients, had good results with the use of trochanteric stabilizing plates in patients with lateral wall fracture. The small sample size and lack of control group, however, limit the power of the study. Babst et al [44] had similarly good results in their prospective clinical study using trochanteric stabilizing plates. The use of proximal femoral nails has been advocated in these fractures; however, this has not been clinically proven in randomized

controlled studies, and most relevant studies have methodological limitations or are of lower level evidence, as shown by Kregor et al [45] in their review paper.

Optimal Implant Positioning

Tip to Apex Distance

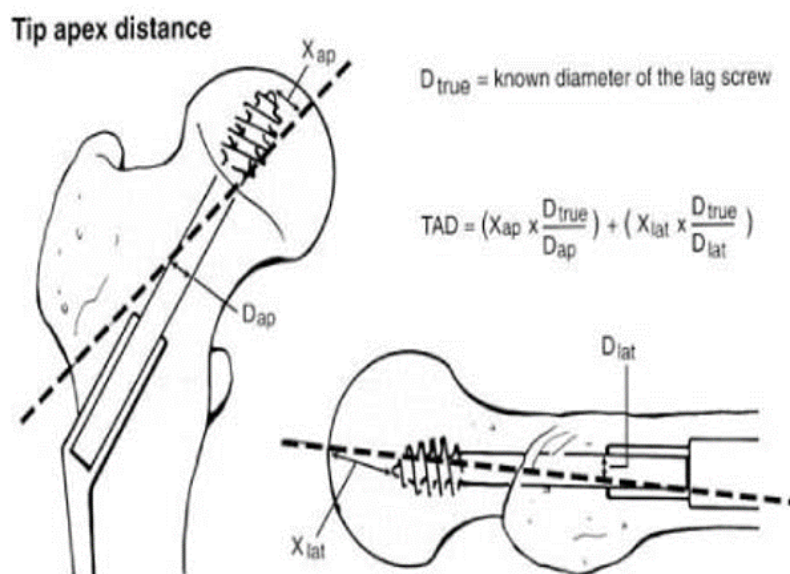
TAD was defined in the original work of Baumgaertner et al [21] as the sum of the distance from the tip of the screw to the apex of the femoral head in the anteroposterior and lateral views, after controlling for magnification (Figure 6).

TAD is being widely considered [37,40,46-48] as the only independent predictive factor of cut-out. Additionally, the awareness of TAD among surgeons was shown to reduce mechanical failure [49]. A biomechanical cadaveric study by Kane et al [50] challenged the notion that a TAD greater than 24 mm leads to increased cut-out rates regardless of screw position and found that central inferior position of the hip screw was at least as biomechanically stable as the center-center position although the TAD was greater than 25 mm. Hsueh et al [51], in a retrospective evaluation of 937 patients treated with DHS (135° angle), suggested placing the lag screw in the middle/middle or inferior/middle position with appropriate TAD (<15 mm).

Position of Lag Screw

In most reports, cut-out has been evaluated on two-dimensional radiographs, showing varus collapse of the femoral head and superior cut-out of the lag screw. The biomechanical studies are almost exclusively based on axial static or dynamic loading in only one plain. Ehmke et al [52], in their study, applied multiplane loading of pertrochanteric fracture models and suggested that cut-out occurs due to combined axial loads and rotational moments as in normal walking. Lenich et al [53] advocated a central position of the hip screw or blade as the optimal position to minimize rotational forces on the femoral head.

Figure 6. Calculation of tip to apex distance in the anteroposterior and lateral view.



Distal Locking

Distal locking in pertrochanteric fractures nailing is the standard of practice. The necessity of distal interlocking screws in stable intertrochanteric fractures has been biomechanically challenged in a study by Rosenblum et al [54]. This study, however, used the first-generation gamma nail, and the results cannot be safely applied to newer generation trochanteric nails that tend to be less stiff than the original. Skála-Rosenbaum et al [55], in their prospective clinical study, compared stable trochanteric fractures treated either with distal dynamic locking (44 cases) or without locking (77 cases) and found no difference in terms of time to healing, functional results, and complications. The authors proposed that distal locking is unnecessary in stable intertrochanteric fractures. Finally, Lobo-Escolar et al [46], in their case controlled clinical study, found positive correlation between distal static locking and cut-out, but these results did not reach statistical significance. Currently, use of the FE methods to study trochanteric fractures has been confined to simple static stress analyses of existing tools aiming to recognize the critical stresses and strains in the bone.

Strengths and Limitations

Strengths of this study include the use of uniform material and digital resources, thus negating the need for adjustments and variability between the biomechanical testing and subsequent

FEA validation. This is, to the best of our knowledge, the first biomechanical study to evaluate the effect of both reduction angle and implant angle in fracture treatment.

The main weakness of the study is the static nature of the loading used. Despite the fact that in clinical practice failure is a dynamic effect, this study tests the initial loading characteristics of various fracture configurations, a necessary prerequisite for any future cyclic loading studies.

Conclusion

Despite recent advances, cut-out remains the most common and devastating mechanical complication of intertrochanteric fracture treatment. Taking into consideration the increased health risks related to the treatment of this complication alongside the increased hospitalization and health care costs in the setting of an aging European population, the need to improve treatment outcomes of these fractures is evident. This entails both enhancing our understanding of the prognostic factors of cut-out and improving all aspects of intertrochanteric fracture treatment. The optimization of the biomechanical behavior of the fracture-osteosynthesis model by the application of the ideal reduction angle and implant is expected to have a positive effect on the rate of mechanical failure and, subsequently, the healing rates, morbidity, and mortality in this fragile patient group.

Conflicts of Interest

None declared.

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Abbreviations

CMN: cephalomedullary nails
DHS: dynamic hip screw
DRIFT: Design of Improved Intertrochanteric Fracture Treatment
FE: finite element
FEA: finite element analysis
TAD: tip to apex distance

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Protocol

Mindfulness-Based Cognitive Therapy Experiences in Youth With Inflammatory Bowel Disease and Depression: Protocol for a Mixed Methods Qualitative Study

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Abstract

Background: Mindfulness-based programs are increasingly used as a part of integrated treatment for inflammatory bowel disease (IBD). However, the majority of research has been quantitative with limited qualitative exploration of patients' experiences of mindfulness programs and no studies among adolescents and young adults with IBD. Furthermore, there has been a paucity of research exploring the role of common psychotherapy and group factors within mindfulness programs.

Objective: This study aims to explore the experiences of adolescents and young adults with IBD and depression who completed a mindfulness-based cognitive therapy (MBCT) group program, as well as the role of therapeutic alliance, group affiliation, and other common psychotherapy and group factors.

Methods: This mixed methods qualitative study, nested within a randomized controlled trial (RCT) of MBCT for adolescents and young adults with IBD, will obtain qualitative data from focus groups and open-ended survey questions. The study aims to conduct three to four focus groups with 6-8 participants in each group. It will employ data and investigator triangulation as well as thematic analysis of the qualitative data.

Results: The study was approved by the Mater Hospital Human Research Ethics Committee and recruitment commenced in May 2019; study completion is anticipated by early 2020.

Conclusions: The study will contribute to the assessment of acceptability and feasibility of the MBCT program for adolescents and young adults with IBD. It will also elucidate the role of previously unexplored common psychotherapy and group factors within mindfulness training and help inform the design of a future large-scale RCT of MBCT in this cohort.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12617000876392; <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373115>

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KEYWORDS

mindfulness; inflammatory bowel disease; qualitative research; adolescents; young adults

Introduction

Background

Inflammatory bowel disease (IBD) is an immune-mediated condition characterized by chronic inflammation of the gastrointestinal tract, a relapsing and remitting course, and frequent systemic manifestations [1-3]. The peak age of onset is between the ages of 15 and 29, with wide-ranging implications in all areas of life, including relationships, education, and employment opportunities [4,5]. As a result of the high burden of illness in IBD, adolescents and young adults (AYAs) with IBD experience disruption at a crucial developmental stage with significantly impaired quality of life as well as rates of depression and anxiety two to three times higher than in the general population or among youth with other chronic diseases [6,7]. There is well-documented research evidence supporting the impact of depression on the course of IBD as well as the bidirectional relationship between IBD and depression, showing that they can both precipitate the onset and worsen the course of each other [8].

Mindfulness, Inflammatory Bowel Disease, and Depression

Mindfulness interventions are defined as therapeutic interventions based on core mindfulness principles; they contain various informal and formal practices, such as mindfulness of the breath, body scanning, mindful movement or yoga, and open or choiceless awareness. Mindfulness as a concept is described as a process of nonjudgmental, intentional awareness of one's internal and external reality, characterized by "paying attention in a particular way: on purpose, in the present moment and non-judgmentally" [9]. Mindfulness-based interventions have been increasingly trialed in IBD patients because of their potential to treat both depression and IBD [10,11], as well as attenuating immune system abnormalities, thereby improving the course of IBD [12,13]. Mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) are two manualized, 8-week group programs with strong evidence in the treatment of depression and anxiety that have been used successfully in integrated treatment of individuals with IBD [14-17]. The mindfulness-based cognitive therapy program used in this study is an 8-week group mindfulness program with weekly sessions of 2 hours, which contain a mixture of various cognitive skills and mindfulness practices. These are taught and practiced during the sessions as well as between sessions in home practices. The program closely follows the original MBCT curriculum designed by Segal, Williams, and Teasdale [18], adapted for both IBD and young adults. Modifications related to IBD include IBD-specific teaching content, such the role of stress in flares and gut-brain axis, as well as modified mindful movement practices with more restorative yoga and adapted postures for those with joint pain and perianal disease. Developmental modifications include shortened mindfulness practices, as AYAs often cannot sustain longer practices compared to adults; modified mindful movement practices, as AYAs often prefer mindful movement and yoga to body scanning and often prefer a slightly faster pace; fun postcards to help identify emotional states; and youth-friendly poetry.

Although mindfulness-based treatments have been used successfully in adults with IBD [14-17] and among AYAs with other chronic illnesses and depression [19-21], there have been no studies of mindfulness programs in AYAs with IBD. The majority of research has involved quantitative clinical trials investigating the impact of mindfulness training on psychosocial and disease-related parameters in individuals with IBD, with only one qualitative study exploring adult IBD sufferers' experiences of a mindfulness-based program [22]. Importantly, there have been no studies investigating mindfulness in AYAs with IBD.

We will therefore conduct a mixed methods qualitative study to explore experiences of MBCT in AYAs with IBD who are currently participating in the randomized controlled trial (RCT) of an IBD-focused and developmentally informed MBCT program; we will also explore the role of common psychotherapy and group factors in the MBCT program. The study will collect and analyze qualitative data from two different sources: focus groups and open-ended questions from the post-MBCT evaluation survey.

Common Psychotherapy Factors and Group Factors in Mindfulness Training

Common factors in psychotherapy are therapeutic elements that are common to diverse psychotherapies and are responsible for many of their therapeutic benefits [23,24]. These factors may account for relative therapeutic equivalence of outcomes for a range of psychotherapeutic models that are found in meta-analytic studies [23-29]. The notion of common factors was first introduced in 1936 in Rosenzweig's seminal paper, which outlined the therapeutic relationship, therapy rationale or ideology, and integration of subsystems of the patient's personality and the therapist's personality as key common factors present in all types of psychotherapies [23]. Common factors were subsequently expanded to include delivery of prescribed treatments or *rituals* [30] and *enactment* of adaptive or health-promoting actions [24]; factors were grouped into nonspecific common factors, such therapeutic alliance and expectations, and specific factors, such as exposure and sense of mastery [25,27]. It is likely that common psychotherapy factors operate within mindfulness programs as they, in addition to mindfulness skills training, contain reflective, exploratory, and supportive elements; mindfulness itself has been postulated as one of the core common factors in psychotherapy [31]. Despite this, there has been only one study to date exploring the role of common factors in mindfulness training [32] and no studies exploring group factors in mindfulness interventions.

Group factors are key psychotherapeutic factors that facilitate change in group therapies and include the following: instillation of hope, universality, imparting information, altruism or helping others in the group, corrective recapitulation of the primary family group through developing connections within the group, development of socializing through group communication, interpersonal learning, group cohesiveness or social affiliation, experience of relief associated with free emotional expression, and existential factors [33]. Although these group factors were initially considered specific to psychotherapeutic groups, it has since been accepted that they are present in most group settings,

including education and support groups [34,35], and they are likely to have a role within mindfulness groups.

Our decision to explore the role of common psychotherapy and group factors in mindfulness training was driven by an informed hypothesis of their potential role in mindfulness-based therapies, as well as consistent and recurrent feedback from MBCT group participants that the most important factors in their recovery were *mindfulness* and *friendship*. Many of the reported benefits were related to the common factors of exposure, mastery, and expectations. They also commented on their perceived positive impact of the therapy, the facilitator's skills, and their engagement to the group facilitator, which were consistent with common factors of therapeutic alliance and the therapist's personality. Their description of *friendship*, which they rated as the most important of all MBCT benefits, focused on a sense of belonging, social affiliation, and peer support. These experiences of *friendship* or *belonging* are in stark contrast to their pre-MBCT experience of feeling isolated with a chronic illness. Their description of *friendship* created within and outside of the MBCT group corresponded to the therapeutic group factors of social affiliation and engendering hope.

Objectives

The purpose of this study is to explore AYAs' experiences of a developmentally informed and IBD-focused MBCT group with a focus on their views of the program's benefits and acceptability, perceived barriers, and suggestions for further adaptation. A secondary objective is to investigate the role of therapeutic alliance, group affiliation, and other common psychotherapy and group factors within mindfulness training.

Methods

Study Design

This is a mixed methods qualitative study exploring experiences of AYAs with IBD participating in an MBCT program. This qualitative study is embedded within the RCT of an adapted MBCT program for AYAs with IBD and depression, which is described in detail in the study protocol [36]. The design adheres to the consolidated criteria for reporting qualitative research (COREQ) guidelines, a 32-item checklist for interviews and focus groups [37]. The study will use two different sources of qualitative data, including focus groups and free-text questions from the post-MBCT evaluation survey. Focus groups will be conducted and analyzed according to Krueger and Casey's focus groups guide [38]. An inductive thematic analysis approach will be used to analyze the qualitative data [39].

Rationale for Employing a Mixed Methods Qualitative Approach

Mixed methods research is defined as the use of different methodological approaches in a single study or a set of related studies, which are likely to create more meaningful and ultimately more useful data in answering the research questions [40]. In recent years, the concept of mixed methods research has been expanded to any research that combines different styles of research, not restricted to combining quantitative and qualitative methods. Mixed methods research is also known as "between research paradigm mixing" but may also include

"within research paradigm mixing." The latter can refer to mixing different qualitative approaches, such as qualitative interviews, participant observation, and qualitative documents, as well as mixing different quantitative approaches, such as quantitative surveys combined with quantitative experimental research [40,41].

We chose a mixed methods approach combining qualitative data from different sources, as previous research in this area has supported the use of focus groups in combination with surveys [22]. Focus groups also fit the study's dual purpose of evaluating the MBCT program through participants' views of its feasibility and acceptability, while exploring their experiences and views of common therapeutic and group factors within the mindfulness group. They are particularly well suited to understanding MBCT group experiences, given their permissive and inclusive group processes and nondirective interviewing techniques that facilitate expression of participants' views, attitudes, verbal and nonverbal interactions, and shared experiences [38,42]. Furthermore, focus groups may hold an advantage over individual interviews in that they can provide additional information through promoting group exchanges and self-disclosure in this cohort of young participants with similar backgrounds, as participants "tend to disclose more of themselves to those who resemble them in various ways" [38].

Combining qualitative data from focus groups and MBCT evaluation surveys, as well as using two researchers for coding and analysis, will ensure a rich dataset and facilitate data and investigator triangulation and thematic saturation, thus strengthening the study validity.

Recruitment and Sampling

Participants will be recruited from the 64 participants enrolled in the RCT of MBCT for AYAs with IBD and depression. Inclusion criteria will be participation in the RCT of MBCT for AYAs with IBD and completion of the MBCT course, defined as attendance at a minimum of five out of eight sessions of the program, the accepted benchmark for completion. We will also record the reasons for nonengagement among those who decline participation or drop out before completion; these will be collated and discussed in the final study report.

All the participants who completed the MBCT group program will be asked to complete a post-MBCT evaluation survey, which contains qualitative questions about their group experiences. They will also be invited to participate in the focus groups. Participants will be offered parking vouchers and public transport cards; focus groups will be conducted after hours to accommodate those studying or working.

As there will be four MBCT group programs conducted over 2 years, participants will provide their post-MBCT evaluation surveys upon completion of the MBCT group program; this qualitative data will be collated and analyzed following the last MBCT group program completion. Participants will also be invited to participate in focus groups upon completing the MBCT program and after completing the MBCT evaluation survey. The recruitment for focus groups commenced following the second MBCT group program completion in May 2019 to ensure sufficient focus group participant numbers. Focus groups

will be conducted between June and December 2019. Participants will be invited to participate in focus groups via face-to-face meetings, email, and phone, and those who express interest will meet with the research assistant who will explain the focus group process in more detail and will obtain consent.

Sampling will be purposive, in keeping with the definition of purposive sampling from the COREQ guidelines, which state that this “involves selecting participants who share particular characteristics and have the potential to provide rich, relevant and diverse data pertinent to the research question” [37]. Purposive sampling selects participants based on the study purpose, in contrast with convenience sampling, which selects participants based on “certain practical criteria, such as easy accessibility, geographical proximity, availability at a given time, or the willingness to participate” [43]. We are therefore selecting all participants who completed the MBCT program, as this is a characteristic relevant to our study purpose of exploring the experience of MBCT in AYAs who completed the program. Specifically, we will invite all the participants who completed the MBCT program to complete the MBCT evaluation survey and to participate in focus groups. The sampling for the focus groups will also be consecutive; it will proceed until the desired number of participants have been recruited to conduct a sufficient number of focus groups in order to achieve thematic saturation. We envisage running three to four focus groups of 6-8 participants in each. This size of focus group is consistent with the recommended number of

participants for clinical focus groups to accommodate for the clinical nature of the group; facilitate moderation and expression of individual opinions; and provide rich, but not overwhelming, data [39,44,45]. Therefore, our proposed group size of 6-8 participants is in keeping with these generally accepted recommendations and fits the nature of our clinical sample. The recommended number of focus groups varies depending on the purpose of the research, group homogeneity, and use of additional sources of qualitative data, with most guides proposing that three to four focus groups are likely to be sufficient to achieve across-group analysis and thematic saturation [38,44,45]. Our proposed number of focus groups and their size is consistent with these recommendations and, therefore, likely to provide us with a sufficient sample size to achieve thematic saturation.

Development of Questioning Route for Focus Groups

We followed Krueger and Casey’s recommendations in developing the questioning route by creating questions that are clear, engaging, and likely to evoke conversation among the participants [38]. Our questioning route contains a mixture of open-ended and more targeted questions about participants’ group experiences. We also created questions regarding their views on the role of common psychotherapeutic factors (eg, engagement with and the role of the group facilitator) and affiliation with peers in the same age group with the same medical condition. The questioning route for focus groups is summarized in [Textbox 1](#).

Textbox 1. Questioning route for inflammatory bowel disease (IBD) focus groups.

Purpose: Thank you for coming. The purpose of this group is to understand your experience of participating in the IBD mindfulness study. We want to know what it was like for you. There are definitely no “right” or “wrong” answers. It’s all about how you found it. Please feel free to share your point of view even if it differs from what others have said.

We will be recording today’s session so that we can transcribe it later. All names and any identifying information will be removed from any publications. You won’t be identified in any way.

You can take a break at any stage, please just let me know.

Does anybody have any questions? OK, well let’s go...

Question 1. To start with, can you say who you are and when you started practicing mindfulness/completed the MBCT group.

Question 2. What was the group like for you?

Question 3. What was it like being in a group with other young people that live with inflammatory bowel disease (IBD)?

Question 4. How did you find the facilitator?

Question 5. Which components of the MBCT program did you find the most/least beneficial and why (ie, body scanning, mindfulness of the breath, mindful movement, homework, or teaching)?

Question 6. If there is one thing you’re taking away from this group, what’s that?

Question 7. Let’s say you never did this group. Where would you be now?

Question 8. Would you recommend this group to someone else?

– What if they said, “I’m too nervous”?

Question 9. Is there anything you did not like, or that you think we should do differently?

Question 10. All things considered, of all issues that we’ve discussed today, what do you consider to be the most important?

Question 11. Have we missed anything?

Question 12. Summary question (after a brief oral summary): Is this an adequate summary?

Focus groups will be conducted in a facility purposefully designed for focus group interviewing, with equipment for audiotaping and a viewing room allowing observers to unobtrusively watch the interviews through a one-way mirror. Each focus group will last from 1 to 2 hours. Focus groups will be run by the moderator and an assistant, with an observer behind the one-way mirror. The observer and the assistant will observe participants' verbal and nonverbal interactions that may be missed by the moderator who is immersed in running the focus group; they will also take notes of relevant quotes, key points, ideas, and themes.

The moderator (AH) is a psychologist whom most of the participants have not met prior to the focus groups. The assistant is the study research assistant with a degree in public health, and the observer (TE) is the study principal investigator who is a psychiatrist by training. Participants will meet the research assistant and the observer during the RCT recruitment.

The moderator will follow the questioning route guide and facilitate discussion relevant to the study purpose. As soon as the focus group is finished, the moderator, assistant, and observer will meet outside the room to discuss any additional observations and decide on asking any follow-up questions. For instance, it may be that the observer or assistant notice that a participant was interrupted while raising an interesting point. In such cases, the facilitator will return and ask a follow-up question. These additional observations and questions will be included in the follow-up research team meetings and potentially provide a richer dataset.

Participants will be given the opportunity to review focus group transcripts. They will be provided with the results of preliminary analysis and given the opportunity to comment. At the end of the study, a summary of the study findings will be given to all participants.

Mindfulness-Based Cognitive Therapy Evaluation Survey

Upon conclusion of the 8-week MBCT program, all participants who completed the course will be asked to fill out the post-MBCT evaluation survey (see [Multimedia Appendix 1](#)). The survey contains a mixture of closed-ended and open-ended free-text questions exploring participants' experiences, expectations, perceived barriers, and benefits, as well as suggestions for program improvement. Surveys are a commonly used method in health research, and qualitative analysis of free-text open-ended survey questions has been recognized as an important tool in providing valuable insights into participants' views and experiences [46,47]. Open-ended survey questions complement the focus group questions and combining their qualitative data in thematic analysis will provide a richer dataset and strengthen the study validity.

Data Analysis

Focus groups will be audiotaped and transcribed verbatim. Qualitative data from focus groups and open-ended survey questions will be analyzed using thematic analysis [39]. Thematic analysis has been chosen because it is a flexible qualitative research method for identification, analysis, and reporting of key themes and subthemes within data that can

highlight similarities and differences within the data and generate insights [39]. Furthermore, an inductive thematic analysis approach will suit the exploratory nature of our study.

Analysis will start with two research team members—moderator and observer—who will first familiarize themselves with the data through reading and rereading of the collected data. They will individually and separately develop initial codes based on emerging clusters of statements. The coding process will follow the recommendations outlined in Saldaña's Coding Manual for Qualitative Researchers [47] in that the researchers will develop and test the codes in two cycles. Initial codes will be developed in the first coding cycle and tested on the subsection of data to eliminate any overlapping codes, refine the existing codes, and introduce any new codes. The second coding cycle will further refine and highlight salient features of the codes to facilitate subsequent generation of categories, concepts, and themes. The final codes will be independently applied to the full dataset by the two researchers and discussed until an agreement is reached on the interpretation. The analysis and grouping of the codes will enable identification of categories, followed by analysis and comparing of the major categories, leading to emergence of relevant themes and concepts.

The researchers will work iteratively and inductively with the data until distinct themes develop and no new themes emerge (ie, thematic saturation is achieved). The emerging themes will be discussed among the investigators to achieve triangulation and ensure that all relevant data are captured. Further triangulation will be achieved by combining different sources of data: focus groups transcripts and open-ended free-text qualitative questions from the post-MBCT evaluation survey. Representative quotes will be used to illustrate the codes and themes.

Results

This study was funded by the Brain-Injured Children's Aftercare Recovery Endeavours (BICARE) project grant in January 2018 and approved by the Mater Hospital Human Research Ethics Committee. Recruitment commenced in May 2019; completion of the qualitative data analysis and results are anticipated by early 2020.

Discussion

There is a paucity of qualitative studies investigating mindfulness program participants' experiences among the IBD population, despite a multitude of quantitative trials exploring the efficacy of mindfulness programs in treating IBD-related psychosocial comorbidities and their impact on the course of IBD. The only study to date of MBCT experiences among individuals with IBD was conducted in adults and focused predominantly on participants' views of the MBCT program's barriers and benefits [22]. Furthermore, there has been only one study to date investigating the role of common factors in mindfulness interventions [32] and no studies exploring the role of group factors in mindfulness-based interventions.

To our knowledge, this mixed methods qualitative study will be the first to use a more inductive approach to explore

participants' MBCT experiences and the only study conducted in AYAs with IBD. This study will also be the first to investigate the role of therapeutic alliance, sense of mastery, group affiliation, and other common psychotherapy and group factors within mindfulness training. It will employ thematic analysis of qualitative data from focus groups and open-ended qualitative survey questions. The study will fulfil the dual purpose of

exploring the experiences, feasibility, and acceptability of the MBCT program among AYAs with IBD, as well as providing greater understanding of the role of common psychotherapeutic and group factors within the mindfulness program.

The study findings will facilitate interpretation of the results of the RCT of MBCT in AYAs with IBD and will help inform the design of a future large RCT of MBCT in this patient cohort.

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Authors' Contributions

The protocol and manuscript were drafted by TE, with assistance from SK, MK, JB, and AH. All authors read and revised the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1

The mindfulness-based cognitive therapy group evaluation survey.

[[DOCX File, 16KB - resprot_v8i7e14432_app1.docx](#)]

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Abbreviations

AYAs: adolescents and young adults

BICARE: Brain-Injured Children's Aftercare Recovery Endeavours

COREQ: consolidated criteria for reporting qualitative research

IBD: inflammatory bowel disease

MBCT: mindfulness-based cognitive therapy

MBSR: mindfulness-based stress reduction

RCT: randomized controlled trial

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Protocol

Community-Directed Bacterial Sexually Transmitted Infection Testing Interventions Among Men Who Have Sex With Men: Protocol for an E-Delphi Study in Toronto, Canada

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Abstract

Background: HIV-positive and HIV-negative (gay, bisexual, and other) men who have sex with men (MSM) have experienced a dramatic increase in bacterial sexually transmitted infections (STIs)—syphilis, gonorrhea, and chlamydia. STI testing and treatment mitigate adverse health outcomes and substantially reduce transmission; yet, testing rates remain below recommended levels. Innovation is needed to produce the required increases in testing levels, frequency, and the use of appropriate testing technologies in ways that are engaging, nonstigmatizing, and acceptable to men.

Objective: The aim of this study is to build consensus with regard to interventions with the greatest potential for improving local STI testing services for MSM communities in Toronto, Canada.

Methods: Following a literature review of evidence regarding the effectiveness of novel testing interventions, and focus groups, and surveys to describe local barriers and facilitators of testing among MSM, we will conduct a Web-based, modified Delphi study (e-Delphi). We will form expert panels of community members and STI test providers. Panelists will rate potential interventions in terms of their priority, using a 7-point Likert scale from *definitely not a priority* to *definitely a priority*. They will also rank their preferences by selecting their top 3 preferred interventions. Surveys will be distributed in 3 rounds, with feedback on the distribution of responses from preceding rounds provided in rounds 2 and 3. We will define consensus as having $\geq 60\%$ (18/30) members indicate a preference within 2 adjacent response points. Qualitative data on disagreements will be obtained using open-ended text responses to explain for ratings and rankings that are different from the majority.

Results: On the basis of a literature review and identification of barriers and facilitators to STI testing among community members and test providers in Toronto, we have selected 8 potential interventions for inclusion in the e-Delphi panel surveys.

These include 4 interventions that streamline STI testing for asymptomatic individuals, 2 interventions that are targeted at clients and 2 interventions that are targeted at providers.

Conclusions: Findings will provide community direction for informed decision making regarding the implementation of STI testing interventions in this setting. They will characterize the intervention climate for innovation to STI testing services, including perceived needs for changes to test delivery, relative priorities for change, and readiness for implementation. These methods may be transferable to other urban jurisdictions experiencing similar epidemics and for other contexts where stakeholder input is needed to manage sensitive areas of concern.

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KEYWORDS

sexual and gender minorities; sexually transmitted diseases; community-based research; mass screening; patient acceptance of health care

Introduction

Delphi Studies

Delphi studies are a valuable approach for building consensus around an issue where little knowledge or agreement previously existed [1]. They use “structured anonymous communication between experts...to gather consensus perspectives about an issue or topic that can then be...used to inform decision making” [2]. Traditionally applied using an *in person* format, this design is increasingly being adapted for Web-based environments. Briefly, the Web-based modified Delphi study (*e-Delphi*) involves rounds of Web-based questionnaires in which experts are asked to provide their opinion on particular topics [1,3]. Initially this is done independently, but in subsequent rounds, experts are made aware of the opinions of the group when making their decisions, with the goal of reaching consensus. The key features of the e-Delphi methods are that they are iterative and anonymous, which are particularly beneficial for community-based and patient-oriented research [2,4]. Anonymity and the Web-based format encourage opinion sharing from all panel members, thus preventing dominant individuals from controlling discussion; this is important within hierarchical environments involving the health care system [2,4].

Bacterial Sexually Transmitted Infections

We will adapt the e-Delphi method to learn community perspectives to address a pressing health care system issue in our setting: the rise of bacterial sexually transmitted infections (STIs)—specifically syphilis, gonorrhea, and chlamydia. These infections pose a heavy burden on population health, with most cases occurring among HIV-positive and HIV-negative gay, bisexual, and other men who have sex with men (MSM) [5-9]. Untreated syphilis may progress to neurosyphilis, in which symptoms such as meningitis or dementia may develop [10]. Globally, public health agencies are pressing for increased vigilance of antibiotic-resistant gonorrhea strains [11,12]. Certain serovars of *Chlamydia trachomatis* may cause Lymphogranuloma venereum with painful proctitis and rectal bleeding. Unlike HIV, these STIs can easily transmit via oral sex [13]. In 2014, there were 109,263 chlamydia, 16,285 gonorrhea, and 2357 syphilis cases reported in Canada, much greater than a decade earlier [14]. The true counts are *even*

higher, as many cases are asymptomatic and go unreported. Gonorrhea and syphilis rates have dramatically increased among males in the province of Ontario, with nearly all syphilis cases and approximately 40% of gonorrhea cases among MSM and >40% of syphilis cases among HIV-positive MSM [15,16]. We have documented that 23% of HIV-positive MSM have had syphilis, and new infections occur at minimum rates of 1 gonorrhea, 1 chlamydia, and 4 syphilis cases per 100 person years [5-8]. Most cases occur in the city of Toronto, with no signs of a decline [17-19]. Within Toronto, the syphilis epidemic is mature and not restricted to a core sociodemographic group among MSM [8,20], requiring broadscale approaches for control.

STI testing and treatment could mitigate adverse health outcomes and substantially reduce population-level transmission among MSM [21]. However, innovation is needed to produce the required increases in testing levels, frequency, and the use of appropriate testing technologies in ways that are engaging, nonstigmatizing, and acceptable to men. Canadian STI Guidelines recommend annual screening for bacterial STIs among sexually active MSM and as frequently as every 3 months for individuals at *ongoing risk for STIs* [13]. Unfortunately, there are suboptimal levels of STI testing and frequency of testing among MSM in Toronto. STI testing patterns are best known for HIV-positive MSM. In 2009, 55% had tested for syphilis, on average, once per year [8]. As of 2013, we observed only a modest increase to 64% being tested annually, with a few testing more frequently than once per year [22]. Testing rates for chlamydia and gonorrhea are lower than those for syphilis [7,23]; from 2010 to 2013, only 25% of HIV-positive MSM tested annually for genital infection using urine-based tests. Few MSM undergo extragenital testing for gonorrhea and chlamydia, despite Canadian and international guidelines [7,12,23-27]. Without rectal and pharyngeal tests, 71% to 100% of cases will be missed [28,29].

We describe herein our plans to conduct an e-Delphi study as part of a larger mixed-methods study that aims to identify bacterial STI testing interventions for implementation and evaluation among MSM in Toronto. We will assemble 2 expert panels: the first with community members with lived experience as MSM seeking STI testing, and the second with health care providers and public health professionals with expertise in providing STI testing for MSM communities in our setting. Our

objective is to build consensus regarding intervention(s) with the greatest potential for improving local STI testing services.

Methods

All procedures have been reviewed and approved by the research ethics boards of St Michael's Hospital, Toronto, and the University of Toronto.

Setting

Toronto is a metropolitan city with a population size of 2.71 million in the province of Ontario [30]. All residents with citizen, permanent resident, refugee, and refugee claimant status have access to provincial or federal health insurance for medically necessary services. STI testing services are available from a variety of sources, including primary care practices, specialist services, or dedicated sexual health clinics.

Knowledge Synthesis to Select Candidate Interventions

To select STI testing interventions for primary inclusion in the e-Delphi panel, we undertook a review of the published literature [31]. To further refine the interventions, we conducted focus groups with MSM STI testing clients [32] and surveyed health care providers [33] in Toronto. Briefly, the focus groups were conducted with HIV-positive, HIV-negative, and trans-identified men (of any HIV serostatus) to identify barriers and facilitators to bacterial STI testing. Health care providers were surveyed about their current practices, barriers, and attitudes to improve bacterial STI testing rates. Manuscripts for these findings are in preparation.

Literature Review

For our literature review, systematic reviews published in 2016 were used as a baseline and updated. These reviews summarized evidence for the effectiveness of STI control interventions, including screening in and outside clinic-based settings published in 2000 or after [24,34]. In addition to repeating the 2016 searches, we expanded literature searches in MEDLINE

up to April 2017 using the following keywords: sexually transmitted diseases/STI, chlamydia, gonorrhea, or syphilis. Inclusion criteria for our search were that the article described an intervention aimed at increasing bacterial STI testing; used high-income country settings in urban or semiurban cities; had a study population that included men; and used a study design that was either a trial with a comparison group (controlled, uncontrolled, or pre-post historical controls) or an observational design if it was set in Canada, focused on MSM, or described a Web-based STI testing service. Publications were ineligible if they included only women or heterosexual couples or if they were a study protocol.

Next, we classified the interventions into 3 categories: (1) streamlined testing for asymptomatic individuals, (2) interventions targeted toward clients, and (3) interventions targeted toward providers (Table 1). We use the term *clients* to refer to users of STI testing services, whether or not they are experiencing signs or symptoms of an STI. Using the same strategy as Taylor et al [34], examining outcomes in increasing the proportion tested or increasing frequency of testing, interventions with a comparison group were categorized as very effective (absolute difference (AD) $\geq 20\%$ or relative difference (RD) $\geq 100\%$), moderately effective (AD 5%-19% or RD 10%-99%), or ineffective (AD $< 5\%$ or RD $< 10\%$). Classifications and categorizations were done by JR and verified by ANB. A complete list of the publications used for the final selection of interventions can be found in Multimedia Appendix 1.

The investigators then reviewed the above findings in a series of meetings and selected promising interventions for the Toronto setting to be included in the Delphi panel exercise. Our selection focused on novel approaches for testing rather than efforts that would reinforce existing STI test practices (eg, patient or provider education alone). To minimize respondent burden for panelists, choices are limited to 6 (for community panelists) or 8 (for provider panelists) intervention options.

Table 1. Categories of interventions.

Category	Definition
Streamlined STI ^a testing for asymptomatic individuals	Interventions that focus on testing asymptomatic individuals with a focus on collection of specimens and reducing the time patients spend in clinics
Client-targeted STI testing interventions	Interventions that are targeted at clients to increase client engagement in STI testing
Provider-targeted STI testing interventions	Interventions that are targeted at health care providers to increase provision of STI testing

^aSTI: sexually transmitted infection.

Recruitment of E-Delphi Panelists

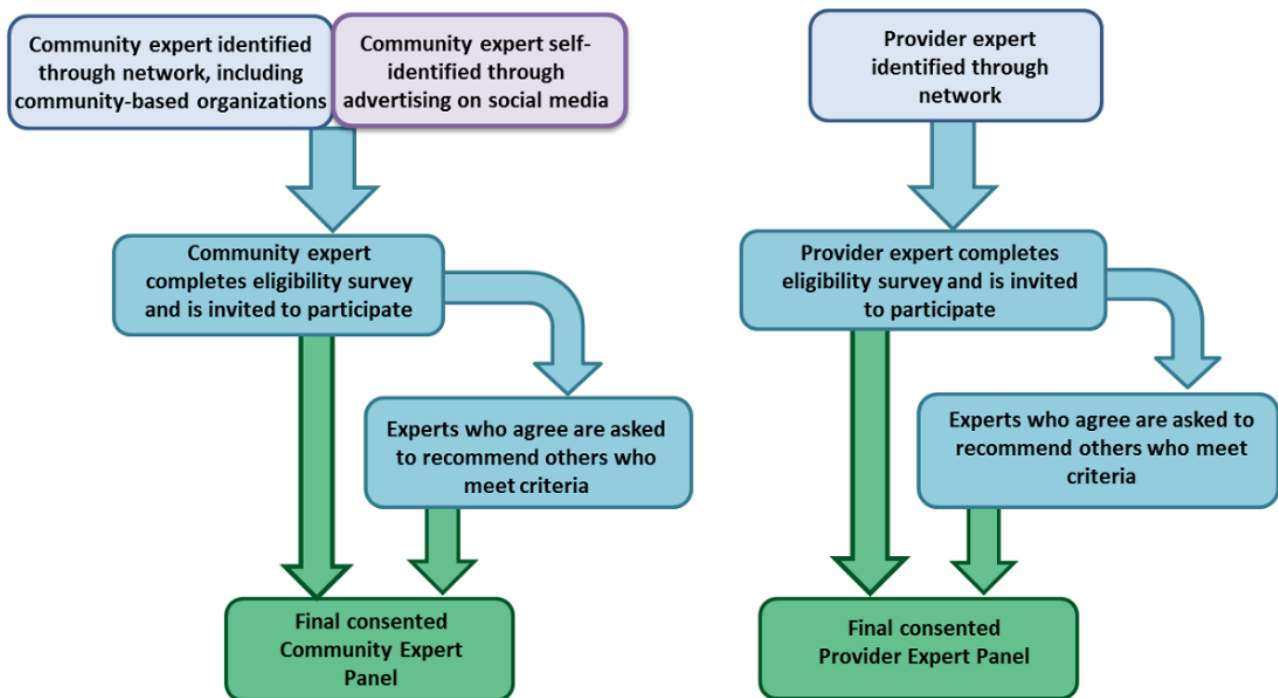
In our application of the e-Delphi method, the term *expert* is meant to include persons with lived experience alongside health care professionals. We will form 2 panels: the first with community members with lived experience as MSM, seeking STI testing in Toronto (*Community Experts*), and the second with health care providers and public health professionals with expertise in providing STI testing for MSM communities in Toronto (*Provider Experts*). We opted to recruit these 2 panels separately, rather than combined, as it was of interest to identify differences in prioritized interventions between the 2 groups,

if these exist, rather than forcing consensus between community and provider experts.

To be eligible for the Community Panel, candidates (1) must be a cis- or trans-identified man aged 18 years and older, living in Toronto, and who has sex with men in the preceding 18 months and (2) must have sought and/or underwent STI testing in Toronto in the preceding 18 months.

To be eligible for the Provider Panel, candidates must have a minimum of 1-year experience providing STI testing and management care in Toronto.

Figure 1. Flowchart for recruitment of community and provider expert panel. Left: To be eligible for the Community Panel, candidates (1) must be a cis- or trans-identified man aged 18 years and older, living in Toronto, and who has sex with men in the preceding 18 months and (2) must have sought and/or undergone sexually transmitted infection testing in Toronto in the preceding 18 months. Right: To be eligible for the Provider Panel, candidates must have a minimum of 1-year experience providing sexually transmitted infection testing and management care in Toronto.



The choice of experts for an initial invitation will be informed by our team's community and professional networks. Experts who agree to participate will be encouraged to refer other eligible experts, mitigating potential bias from our team's selection of members.

Using the approach shown in Figure 1, invitations will be informed by our team's community and professional networks. Community participants will also be recruited via the existing social media channels (eg, Facebook and Twitter) of our community-based partner and through paid banner advertisements on popular gay dating apps (eg, Grindr). In addition, targeted emails will be sent to other organizations that serve the MSM community, including AIDS Service Organizations that cater to specific ethnoracial groups. These methods were successfully used in the recruitment of MSM for the focus groups and other studies conducted by our community-based partner [32]. Providers will be recruited using targeted emails to health care organizations known to serve large MSM patient populations, as we have done previously in our provider survey [33]. We aim to recruit a minimum of 30 experts with diverse backgrounds (including ethnoracial identity, gender identity, sexual orientation, and age) for each panel—feasible and sufficient for a Delphi study [2-4,35]. For community panelists, we have set target goals to recruit a minimum of 40% to be men aged ≤ 40 years and 40% to identify as non-white race/ethnicity.

Recruitment email invitations, social media, and dating app advertisements will include a link to an eligibility survey.

Interested participants will need to complete the eligibility survey to identify those who meet the inclusion criteria. This step serves to minimize false participation. Eligible participants will then be sent a consent form to provide an email address or a phone number to receive the e-Delphi surveys. This information is not linked to the survey responses.

E-Delphi Methods

The online surveys for each round of the e-Delphi will be delivered through Qualtrics (Provo, United States). Qualtrics is a secure Web-based survey platform and allows for anonymous participation. All data collected in Qualtrics will be stored in Canada and are protected with high-end firewalls and are treated confidentially. We will own and manage all the data collected via Qualtrics. All identified and interested members of the expert panel will be sent a personalized link to fill out each round of the survey. Although a personalized link will be used to access the survey, personal information will not be stored, and contact details will be removed in the completed survey.

Rounds

In the first round, panelists will review and consider the selected STI testing interventions. The preamble for each intervention will include a brief description and a list of considerations; panelists will also be given the opportunity to provide their opinion in an open text field. Panelists will be asked to rate each bacterial STI intervention on a 7-point Likert scale: 1=*definitely not a priority*, 2=*not a priority*, 3=*somewhat not a priority*, 4=*undecided*, 5=*somewhat of a priority*, 6=*a priority*,

7=*definitely a priority*. An open text field will be available for panelists to explain their priority choice. Finally, panelists will be invited to suggest an alternative STI testing intervention that was not listed but that they believe to be important. Panelists will also report their sociodemographic characteristics, specifically age, race/ethnicity, transgender identity, sexual orientation, and HIV serostatus (optional).

In the second round, panelists will be asked to prioritize the same interventions they considered in round 1. However, this time they will see the distribution of responses from the previous round (eg, the proportions of persons selecting each of the Likert scale options), as well as a summary of the rationale for prioritizing that particular intervention. Those who select a priority rating that does not agree with the majority will be asked to provide details for their choice with an open text field question, such as the following example: “Most guys chose an Online App for Booking Bacterial STI testing as ‘A priority’. Why did you not prioritize this option?”. Panelists will also be asked to rank their top 3 interventions that they consider the highest priority. If consensus is achieved after round 2, then that intervention option will be removed for round 3 prioritization (although they would still be included as options for respondents’ top 3 ranked interventions).

In round 3, panelists will again rate and rank the interventions alongside summaries of the prioritization and ranking responses from round 2, that is, they will have a third chance to rate interventions and a second chance to rank them. Those who rank a bacterial intervention component different from the majority will be asked to provide details for their choice with an open text field question: “One or more of your responses is a different priority than the other experts, please explain why you chose your response.”

Compensation

Each survey round will be accessible for 2 weeks, with 1-week breaks to conduct the analyses and provide response summaries for the subsequent round. To encourage retention throughout, we will provide increasing incentives at rates of Can \$25, \$35, and \$40 for completion of rounds 1, 2, and 3 (total Can \$100 for all 3 rounds), respectively. To receive this compensation, panelists will be provided with a link at the end of their survey which will take them to a reimbursement form to fill in contact information. The contact information will be collected and stored separately from study data and is asked for the purposes of reimbursement only.

Analysis

The analysis of responses from each round will occur iteratively and independently for the Community and Provider panels. The primary purpose is to achieve consensus within each of the panels to identify which subset of the proposed 8 interventions have the greatest potential for increasing testing levels among

MSM in Toronto. As there is no standard definition of consensus for Delphi studies [35], we will define consensus as having $\geq 60\%$ members ($\geq 18/30$) indicate a preference within 2 adjacent response points (± 1) on a 7-point Likert scale. We will supplement the quantitative analyses with a thematic analysis of open-ended text data [36,37] to better understand disagreements within and between panels, should this occur. The top 3 ranked interventions will be determined based on frequency counts.

Results

Progress to date includes knowledge synthesis and selection of candidate interventions for the e-Delphi surveys. In our updated literature review, we identified 246 publications, of which 88 were in the original published systematic reviews [24,34]. After applying our inclusion and exclusion criteria, 203 publications were excluded because of the following reasons: (1) the article did not describe an intervention aimed at increasing bacterial STI testing ($n=176$), (2) the intervention was implemented in a rural setting ($n=1$), (3) the study population included only women or heterosexual participants ($n=22$), and (4) study protocol of intervention ($n=4$).

In our final review, we included 43 publications describing 49 interventions. The largest number of publications were from Australia ($n=15$). Only 2 publications were from Canada. Effectiveness was categorized for these 49 interventions (Multimedia Appendix 1). A total of 37 interventions were deemed effective, with 24 moderately effective and 13 very effective.

In the category of streamlined testing among asymptomatic individuals, routine testing was the predominant intervention, with all 9 effective, followed by Web-based or home-based testing, with 6 out of 7 effective. A total of 8 effective interventions in this category incorporated testing of extragenital sites for chlamydia and gonorrhoea, with 7 employing self-collection of anal swabs.

In the category of the client-targeted interventions, the most common intervention was client reminders, with 6 of 8 being effective, followed by 3 effective client counseling interventions. Both client incentive interventions ($n=2$) were ineffective.

In the category of the provider-targeted interventions, audit and feedback ($n=2$) and provider alerts ($n=2$) were effective. The effectiveness of provider education interventions was variable with 1 very effective and 1 ineffective study.

On the basis of the above evidence for effective interventions and emerging findings from our focus groups and provider survey, we selected the following interventions and their rationales for inclusion in the e-Delphi surveys (Table 2).

Table 2. Descriptions and rationale for interventions.

Category and intervention	Description	Rationale for inclusion	Summary of effectiveness
Streamlined testing among asymptomatic individuals			
Routine testing	Clients are tested at every visit using standing orders.	Routine STI ^a testing was effective in improving STI testing rates in all 9 studies identified by reducing stigma and normalizing testing.	Very effective: 5/10 studies [38-42]; Moderately effective: 4/10 studies [43-46]; Unknown effectiveness: 1/10 studies [47]
Web-based/home-based testing	STI tests are ordered on the Web, client can opt for in-person lab testing or mailed self-testing kits.	Web-based or home testing was effective in improving STI testing rates in most studies, identified by increasing convenience and reducing the need to see a health care provider.	Very effective: 2/11 studies [48,49]; Moderately effective: 4/11 studies [50-53]; Ineffective: 1/11 studies [54]; Unknown: 4/11 studies [55-58]
Nurse/nonphysician-led testing	A health care provider who is not a doctor (such as a nurse) collects information on a client's sexual history and symptoms and collects samples.	A total of 2 identified studies demonstrated that having nurses provide testing is effective in improving STI testing rates with reducing the need to see a doctor and increased convenience.	Moderately effective: 2/2 studies [59]
Express testing at clinics with self-collection of sample	On the basis of a self-completed questionnaire on sexual history and symptoms, clients are directed to self-collected testing if asymptomatic.	Express testing was effective in improving STI testing rates in 1 study by increasing convenience and reducing the need to see a health care provider.	Moderately effective: 1/2 studies (express clinic with self-collection of some specimens) [60], 1/2 studies (self-collection of samples in clinic) [61]
Client-targeted			
Client reminders	Client gives permission to clinic to receive reminders via short message service text message, email, or mailed letter.	Client reminders were effective in improving STI testing rates in most studies identified. Clients are notified to test, and it becomes part of the health care routine.	Very effective: 4/9 studies [62-65]; Moderately effective: 3/9 studies [66-68]; Ineffective: 1/9 studies [69]; Unknown effectiveness: 1/9 studies [70]
Web-based educational and testing booking app	Clients find information about bacterial STIs on an app/website and use it to book an appointment at a clinic.	A Web-based personally controlled health system manager was effective in improving STI testing rates by increasing knowledge and convenience.	Moderately effective: 1/1 study [71]
Provider-targeted			
Provider audit and feedback	Providers receive a report on their own STI testing practices.	Providing feedback reports on STI testing rates was effective in improving STI testing rates by identifying good performance and areas to improve.	Very effective: 1/2 studies [72]; Moderately effective: 1/2 studies [73]
Provider reminders	Providers receive alerts through electronic medical record systems to prompt an offer of STI testing.	Provider reminders to test clients at increased risk of STI acquisition were effective in improving STI testing rates by notifying provider to offer STI testing.	Moderately effective: 2/2 studies [74,75]

^aSTI: sexually transmitted infection.

Discussion

Overview

By conducting an e-Delphi exercise with community members and providers in Toronto, Canada, we will produce evidence to allow for community-directed, informed choices regarding the implementation of novel STI testing interventions for MSM. To maximize the chances for successful implementation, we first need to better understand the barriers to access testing and

the intervention contexts in other settings, then work with community partners to determine which candidate intervention(s) would best overcome these barriers and how they may need to be adapted for the local context. Interventions must be acceptable to members of communities that they intend to serve [76]. Our choice of the e-Delphi method to prioritize potential interventions allows community members to have an equal voice alongside professional stakeholders.

Our plan is not without potential pitfalls. One challenge was selecting interventions for consideration by panelists. Our choices were based on an extensive literature review and qualitative and quantitative data on local patient and provider barriers and facilitators for STI testing. Nevertheless, it is possible that we overlooked or excluded interventions that could be effective in our setting. A second challenge is ensuring diversity in representation among members of the Community and Provider panels, as MSM communities are particularly heterogeneous in large urban cities, such as Toronto. We will seek out as representative a sample as possible to identify diverse perspectives but acknowledge that the opinions of panelists are unlikely to capture all possible views within a small sample size. Motivated panelists are crucial to ensure carefully considered ratings and high response and retention throughout the rounds. We will maximize input by limiting the number of questions asked and providing increasing incentives for completing each round. The potential for false participation is a concern (eg, participation by individuals pretending to meet the inclusion criteria), particularly for the establishment of the Community Panel. Procedures will minimize false participation including study promotion and direct invitations via established MSM community channels, an eligibility questionnaire step as we form the panel (without compensation), and a sliding scale

of compensation, such that the highest amount is provided for completion of the third and final questionnaire. Finally, consensus may not be reached at the end of the 3 rounds within and between each expert panel. However, in conducting the Delphi panels, we will gain a better understanding of the interventions with the greatest potential for improving local STI testing services for MSM in Toronto and be better positioned to anticipate potential roadblocks to implementation.

Conclusions

Innovative approaches to health care delivery are needed to produce the required increases in bacterial STI testing levels, frequency, and the use of appropriate testing technologies in ways that are engaging, nonstigmatizing, and acceptable for MSM [21]. Many community- and clinic-based bacterial STI test interventions have demonstrated effectiveness in the international literature [24,34] and/or are being attempted as pilot projects in Canada [22,55]. Yet the choice of intervention to implement can be daunting without local evidence regarding the best fit. The results of the proposed e-Delphi will characterize the intervention climate including perceived needs for changes to test delivery, relative priorities for change, and readiness for implementation [77]. Our approach may be transferable to other settings where stakeholder input is needed to manage sensitive areas of concern.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Effectiveness of 49 interventions from 43 articles.

[PDF File (Adobe PDF File), 651KB - [resprot_v8i7e13801_app1.pdf](#)]

Multimedia Appendix 2

Peer-reviewer report from the Canadian Institutes of Health Research.

[PDF File (Adobe PDF File), 448KB - [resprot_v8i7e13801_app2.pdf](#)]

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Abbreviations

AD: absolute difference

CIHR: Canadian Institutes of Health Research

MSM: men who have sex with men

RD: relative difference

STI: sexually transmitted infection

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Corrigenda and Addenda

Corrigendum and Editorial Warning Regarding Use of the MMAS Scale (The Ready to Reduce Risk (3R) Study for a Group Educational Intervention With Telephone and Text Messaging Support to Improve Medication Adherence for the Primary Prevention of Cardiovascular Disease: Protocol for a Randomized Controlled Trial)

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Authors' Corrigendum

The authors of "The Ready to Reduce Risk (3R) Study for a Group Educational Intervention With Telephone and Text Messaging Support to Improve Medication Adherence for the Primary Prevention of Cardiovascular Disease: Protocol for a Randomized Controlled Trial" [*JMIR Res Protoc* 2018;7(11):e11289] require corrections in relationship to the use of the Morisky Medication Adherence Scale (MMAS-8).

The following text was omitted from the Acknowledgements and as a footnote in Table 1 and should be added:

Use of the MMAS is protected by US and International copyright laws. Permission for use is

required. A license agreement is available from: Donald E Morisky, MMAS Research (MORISKY), 294 Lindura Court, Las Vegas, NV 89138-4632; dmorisky@gmail.com.

Two additional references should be cited after reference 37 in the following sentences:

- In addition, the self-reported 8-item Morisky Medication Adherence Scale (MMAS) was completed at baseline and 12 months. This is an established and validated scale that is commonly used to measure adherence [37].
- Self-report: 8-item Morisky Medication Adherence Scale (MMAS) [37].

- Therefore, we have also used a self-reported validated questionnaire (MMAS) [37] and repeat prescription history as supporting outcome measures.

The references to be cited are:

- Berlowitz DR, Foy CG, Kazis LE, Bolin LP, Conroy MB, Fitzpatrick P, SPRINT Research Group. Effect of Intensive Blood-Pressure Treatment on Patient-Reported Outcomes. *N Engl J Med* 2017 Dec 24;377(8):733-744.
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These have become references 50 and 51, respectively, and all subsequent references have been renumbered accordingly.

The correction will appear in the online version of the paper on the JMIR website on July 24, 2019, 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 also has been resubmitted to those repositories.

Editorial Notice

Authors and journal had to publish this correction due to legal threats by Steven Trubow and Donald Morisky from the

company MMAS Research LLC, the copyright holder of the instrument. This is unfortunately not an isolated case, as the developers of this scale are known to comb the literature and ask those who used the scale for research to pay for a retroactive license which may cost thousands or tens of thousands of dollars, and to add references to their work [1]. This is now the fourth correction JMIR has to publish related to studies using the MMAS instrument [2-4].

The Committee on Publication Ethics (COPE) has recently discussed the ethics of this type of behavior by copyright holders of scales (“holding authors to ransom in this way”) and recommends to emphasize “the fact that this is not good for the advancement of scientific knowledge or in the public interest” [5]. As open access and open science publisher we remind our authors of our policies and preference for public and free availability of research tools, including questionnaires [6]. We actively discourage use of instruments which are not available under a Creative Commons Attribution license, and encourage our authors to use or develop/validate new instruments. We continue with our special call for papers for short paper instruments or electronic tools licensed under Creative Commons or available under an Open Source license that can be used as a free alternative to measure medication adherence, and will waive the article submission fee for such development and validation papers.

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Protocol

Connecting Youth and Young Adults to Optimize Antiretroviral Therapy Adherence (YouTHrive): Protocol for a Randomized Controlled Trial

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Abstract

Background: Despite intensive efforts to engage people living with HIV in the United States, less than half of the youth aged 13 to 24 years achieve viral suppression. There is a clear and continued need for innovative behavioral programs that support optimizing adherence among young persons with HIV.

Objective: There are 3 phases of this project. Phase 1 involves conducting focus groups to obtain feedback from youth about an existing technology-based antiretroviral therapy (ART) adherence intervention. Phase 2 will be used to conduct beta testing with youth to refine and finalize the YouTHrive (YT) intervention. Phase 3 is a randomized controlled trial (RCT) to test the efficacy of the YT intervention among youth living with HIV (YLWH).

Methods: In phase 1, we will conduct 6 focus groups with approximately 8 youths (aged 15-19 years) and young adults (aged 20-24 years), each in 3 US cities to obtain (1) feedback from YLWH about the *look and feel* and content of an existing adult-focused Web-based ART adherence intervention and (2) suggestions for adapting the intervention for YLWH similar to themselves. Phase 2 will involve updating the existing intervention to include features and functionality recommended by YLWH in phase 1; it will conclude with beta testing with 12 participants to gain feedback on the overall design and ensure proper functionality and ease of navigation. For phase 3, we will enroll 300 YLWH in 6 US cities (Atlanta, Chicago, Houston, New York City, Philadelphia, and Tampa) into a 2-arm prospective RCT. Participants will be randomized 1:1 to YT intervention or control group. The randomization sequence will be stratified by city and use random permuted blocks of sizes 2 and 4. Participants randomized to the control condition will view a weekly email newsletter on topics related to HIV, with the exception of ART adherence, for 5 months. Participants randomized to the YT intervention condition will be given access to the YT site for 5 months. Study assessments will occur at enrollment and 5, 8, and 11 months post enrollment. The primary outcome that will be assessed is sustained viral load (VL), defined as the proportion of participants in each study arm who have suppressed VL at both the 5- and 11-month assessment; the secondary outcome that will be assessed is suppressed VL at both the 5- and 11-month assessment between drug-using and nondrug-using participants assigned to the YT intervention arm.

Results: Participant recruitment began in May 2017 for phase 1 of the study. The data collection for aim 3 is anticipated to end in April 2020.

Conclusions: The efficacy trial of the YT intervention will help to fill gaps in understanding the efficacy of mobile interventions to improve ART adherence among at-risk populations.

Trial Registration: ClinicalTrials.gov NCT03149757; <https://clinicaltrials.gov/ct2/show/NCT03149757> (Archived by WebCite at <http://www.webcitation.org/73pw57Cf1>)

International Registered Report Identifier (IRRID): DERR1-10.2196/11502

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KEYWORDS

treatment adherence; antiretroviral therapy; adolescent; HIV; mobile apps; mobile phone

Introduction

Background and Study Aims

Youth aged between 13 and 24 years accounted for 22% of all new HIV infections in the United States in 2015. The majority of these infections (81%) occurred among gay and bisexual young men [1]. Less than half (44%) of youth living with HIV (YLWH) in the United States are virally suppressed, which is a well-recognized critical factor in individual health and noninfectiousness. Drivers of viral suppression for all people living with HIV (PLWH) include access to effective antiretroviral therapy (ART), initiation of and persistence with ART regimens, and consistent ART adherence. Predictors of ART adherence among youth are multifactorial and include medical (eg, side effects and dissatisfaction with the medical team), logistical (eg, forgetting and inconvenience), and psychological (eg, depression, lack of support, and perceived stigma) barriers [2]. In addition, substance use among adolescents and young adults remains high and is associated with ART nonadherence [3,4], making it an important, although underutilized [5], target for ART interventions with YLWH. For these reasons, there is an ongoing need for innovative programs that leverage current communication channels to foster social support for ART adherence behaviors.

Social support has been conceptualized as a basic human need, acts as a buffer to stress, is a fundamental coping strategy, and serves to engender understanding and assistance [6]. Greater social support is associated with improved behavioral and health outcomes for adults with HIV, including serostatus disclosure [7] and lower sexual risk-taking among gay male couples [8]. Among children and adolescents, having a *buddy system* for remembering to take ART is associated with greater adherence [9]. For these reasons, a leading group of medical and behavioral science experts has recommended that peer support may be considered to improve ART adherence outcomes [10].

Traditional, in-person peer-support ART promotion interventions have been conducted for adolescents [11] and adults [12,13]. For example, Simoni et al randomized 224 adult HIV-positive patients at a public HIV specialty clinic in Seattle, Washington, to receive either in-person peer-support, pager messaging, both in-person and peer messaging, or usual care [13] for a 3-month period. Those receiving the peer intervention had higher self-reported adherence at the immediate postintervention assessment, although intervention effects diminished at later assessment periods (with the final assessment point at 9 months) [13].

Technology-based ART adherence approaches have proliferated in recent years [14-16] because of the widespread adoption of

technology across sociodemographic groups [17], their ability to reach a broad audience, and their low implementation costs [18]. Youth are especially appropriate candidates to receive technology-based ART adherence interventions. Youth were early and heavy users of technology [19]. Recent data from the Pew Research Center showed that most (95%) US teens are online, 80% own a desktop or laptop computer, and 78% and 37% own a mobile phone or smartphone, respectively [20,21]. Most (92%) 18- to 29-year-olds own a smartphone [22], allowing mobile access to the internet for most youth. Technology provides ways to create virtual support networks that bypass geographic boundaries, thereby providing access to supportive others that may otherwise be unavailable because of geographic or stigma barriers. A recent analysis of message posts from a closed Facebook group for patients who were part of a young adult (aged 16-25 years) HIV program showed that members provided high levels of emotional and network support and moderate levels of informational support [23]. However, most computerized ART adherence interventions [24,25] are individually delivered, and most fail to leverage peer-to-peer interactivity that has come to symbolize Web 2.0. Given the increasing use of social media as important and influential communication channels and the high demands of social identity development during adolescence and early adulthood, interventions that leverage support networks for HIV-positive youth may be an important avenue to address HIV care outcomes.

The *Thrive With Me* (TWM) intervention was developed by members of this study team and leverages online peer support to improve ART adherence among adult men who have sex with men (MSM) residing in New York City, New York [26]. TWM is a responsive website that adjusts to the size of the device (computer, pad or tablet, or phone) on which it is being viewed. Responsive websites, sometimes referred to as *Web apps*, can have a similar appearance and functionality as a native app but are less costly to develop and can be viewed across multiple devices. TWM is a peer-support, tailored information, and self-monitoring ART adherence intervention grounded in the Information, Motivation, and Behavioral Skills (IMB) model [27,28]. A pilot of TWM was conducted between February and April, 2010, to assess its feasibility, acceptability, and preliminary efficacy among adult MSM primarily recruited online in the United States [29]. MSM (n=123; mean age 43 years; 64% white, non-Hispanic; and 16% used drugs, excluding marijuana, in the past 30 days) were randomly assigned to receive either the TWM intervention (n=66) or no intervention (n=57) for 2 months. Assessments occurred at baseline and 2- and 3-month follow-up periods. Moreover, 90% of participants were retained at the 3-month follow-up assessment, and those

randomized to TWM reported high levels of perceived information and system quality, usefulness, and overall satisfaction of the intervention. Adherence scores were not significantly different for the full sample. However, there was some evidence of greater improvement in timely dosing (ie, taking ART within 2 hours of the usual dosing time [$P<.10$] and taking ART correctly with food [$P<.05$]) among the intervention group than the control group. Improvement in ART adherence outcomes was most pronounced for current (ie, ≤ 30 days) drug-using MSM among whom the TWM intervention arm reported significantly higher overall ART adherence ($P=.02$) and ART taken correctly with food ($P=.01$) than those in the control condition. Currently, TWM is being assessed in a large ($n=400$) efficacy trial of MSM residing in NYC [26].

This study describes the protocol for a randomized controlled trial (RCT) of the YouTHrive (pronounced “Youth Thrive” or abbreviated as YT) Web-based intervention, which is being adapted from the TWM intervention. The primary goal of YT was to improve ART adherence and HIV treatment outcomes among viremic YLWH. YT uses a multicomponent package of peer-to-peer social support, tailored HIV and ART information, and self-monitoring to achieve this goal.

The aims of the research include the following:

The primary objective is to assess the efficacy of YouTHrive (YT) in a 2-arm RCT ($n=300$) to sustain suppressed viral load (VL) among YLWH, compared to an HIV information-only control condition.

H1: A higher proportion of participants in the YT intervention arm than in the information-only control arm will have undetectable VL at both the 5- and 11-month follow-up time points.

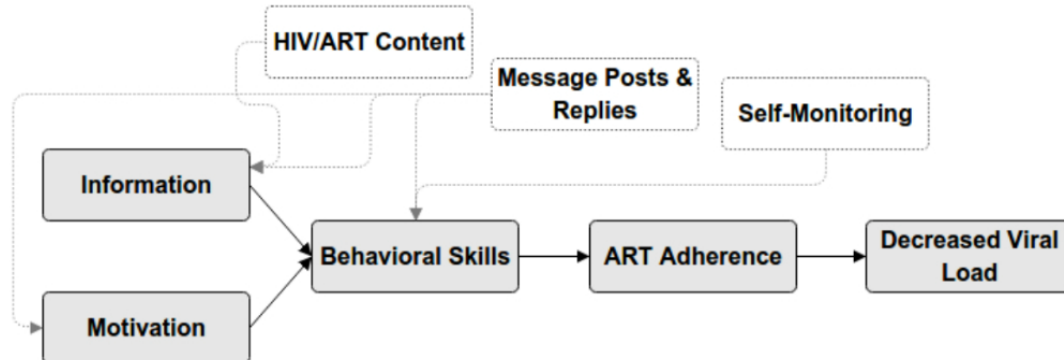
The secondary objective is to assess whether YT is more beneficial for substance-using than nonsubstance-using YLWH.

H2: Among YLWH in the YT intervention arm, a higher proportion of substance-using YLWH will demonstrate VL suppression at both the 5- and 11-month follow-up time points compared to nonsubstance-using YLWH.

Theoretical Basis for YouTHrive

The IMB model proposes that health behavior and behavior change results from being well and accurately informed, having the personal and social motivation to engage in the behavior, and having the appropriate behavioral skills and self-efficacy to use them [27,30]. The associations between core YT intervention components (described in detail below) and the IMB model components are shown in Figure 1. The IMB model has been used to predict risky sexual behavior among adolescents in Los Angeles, CA [31] and has been used as the theoretical basis of adolescent risk reduction interventions [32]. The model has also been evaluated and supported in studies of ART adherence using clinic-based samples of adults in Puerto Rico [28], Italy [33], and Mississippi [34] and among a community-recruited sample of HIV-positive MSM in the United States [35].

Figure 1. Thrive With Me intervention components and the Information, Motivation, and Behavioral skills model. ART: antiretroviral therapy.



Methods

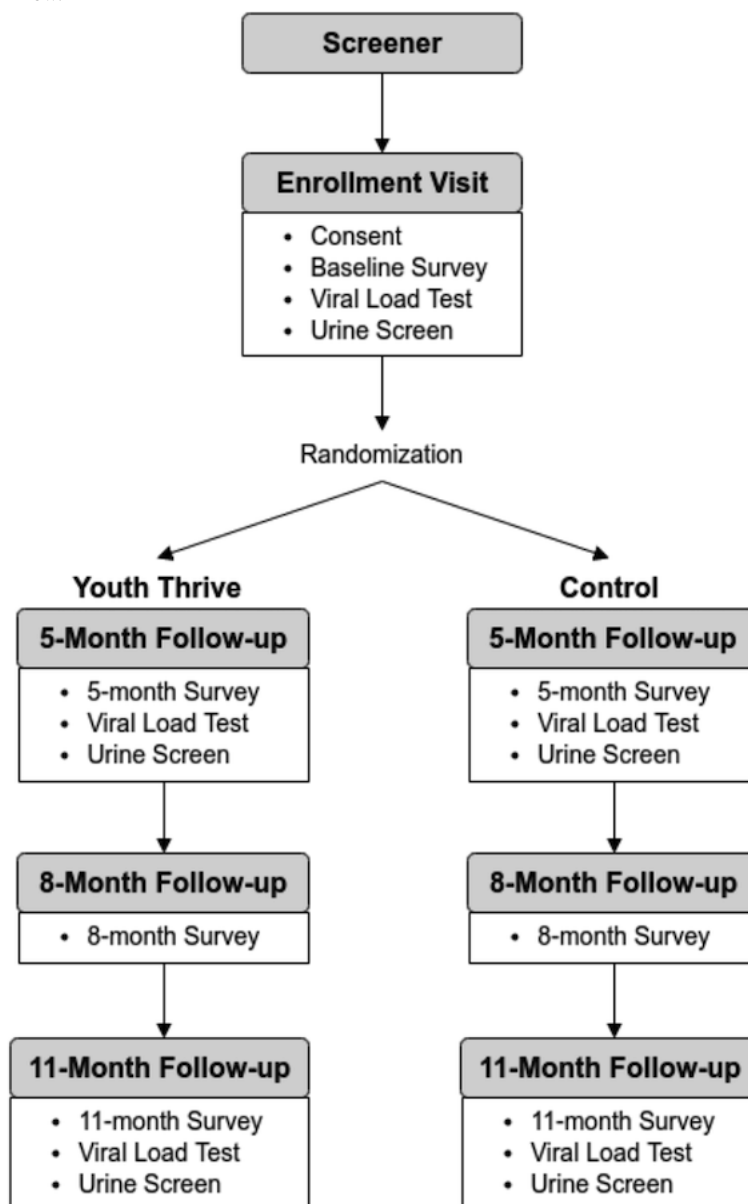
Ethics Statement

The institutional review board (IRB) at the University of North Carolina Raleigh Durham, NC, is the IRB of record for all participating institutions and subject recruitment venues (SRVs) participating in the study. It will review all procedures outlined in this protocol. Procedures for phase 1 of the study (outlined

below) have been approved (UNC IRB 16-3136). A waiver of parental consent was obtained for participants who are aged 15 to 17 years. The study is registered as a clinical trial (Clinical Trials # NCT03149757).

Design

We will evaluate the YT intervention in a randomized controlled efficacy trial (see Figure 2). There are 3 phases of the YT study:

Figure 2. YouThrive intervention flow.**Phase 1: YouThrive Intervention Adaptation**

We will conduct 6 focus groups with approximately 8 youth (aged 15-19 years) and young adults (aged 20-24 years), each at 3 SRVs (Chicago, New York, and Houston) to obtain (1) feedback from YLWH about the *look and feel* and content of the original TWM intervention and (2) suggestions for adapting the intervention for YLWH similar to themselves. Focus groups will be transcribed verbatim, and a content analysis will be assisted by the analytic core (AC). Feedback from the focus groups will be used to inform phase 2.

Phase 2: YouThrive Adaptation and Beta Testing

We will work with our technology partner, Radiant Creative Group (RCG), to adapt the TWM intervention to include features and functionality that are identified in the first phase of our research. Beta testing with 12 participants will be conducted to get feedback on intervention design (ie, the overall *look and feel* of YT), functionality (ie, whether YT is functioning properly), and navigability (ie, users can easily navigate

features) to finalize all features and components of the intervention for phase 3.

Phase 3: Randomized Controlled Trial to Test Efficacy of YouThrive

YLWH (n=300) will be recruited by staff from 6 SRVs located in Atlanta, Chicago, Houston, New York (the Bronx borough), Philadelphia, Tampa, and (see Recruitment Strategy below). Persons who are interested in the study will be screened for eligibility using an online screening survey. YLWH who meet all inclusion criteria (detailed below) will complete an enrollment visit, which may be on the same day as screening or on a different day.

At the enrollment visit, participants will complete an in-office baseline computer-assisted survey instrument (CASI) and will be randomized at survey outset to either intervention or control. YLWH will then complete in-person overview and training on condition-specific site use. Youth assigned to the YT intervention will be shown example webpages of the

intervention, will be given basic training on how to navigate the intervention, and will be given the opportunity to ask questions they have about the website. Control condition assigned participants will be shown example control arm webpages. Intervention and control conditions are detailed below.

The active intervention and control period will last 5 months. We will employ up to 5 YLHW to be active in the YT site at first until there are 10 participants randomized to the YT intervention arm. This is to ensure that youth entering the intervention arm early have others with whom they can interact and not requiring participants to wait until other participants are enrolled. During the 5-month intervention period, YT intervention arm participants will have continuous access to the YT site, whereas youth in the control condition will receive an email newsletter with HIV-related information once per week.

Follow-up assessments will be conducted at 5-month (ie, immediate postintervention; follow-up 1 in the clinical setting), 8-month (follow-up 2 in an online-only CASI), and 11-month (follow-up 3 in the clinical setting) time points. Follow-up visits 1 and 3 will include an in-office administered CASI, a blood draw to test for detectable VL, and a urine screen for drug use, whereas follow-up 2 is an online CASI only.

Exit Interviews

At the 5-month visit, up to 20 participants randomized to the YT intervention arm will participate in a remote video-based interview conducted by study staff. The purpose of this interview is to elicit feedback on their experiences using the YT site, any technical difficulties encountered, and how the site could be further improved. Participants will be selected for interviews using purposive sampling based on level of engagement with the site (ie, high engagement vs low engagement relative to other users). All interviews will be audio recorded for transcription and analysis. Study staff will track activity levels and select participants for the interview.

Participants and Sample Size

We plan to enroll 360 HIV-positive adolescents and young adults in this study. Up to 48 participants will be recruited for focus group discussions (with the goal of 8 per group) for phase 1, 12 participants will be recruited to conduct beta testing of the YT intervention in phase 2, and 300 participants (n=150 YT and n=150 control) will be recruited to participate in the YT RCT in phase 3. Participants who are pregnant at the time of screening or who become pregnant during the study period will not be excluded from the study.

Inclusion criteria for each phase of the study are described below:

Focus Groups Inclusion Criteria

The focus group inclusion criteria are as follows: (1) self-reporting 15 to 24 years of age at screening; (2) HIV positive; (3) currently taking ART medication; (4) self-reporting missed medication doses in the past month or detectable VL or no VL in past 12 months; (5) engaged in care at the Chicago, Houston, or New York City SRV; (6) owns a cell phone; and (7) proficient in English as determined by study staff (as the

intervention will be built in English). Focus groups will be stratified by age (1 focus group of youth aged 15 to 19 years; 1 focus group of age 20 to 24 years per site) to ensure that the perspectives of both youth and young adults are explored.

Beta Testing Inclusion Criteria

Beta testing inclusion criteria are as follows: (1) 15 to 24 years of age at the enrollment visit; (2) HIV-positive status (medical chart verified); (3) HIV clinical care in Atlanta, Chicago, Houston, New York City, Philadelphia, or Tampa area; (4) currently prescribed ART (medical chart verified); (5) medical chart-verified detectable VL (above the lower limit of detection for the clinical assay) within 52 weeks of enrollment date and an ART prescription for at least 90 days before this VL test date; (6) English-speaking; (7) internet and short message service (SMS) messaging access for the beta testing period (approximately 2 weeks); (8) available to meet with site project staff in person for the first research appointment; and (9) available to meet with University of Minnesota project staff for a remote (ie, telephone or videoconference) feedback interview.

Randomized Controlled Trial Inclusion Criteria

RCT inclusion criteria are as follows: (1) aged 15 to 24 years at the enrollment visit; (2) HIV-positive status; (3) residing in Chicago, Houston, NYC, Philadelphia, Atlanta, or Tampa area and respond that they will be available to meet with SRV staff for visits at baseline, and 5-month and 11-month follow-up assessments; (4) evidence of a current ART prescription; (5) English-speaking; (6) anticipated continuous internet access and SMS messaging for the intervention period (approximately 5 months); and (7) has or is willing to create an e-mail address to use during the study period; (8) not a member of an iTech Youth Advisory Board (YAB); and (9) meets one of the following medical-chart verified or self-reported criteria: (a) one or more detectable VL test result (above the lower limit of detection for the clinical assay if medical-chart verified) in the past 12-months while on ART for at least 3 months, (b) having failed to show up for or missed 1 or more scheduled HIV care appointment in the past 12 months, (c) last HIV care visit was more than 6 months ago, or (d) self-reporting less than 90% ART adherence in the past 4 weeks. Persons enrolled in another ART adherence intervention research study at the time of screening will be excluded from participation.

Study Recruitment

Participants for all phases of this study may be approached and recruited in 1 of 2 ways: (1) in the SRV HIV clinic or (2) in the community. Recruitment procedures may vary slightly depending on the SRV and study phase.

Subject Recruitment Venue HIV Clinic-Based Recruitment

Youth who are patients at the SRV will have his or her medical chart reviewed to assess for potential eligibility (eg, age, HIV status, on ART, and detectable VL in the past 12 months) and, if an appropriate candidate, will be approached for recruitment. Potential participants will be informed of the nature of the study, the information to be collected, and the evaluations and assessments that are involved. Those who express interest in the study will be required to be screened using a computer-based

screeners on a desktop computer or tablet (located at the SRV) to determine if they meet all inclusion criteria (including self-reported criteria that may indicate a high potential for problematic adherence). If eligibility criteria are met, the youth will be invited to enroll in the study immediately or at a later date if they are not available then.

Community Recruitment

Community outreach may bring in youth who are patients at other local HIV clinics or who are out of HIV care and would benefit from the SRV clinical care program. New patients can be considered for this project if they meet eligibility criteria. Outreach to community-recruited youth can include contacting potential participants via telephone or electronically (e.g., text message or email), attendance at community venues where youth not in HIV care spend time or through targeted ads on widely used social media channels (eg, Facebook and Grindr). Youth who are approached for recruitment in person or contacted remotely (e.g., telephone or email) will be asked to complete the online screener and, if preliminarily eligible, scheduled for an enrollment visit. The receipt of clinic services will not depend on expressing interest or enrolling in the YT study (ie, clinical care will be based on usual clinic requirements).

Randomization for Phase 3

Once participants are enrolled and complete the baseline assessment, they will be randomized 1:1 to YT intervention or control group, based on a randomization sequence developed by the AC statistician and programmed into SurveyGizmo. Study staff will not be blinded to which arm youth are randomized; however, because both conditions are active (ie, youth receive content with which they may interact), we have confidence that youth will not be aware of whether they are assigned to the intervention or control condition. The randomization sequence will be stratified by city [36] and use random permuted blocks of size 2 and 4. Although the proportion of YLWH who report recent substance use will not be used to direct recruitment efforts or target enrollment numbers, we do anticipate high rates of alcohol, marijuana, and other illicit drug use based on analyses of substance use in prior Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) studies (87% for ATN 125; 76% for ATN 086-106) [3,37]. The percentage reporting substance use (defined as any alcohol, marijuana, or other illicit drug use) at baseline will be examined once half of the total target enrollment is reached (n=150). If substance use is reported by less than 50% of participants, we will re-examine recruitment efforts and the inclusion criteria to determine if changes are needed to bolster recruitment of substance-using YLWH.

Youth Advisory Board

We will consistently work with Youth Advisory Boards (YABs) at each SRV to elicit feedback from YLWH regarding our language, design, and gaming choices that would be most interesting and relevant to youth. YABs, at most SRVs, meet monthly to review study materials and provide feedback to study teams during phase 2 and as needed in phase 3.

Intervention

In the RCT, intervention participants will have access to the full YT website for 5 months. The YT intervention will be developed as a safe space for sharing information and helping youth feel empowered and supported to make healthy choices around living with HIV. To be available to answer questions and enforce community standards (eg, no hostile exchanges), the YT website is moderated by trained research staff. Moderating includes reading through posted comments on the wall each day and identifying posts that are concerning (eg, suicidal ideation, pleas for assistance, and potentially hostile comments to other users). The study protocol and procedures manual for moderating details the exact steps taken for each potential situation. Note that posts are not delayed or held until *cleared* for posting. Rather, the moderator reviews posted material and acts accordingly. This is to retain the immediacy of posting, which users of social media largely expect. Similar to the TWM intervention for adult MSM [35], there are 3 core components in the YT intervention, which are described below.

Message Posting and Receiving

The YT homepage will consist of an interface for participants to asynchronously interact with one another through message posting. Unlike widely used social networking platforms such as Facebook, participants will view all posts on 1 shared feed (vs individual feeds or direct messaging). Other users may comment on a post as well as use reaction buttons (eg, thumbs up and Superman symbol). Message posting is the primary social support component of the intervention, as it allows participants to directly and voluntarily interact with one another in a similar manner as a face-to-face peer support group (see [Multimedia Appendix 1](#)).

Antiretroviral Therapy and HIV-Related Content

Adherence and HIV content (see [Multimedia Appendix 2](#)) will be presented as “Thrive Tips” on the YT site. Youth in the YT intervention arm will receive approximately 3 Thrive Tips each day. Thrive Tips can include (1) brief tips about how to live with HIV and better manage medication adherence, (2) videos or links to videos of youth discussing challenges to ART adherence and ways to overcome them, and (3) image-based content such as memes or infographics. Study staff created approximately 300 Thrive Tips total, with two-thirds dedicated to theory-based adherence barriers, and the remaining one-third considered *Grab Bag* tips that include content about general well-being while living with HIV (stress management, dealing with HIV while in school, dating and relationships, and healthy sexuality). All participants in the intervention arm will receive every Thrive Tip in the first half of the 5-month intervention period. Tips that reflect a participant’s unique adherence information, motivation, and adherence self-efficacy barriers, as assessed from the baseline survey responses, will be identified with an icon (eg, a fire symbol) to encourage greater engagement with tips tailored to youth’s specific adherence barriers. At the halfway point, youth in the YT condition will retake the IMB-related adherence information and motivation scales and the Adherence Self-Efficacy Scale (ASES) to update their adherence barriers profile, and all of the Thrive Tips will be shown a second time for the last half of the intervention period.

Content for the Thrive Tips is curated and created by the study team with input from the YABs. Aim 1 focus groups will be used to guide revisions of Thrive Tips from the TWM intervention to include youth-oriented language, images, and videos as well as content that is inclusive to all genders and sexual identities (because the TWM intervention is designed specifically for adult MSM). As participants are in the intervention for longer periods, they accumulate more saved Thrive Tips. They can search and revisit all accumulated Thrive Tips through a keyword search.

Medication Adherence and Mood Self-Monitoring

At setup, participants will be guided in setting up their profile with their current ART medication and next HIV care appointment, both of which can be updated throughout the intervention period. Youth will have the ability to self-monitor whether they took their dose(s) of ART each day as well as indicate their daily mood by selecting the representative emoji, through the *My Check-in* feature on the YT interface. Youth will have the ability to retrospectively input their adherence and mood for up to 72 hours. Underneath, a calendar will be displayed that reflects their personal adherence behaviors through color coding (eg, blue-shaded days are days that medications are taken, and red-shaded days represent days for missed doses) with overlaid emojis that indicate their mood for the day to promote greater insight of the connection between participants' adherence behaviors and mood states (see [Multimedia Appendix 3](#)).

Goal Setting and Monitoring

Youth will view an interface called "My Journey" that leads them through steps to set and self-monitor 1 or more goals. Goals will include, but will not be limited to, those about living with HIV and ART adherence. For example, a youth may identify that she or he would like to improve school performance. Participants could choose the goal of determining which time is best to take their HIV medications if the medications interfere with their thinking or could choose the goal of asking for help with their homework from a classmate, teacher, tutor, or parent/guardian. In addition, youth will be given the option of writing in their own goal. Once a goal is set, youth will indicate when they would like to achieve that goal (eg, next week and next month). The goal will then appear as an active goal in which youth will self-monitor how much progress they have made toward that goal with a 7-point scale from "thinking about starting" to "journey complete." Youth will be asked if they would like to share on the community wall that they have completed a journey. Participants may start and complete as many journeys as they wish during the study period.

Weekly Short Message Service Engagement Message

All participants will receive a weekly SMS text message that prompts and encourages them to visit the YT site. SMS text messages will be designed to engage youth with the different aspects of the site, including Thrive Tips ("*Extra, extra! Read all about it! Log in here to see today's tip.*"), goal setting and monitoring ("*You're halfway through your time on YT. Take a minute to update your Journey*"), adherence and mood monitoring (eg, "*Have you had time to check in today? Log into the YT site now.*"), advancing point levels (eg, "*Step up your game! Log into the YT site and see how to earn more points.*"), and trending topics on the community wall (eg, "*People on the YT site are talking about [insert trending topic]. Come join the conversation!*").

Game Mechanics

The YT intervention uses points that accumulate as youth use intervention components to reinforce engagement with the site. As points accumulate, youth move through higher levels (ie, "levelling up") during the intervention period, which unlocks new features of the site (eg, new avatar choices and color theme choices) when a new level is achieved. Points are earned through posting to the YT feed (wall), responding to other users' comments, setting new goals, clicking on a Thrive Tip, and other actions that may be taken in YT. Youth will be able to view the number of points and their current level as part of their profile.

Control Condition

The control condition consists of 21 brief informational text and graphic-based webpages that will be released weekly (1 webpage per week for approximately 5 months), similar to a *newsletter*. This weekly newsletter will be provided to participants as an email with a link they can click on to open the newsletter on their mobile internet browser. The newsletters will contain information on topics related to living with HIV (eg, disclosure of HIV at school and work) and devoted to improving general well-being (eg, managing depression) but not specifically about ART adherence. Informational content will be chosen from a list of topics reported to be of most interest and relevance by participants in phase 1 focus groups and YLWH serving on YAB.

Outcomes

Study outcome measures and the timing of their administration are provided in [Table 1](#). Outcomes are described below.

Table 1. Study outcome measures and administration schedule.

Measure	Baseline	5-month assessment	8-month assessment	11-month assessment
HIV RNA viral load	X ^a	X	— ^b	X
Sociodemographics	X	X	X	X
Technology use	X	X	X	X
System Usability Scale	—	X	—	—
Electronic health literacy	X	—	—	X
Intervention acceptability	—	X	—	—
Antiretroviral therapy (ART) regimen and engagement in HIV care	X	—	—	X
Self-report ART adherence	X	X	X	X
Adherence information and motivation	X	X	X	X
Adherence self-efficacy and adherence support	X	X	X	X
Substance use	X	X	X	X
Sexual behavior	X	X	X	X
Mental health	X	X	X	X
HIV stigma	X	X	—	X
Social support	X	X	X	X
Social support in YT ^c	—	X	—	—
Emotional regulation	X	—	X	—

^aMeasure included at the assessment.

^bMeasure not included at the assessment.

^cYT: YouTHrive.

Primary Outcome

Sustained undetectable VL is the primary outcome, defined as having an undetectable VL at both the 5- and 11-month time points. VL was chosen as the primary outcome as it is one of the most objective and reliable indicators of ART adherence [38]. VL data will be collected either through chart review, if a VL test was conducted and reported in the medical chart within a 30-day window from the study visit date, or through blood draw taken as part of the research protocol at the time of the assessment. Undetectable VL will be measured at the standard level of detectability at each SRV (eg, if the SRV typically uses <40 copies/mm as undetectable, then participants are reported undetectable at that SRV if they are below that level). In addition, the date of the VL test, the VL assay type, the lower and upper limits of the test, and the source of the VL test (eg, laboratory report and clinician's notes) will be noted.

Demographic Factors

Common demographic factors will be collected, including date of birth, race or ethnicity, zip code, sex assigned at birth, sexual identity, outness of sexual identity to others (family, friends, and medical providers), education, employment status, health insurance, family income, housing stability, and history in the criminal justice system.

Self-Reported Antiretroviral Therapy Adherence Variables

We will use the 3-item Adherence Scale developed by Wilson et al [39], which asks how well job participants did at taking their HIV medicines the way they are supposed to, how often in the past 30 days they took their HIV medicines in the way they were supposed to, and a Visual Analog Scale in which participants can report the percentage of HIV medicines they took in the past 30 days. Youth will also be asked to report how many days they missed at least one dose of their HIV medicines in the past 30 days.

To assess theoretically derived ART adherence strengths and barriers, the information and motivations scales from the IMB ART Adherence Questionnaire (IMB-AAQ) [40] will be completed by participants. The IMB-AAQ assesses adherence-related information (9 items) and personal and social motivation (10 items) on a 5-point Likert scale. In addition, participants will complete the HIV ASES, which is designed to measure self-efficacy for adherence to HIV treatment plans, included but not limited to HIV medications [41]. Respondents are asked 12 questions to assess their confidence to carry out important treatment-related behaviors to adherence to treatment plans. Responses range from 1 (cannot do it at all) to 10 (certain can do it). Higher scores indicate higher adherence self-efficacy.

Finally, we will ask youth to indicate the kinds of adherence support they received from their clinic, provider, friends, or family during the intervention period. Adherence support may

include electronic dose monitoring devices, dose reminder texts, alarms, phone calls, pillboxes, reminders, and help from family and friends and support groups.

Antiretroviral Therapy Regimen and Engagement in HIV Care

The following items will be abstracted from the medical chart of participants: (1) date of HIV diagnosis, (2) current and recent HIV medications, (3) past 12 month HIV care visits, (4) missed HIV care appointments in the past 12 months, and (5) future HIV care appointments from the date of abstraction.

Substance Use

Substance use will be assessed in several ways. First, youth will complete a urine screen at baseline, immediate postintervention, and 6-month postintervention time points to assess for the following illicit substances: cocaine, methamphetamines, marijuana, opiates, and phencyclidine, using a generic 5-panel screening test (model WDOA-554; DrugTestsInBulk website, West Hills, CA). The estimated detection periods for the test used are 2 to 4 days for cocaine and opiates, 5 to 30 days for marijuana, 1 to 3 days for ecstasy, and 3 to 5 days for methamphetamine. Second, participants will complete an adapted version of the National Institute on Drug Abuse (NIDA)-Modified Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST). The ASSIST is a 9-item questionnaire developed by the World Health Organization and addiction researchers to screen for all levels of problem or risky substance abuse [42]. The ASSIST will be used to assess the frequency of use and associated problems for tobacco, alcohol, cannabis, cocaine, amphetamines (including methamphetamine and ecstasy), inhalants, sedatives, hallucinogens, and opioids.

Mental Health

Depression and anxiety symptoms will be assessed using the 8-item Patient Health Questionnaire (PHQ-8 [43]) and the 7-item Generalized Anxiety Disorder (GAD-7 [44]) scales. Youth will first be asked the first 2 items for each scale; those who report having some depressive or anxious symptoms (≥ 3 across the 2 PHQ items and/or ≥ 3 on the 2 GAD items) will be asked to complete the reminder items for the scales.

Emotional regulation will be assessed using the Emotional Regulation Questionnaire, which is designed to assess individual differences in the habitual use of 2 emotional regulation strategies: cognitive reappraisal and expressive suppression [45]. Participants will indicate their tendency toward reappraisal (6 items) and suppression (4 items) through a 7-point Likert scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores indicate greater use of the emotional regulation strategy.

HIV stigma will be assessed using the stigma scale developed by Earnshaw et al [46]. Designed to measure HIV stigma mechanisms defined by the HIV Stigma Framework, the measure includes 3 subscales: internalized HIV stigma, anticipated HIV stigma, and enacted HIV stigma [46]. Items are rated on a 5-point Likert-type scale with higher scores indicating greater stigma.

Relationship Status and Sexual Behavior

To assess relationship status, youth will be asked to define their primary relationship status (eg, I am casually dating, I have a boyfriend or girlfriend, and I am single) and for those reporting being in partnership, whether they have sex outside the primary relationship as well. Sexual behavior is assessed by asking whether they have ever and in the past 3 months engaged in vaginal, anal, or oral sex. If they reported having sex in the past 3 months, youth will be asked how frequently (from none of the time to all of the time) they use a condom during insertive and receptive anal sex and vaginal sex.

Social Support

The Patient-Reported Outcomes Measurement System (PROMIS) short-form versions of the Social Relationships Scales will be used to measure perceived social isolation and social support [47]. PROMIS, a National Institutes of Health initiative, uses rigorous processes to develop and test item banks that measure physical, mental, and social health components [48]. The 5 Social Relationships Short-Form Scales, each with 4 items, measure social isolation and social support domains including companionship, emotional support, informational support, and instrumental support [47]. For youth randomized to the YT condition, emotional support, informational support, and social isolation within the YT intervention will be assessed. As instrumental support cannot be provided within this virtual intervention, we will not ask about this type of support within YT.

Technology Adoption and Use

Technology use questions and items assessing participants' attitudes toward technology were taken from items developed by the Pew Research Center's Internet, Science, and Tech initiative. Youth in YT will be asked to report device ownership; how they access the internet; which smartphone operating system they use and how they pay for service; how many hours a day they spend on the internet; how often they use mobile apps; frequency of internet use for social, sex-seeking, work, and health-seeking activities; the frequency with which they use social networking service (eg, Facebook and Instagram); and whether and how they may have faced discrimination while looking for partners on online venues. In addition, the 8-item eHealth Literacy Scale will be used to assess participants' perceptions of their skills for using information technology (ie, the internet) for health [49].

Intervention Ease of Use, Acceptability, and Satisfaction

Youth in both study arms will be asked to rate the ease of use of their respective activities (either the YT intervention or the active control condition) using the System Usability Scale (SUS) [50]. The SUS is a 10-item measure that asks participants to rate on a 1 (strongly disagree) to 5 (strongly agree) scale how much they agree with statements about the ease with which they were able to navigate the intervention (eg, "I found YouTHrive unnecessarily complex" and "I found the various functions in YouTHrive to be very well integrated"). Participants will also answer questions to assess information quality (eg, "The information on YouTHrive is accurate"), perceived usefulness of the information (eg, "YouTHrive helps me quickly find

information and support for healthy living”), and overall satisfaction with the intervention (eg, “Overall, I am very satisfied with YouTHrive”). We also ask youth to rate their respective intervention (YT or control) on information quality (eg, “I trust the information on [project name]”), usefulness (eg, “[name of project] helps me to quickly find information and support for healthy living”), and overall satisfaction (eg, “Overall, I am satisfied with [name of project]”) using items adapted from Horvath et al [35]. Finally, we will collect qualitative data on youths’ experiences by asking participants to state what they like most and least about the intervention, what was most memorable about it, and what features would make it better.

User Engagement

Intervention use data will be collected during the active trial period to assess user engagement with the intervention. Standard use data include (1) participant identification (ID) number, (2) study arm, (3) log-in date and time, (4) type of device used, and (5) total duration of the session. Intervention use data will include the following variables reflecting peer-to-peer interaction: (1) date of post, (2) original post content, (3) participant ID of original post, (4) content of replies to the original post, and (5) participant ID of each reply. Additional user engagement variables collected are (1) frequency of wall posts by participant ID, (2) number of comments by participant ID, (3) number of Thrive Tips viewed, (4) number of tailored Thrive Tips viewed, (5) number of Thrive Tips marked as *favorites*, (6) number of SMS engagement messages clicked on to take the user to the site, (7) number of days ART adherence reported, (8) number of mood responses reported, (9) number of goals set, (10) number of times progress toward goals is reported, (11) total number of active intervention days, (12) number of times the participant updated their outward-facing profile features, and (13) total points earned.

Analysis

Phase 1

Audio recordings from each focus group will be transcribed and checked for accuracy by a member of the AC. Next, all transcriptions will be reviewed by at least three members of the study team. Participants’ overall feedback and their suggestions for changes to the overall look and feel, content, and specific features will be compiled in a document and reviewed by investigators. Recommendations for changes to the user interface will be prioritized and presented to RCG to guide the development of the beta version of YT.

Phase 2

Interviews with YLWH during beta testing will be audio recorded and reviewed by study team members. Feedback from youth will be recorded in a spreadsheet by intervention component, with suggestions for improving the overall design and content recorded separately. A beta testing report will be compiled by Dr Horvath and reviewed by the investigator team and RCG. The report will include a list of common navigation problems by intervention component, suggestions for improvement in design and content by intervention component, and recommended design and content improvements for the

overall site. The study team and RCG will review the beta testing report to prioritize modifications that need to be made, given the importance of the change to the user experience as well as what changes are possible, given time and budget constraints. They will then agree on final modifications to YT.

Phase 3

Stata version 15 (StataCorp) and SAS version 9.4 (SAS Institute) were used for power calculations and will be used for all analyses. The primary study outcome is HIV viral suppression at both 5 and 11 months of follow-up, measured as undetectable VL based on the standard level of detectability. The primary statistical test of intervention efficacy for YT will be the comparison between intervention and control arms of the proportion of participants with undetectable VLs at both the 5-month and 11-month follow-up time points using a differences in proportions test and confidence intervals. If there is evidence of baseline imbalance between intervention arms for important predictors of viral suppression, we will fit logistic regression models that adjust for those covariates.

As a secondary aim, we will investigate whether there is greater benefit from the YT intervention for substance-using participants compared with nonsubstance-using participants. We will use the same modeling approach described above to address this aim. First, we will examine the association between the intervention and viral detection separately among those who did and did not self-report current (since the last visit) substance use (ie, yes/no for problematic alcohol use and/or illicit drug use). Second, to formally test whether there is an interaction between intervention arm and substance use, the models described above will be refit including an interaction term between substance use and intervention arm. Interactions will be evaluated on the additive scale. We will carefully examine the distribution of potential confounders of the substance use and VL association and adjust for them as necessary. As mentioned previously, we will adjust for covariates where appropriate.

The models described use logistic regression to model the outcomes. We will use estimates from these models to report prevalence differences and ratios. However, alternative (log-linear and Poisson) models may be explored to allow easy interpretation of parameters in the presence of common outcomes. In the event of loss-to-follow-up among study participants, we will perform sensitivity analyses of an alternative outcome. We will define an additional outcome where a failure is defined as either detectable VL or loss-to-follow-up. The analyses described above will be repeated with this alternative outcome. All of the models mentioned above can be modified to accommodate missing values in the outcome or covariates over time without dropping participants. Although attempts will be made to limit missing data, in the event that this occurs, we will carefully examine patterns of missingness. Multiple imputation will be implemented, as needed, to deal with missing covariate data.

Finally, we will examine models that include covariates that quantify the degree of site usage and which components were used. The additional outcome of self-reported ART adherence will be examined. The outcome will be defined as the percentage of ART taken in the past 30 days. Differences in this proportion

by study arm will be evaluated using the same approach as described above. To explore the effects of the YT intervention on the intermediate theory-based processes of change, we will use the IMB-AAQ informational and motivational scales, adherence self-efficacy, and social support measures at each time point. These scales will be included as outcome variables in linear regression models to test the main effect of intervention arm.

Incentives

The method for compensation will be determined separately by each site and approved by each SRV's IRB. Participants at all sites will be compensated with the following cash or cash equivalent. Focus group participants will be compensated US \$30 and refreshments during visits. Beta test participants will be paid US \$25 at the first visit and US \$25 at the second visit. RCT participants will be compensated US \$50 at the enrollment visit and the 5-month and 11-month follow-up visits. Participants will be compensated US \$20 for completing the 8-month remote online survey. Participants who complete the exit interview at the 5-month follow-up visit will be compensated an additional US \$50. If a participant is unable to go into the clinic to complete a follow-up study visit, the Web-based CASI survey could be completed on his or her own. SRV study staff will be notified when a participant has completed a CASI survey on his or her own, and the compensation will be provided to the subject. Compensation can be mailed to participants, if allowed at the site.

Power and Sample Size

This study is powered to detect a meaningful effect for the main aim that there will be a difference between the proportion of virally suppressed participants in the intervention and control arm. The sample will consist of people who are and are not virally suppressed at baseline. We assume that 30% of participants will not be virally suppressed at baseline. Among this 30% who are not virally suppressed, we assume 30% of them will be virally suppressed at all follow-up times in the control arm and 47% will be virally suppressed at all follow-up times in the intervention arm (for a difference of .17). Among the 70% who are virally suppressed at follow-up, we assume 80% will be virally suppressed at all follow-up times in the control arm and 95% will be virally suppressed in the intervention arm (for a difference of 0.15). The average risk of the viral suppression in the control arm is therefore 65% and the average risk in the intervention arm is 80.6% (a risk difference of .16 or a risk ratio of 1.24). Assuming a type 1 error rate of 5% and a 1:1 allocation of participants to the treatment and control arm, we have 80% power to detect this difference of .16 or risk ratio of 1.2 if we enroll 256 participants (128 per arm). We assume there will be 15% loss to follow-up and will attempt to enroll 300 participants to account for this.

Results

Participant recruitment began in May 2017 for phase 1 of the study. The data collection for phase 2 is expected to be completed in June 2018 and for phase 3 in October 2020. Final results are anticipated for April 2021.

Discussion

There are a number of challenges to the YT clinical trial. First, it will require a multipronged effort to meet our recruitment goals, especially for younger YLWH. To address this, the research team will work with recruitment venues to reach out to as many of their current clinic population who meet eligibility requirements as possible. In addition, we will implement community and social media recruitment strategies to identify potential participants who may either be out of HIV care or are not current patients at recruitment clinics. Second, we do not provide smartphones or other Web-enabled devices to study participants but rather require that participants own or have access to a Web-enabled device. This may restrict participation by lower socioeconomic status youth and young adults on the one hand but will increase the potential for scale-up on the other hand. Moreover, providing devices to study participants is cost prohibitive and, therefore, not feasible within this protocol. That said, given that nearly all (95%) of teens have access to a smartphone [51], we believe that we will be able to capture most youth and young adults who are eligible for this study. Third, given high rates of mental health problems among HIV-positive youth [52-54], medical and psychological services must be available during the study period. We will implement SRV-specific protocols to assess and provide referrals to medical and psychological services in the event that a participant should report a need for these services or experience any adverse reactions resulting from study procedures.

With these limitations in mind, YLWH face numerous intrapersonal, social, structural, and cultural challenges, many of which impact their engagement in HIV care and, ultimately, interfere with their ability to adhere to ART. Given that the HIV epidemic in the United States has shifted toward younger ages of infection [55] and the high proportion of HIV-positive youth who are not virally suppressed [2], innovations in programs to promote and sustain adherence behaviors over time are critically needed.

There is a growing use of technology as a medium to reach youth with HIV with adherence interventions [56-60]; however, a number of critical questions remain. First, although technology use is highly prevalent among youth [20], there is still a lack of understanding for best practices to engage them in technology-based interventions. This is particularly true with respect to racial and ethnic minority persons [61]. Formative research that asks PLWH to identify which features of technology-based intervention approaches they believe would be most engaging can be useful [62]; however, intervention studies that assess the association between use of different intervention components with primary outcomes are needed to identify those components that are most engaging and effective [63]. Second, although the literature provides results from efficacy trials of computerized [24,25] and text message [64] interventions, trials of mobile ART adherence interventions remain poorly represented in the evidence base [65]. There is a need to rigorously test mobile interventions (including native app and Web app interventions) to advance research in this area. Third, it remains unclear how best to incorporate technology-based ART adherence interventions into clinical

care and into the lives of youth over long periods. Further research is needed to understand if these and similar types of interventions are best delivered continuously or whether they should be available on demand, as youth experience periods of hardship that impact their adherence behaviors. Similarly, it is not clear whether technology-based interventions are most

effective when integrated with clinic electronic health care records or whether concerns about privacy, availability, and autonomy create demand for these types of programs that lie outside of the health care system. The YT study described here will begin to provide answers to some of these important questions.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Screenshots of intervention components.

[[PDF File \(Adobe PDF File\), 226KB - resprot_v8i7e11502_app1.pdf](#)]

Multimedia Appendix 2

YouTHrive beta testing guide.

[[PDF File \(Adobe PDF File\), 23KB - resprot_v8i7e11502_app2.pdf](#)]

Multimedia Appendix 3

YouTHrive focus group discussion guide.

[[PDF File \(Adobe PDF File\), 82KB - resprot_v8i7e11502_app3.pdf](#)]

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Abbreviations

- AC:** analytic core
- ART:** antiretroviral therapy
- ASES:** Adherence Self-Efficacy Scale
- ASSIST:** Alcohol, Smoking, and Substance Involvement Screening Test
- CASI:** computer-assisted survey instrument
- GAD:** Generalized Anxiety Disorder
- IMB:** Information, Motivation, and Behavioral Skills
- IMB-AAQ:** Information, Motivation, and Behavioral Skills ART Adherence Questionnaire
- IRB:** institutional review board
- MSM:** men who have sex with men
- PHQ:** Patient Health Questionnaire
- PLWH:** people living with HIV
- PROMIS:** Patient-Reported Outcomes Measurement System
- RCG:** Radiant Creative Group
- RCT:** randomized controlled trial
- SMS:** short message service
- SRV:** subject recruitment venue
- SUS:** System Usability Scale
- TWM:** Thrive With Me
- VL:** viral load

YAB: Youth Advisory Board
YLWH: youth living with HIV
YT: YouTHrive

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Original Paper

Effect of In-Utero Antibiotic Exposure on Childhood Outcomes: Methods and Baseline Data of the Fetal Antibiotic EXposure (FAX) Cohort Study

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Abstract

Background: The widespread use of antepartum and intrapartum antibiotics has raised concerns about the possible disruption of the child's gut microbiota and effects on the maturation from the infant to the adult microbiome. The Fetal Antibiotic EXposure (FAX) study provides a cohort to examine the association between *in-utero* exposure to antibiotics and adverse childhood outcomes including body weight, atopic diseases, and autism spectrum disorders and to investigate the role of other potential factors mitigating or moderating the risk for adverse outcomes.

Objective: The aim of this paper was to describe the methods, cohort characteristics, and retention of infants included in the study cohort.

Methods: For this retrospective cohort study, we included children born in Kaiser Permanente Southern California (KPSC) hospitals between January 1, 2007, and December 31, 2015, within 22 to 44 completed weeks of gestation with KPSC insurance coverage during the first year of life. Follow-up data collection was performed through electronic medical records.

Results: The study cohort was comprised 223,431 children of which 65.7% (146,720/223,431) were exposed to antibiotics *in-utero*: 19.0% (42,511/223,431) were exposed during the antepartum period, 30.0% (66,896/223,431) during the intrapartum period, and 16.7% (37,313/223,431) exposed during both the antepartum and intrapartum periods. During their first year of life, children had a median of 5 weight and height measurements; the frequency of weight and height measurements declined to a median of 3 in their second year of life and 2 for 3 to 5 years of age. The 5-year retention of children in the health plan was over 80% with the highest retention for Hispanic children.

Conclusions: This cohort of children will provide a unique opportunity to address key questions regarding the long-term sequelae of *in-utero* exposure to antibiotics using real-world data. The high retention and multiple medical visits over time allow us to model the trajectories of body mass index over time.

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KEYWORDS

pregnancy; antibiotic; pediatric obesity; asthma; Outcome Assessment (Health Care)

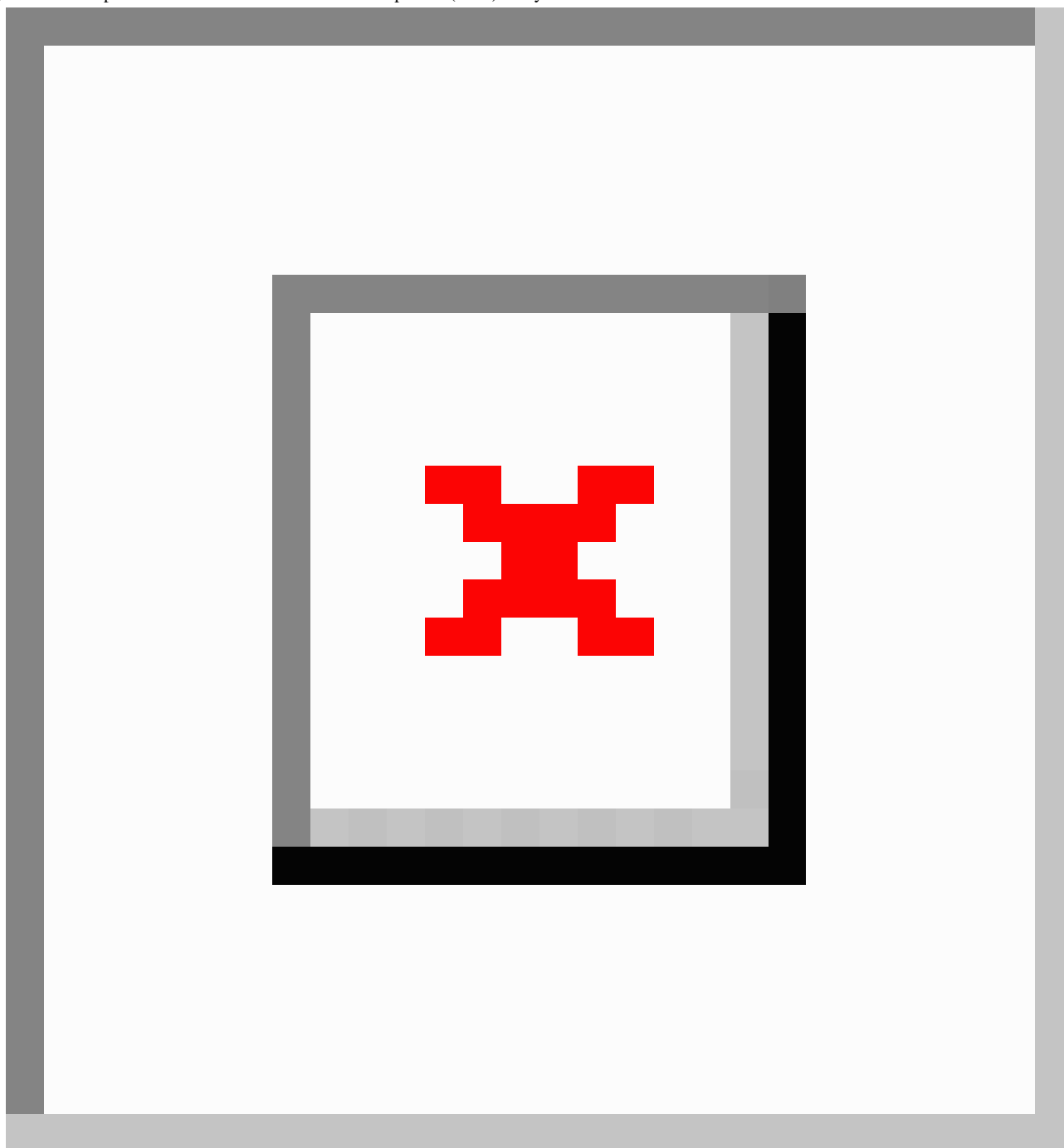
Introduction

Antibiotics are frequently used to prevent and treat infections during pregnancy [1-3]. Antepartum, respiratory, and urinary tract infections as well as pelvic inflammatory disorder are common reasons for antibiotic use [3]. During the intrapartum period, the use of antibiotics is frequent in high-risk women to prevent vertical transmission and early-onset group B streptococcal (GBS) diseases in neonates with an estimated prevalence of GBS colonization in 10% to 30% of pregnant women [4-6]. Moreover, surgical antibiotic prophylaxis is administered to about 19% of women before cesarean incision [7-10]. In Canada, the United States, and Europe, about 40% of pregnant women received antibiotics according to studies using data between 1998 and 2010 [2,3,11]. Although antibiotics are indicated for obstetrical and nonobstetrical conditions in pregnant women, little is known about medium- and long-term health effects in the infant as the consequence of *in-utero* exposure to antibiotics.

The widespread use of antibiotics during antepartum and intrapartum periods has raised concerns about alteration of the

microbiota of the maternal birth canal before birth and interference with the early microbial transfer from the mother to the fetus during pregnancy, delivery, and lactation. This may lead to disruption of the child's gut microbiota [12,13]. The bacterial microbiome in infants undergoes changes until it develops into a more stable adult-like microbiome [14]. Early life disruptions in microbial colonization and maturation may have downstream consequences on the metabolism and health of a child [15,16]. However, it is unclear as to how the exposure to antibiotics *in-utero* affects the *maturation* from the infant to the adult microbiome and, in consequence, how this may affect the health of a child.

The aims of the Fetal Antibiotic EXposure (FAX) study are to examine the association between *in-utero* exposure to antibiotics and adverse childhood outcomes including body weight, atopic diseases, and autism spectrum disorders (Figure 1) and to investigate the role of other potential factors mitigating or moderating the risk for adverse outcomes. Here, we describe the methods, cohort characteristics, and retention of infants included in the study cohort.

Figure 1. Conceptual model of the Fetal Antibiotic EXposure (FAX) study.

Methods

Setting and Study Design

For this retrospective cohort study, we used longitudinal electronic medical record data from Kaiser Permanente Southern California (KPSC), the largest integrated health care system in Southern California. KPSC provides comprehensive health services to over 4 million health plan members. The membership represents approximately 17.0% of the population in the coverage area and has similar sociodemographic characteristics such as neighborhood-level education and income [17]. Medical services are provided almost solely in KPSC-owned hospitals and medical offices. Labor, delivery, and pharmacy records contain detailed data on drug dispenses and administration.

About 42,000 babies were delivered in KPSC hospitals in 2017. All children are linked with their biological mothers using unique identifiers. For the assessment of study outcomes, infants will be followed longitudinally using information from the electronic medical records. The study protocol was reviewed and approved by KPSC's Institutional Review Board.

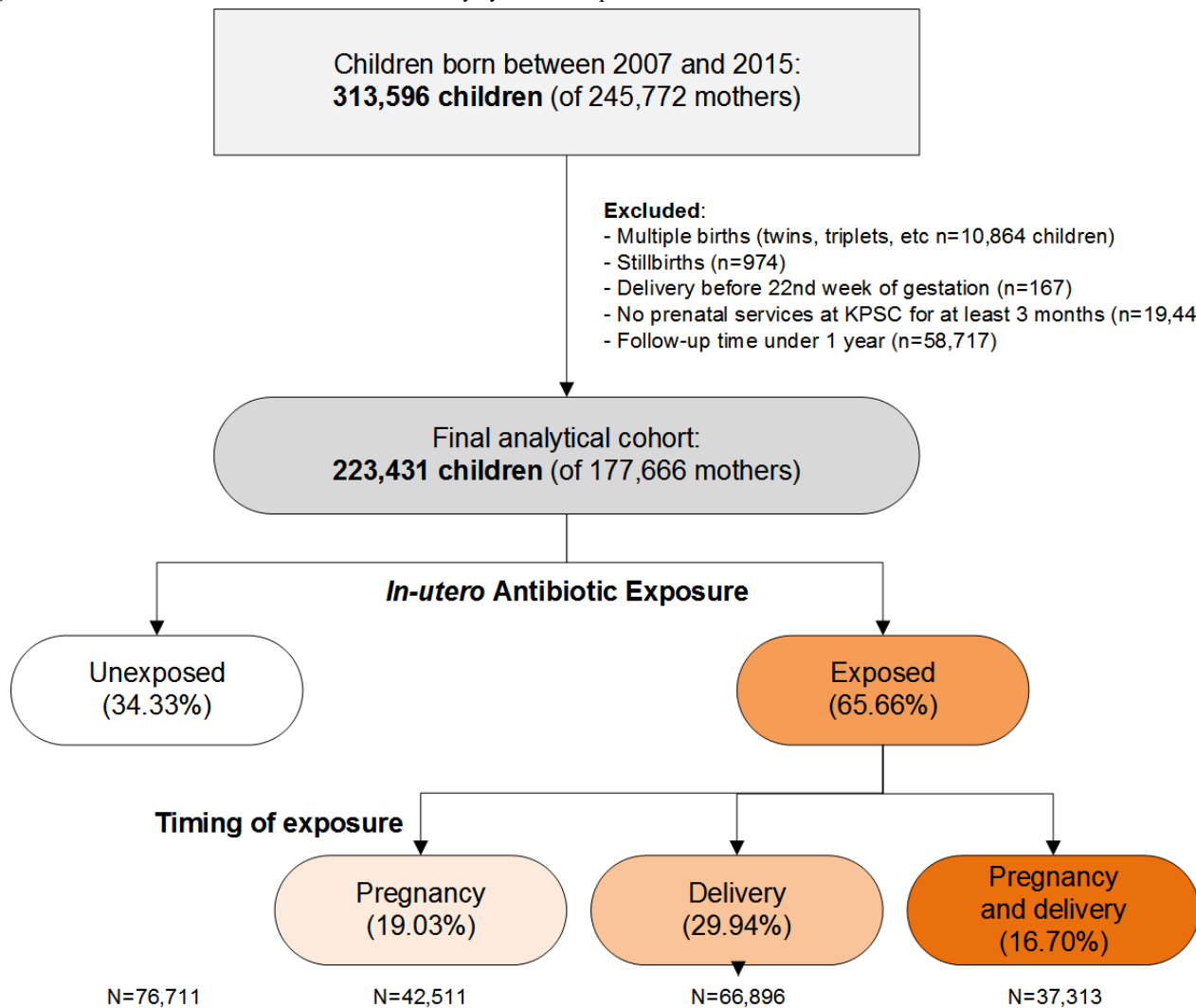
Study Population

We included children born in KPSC hospitals between January 1, 2007, and December 31, 2015, within 22 to 44 completed weeks of gestation with KPSC insurance coverage during the first year of their life. We excluded infants from multiple births, infants with less than 2 medical encounters with documented vital signs including weight and height measurements during

follow-up, and infants whose mothers did not have KPSC health insurance coverage for at least 3 months before delivery to be able to assess *in-utero* antibiotic exposure antepartum. After

applying all inclusion and exclusion criteria, the cohort size was 223,431 children (71% of all children born in KPSC hospitals; Figure 2).

Figure 2. Flow chart of infants enrolled in the FAX study by in-utero exposure to antibiotics. KPSC, Kaiser Permanente Southern California.



Exposure Ascertainment

Primary exposure of interest is the *in-utero* exposure to antibiotics during pregnancy and includes oral, intramuscular, and intravenous administration. We divided the timing of antibiotic exposure into (1) time between conception and onset of labor (or admission for delivery) and (2) intrapartum, defined as the time between maternal admission for labor and delivery of the infant. For cases with longer inpatient stays before delivery, the intrapartum period is defined as 48 hours before delivery order to distinguish false labor from true labor.

Ex-utero exposure to antibiotics during childhood (including the neonatal period) and as indirect exposure to maternal antibiotic use during lactation will be extracted to control for independent effect of *ex-utero* exposure on the outcome of interest.

Outcome Ascertainment

Childhood Body Weight and Obesity

At KPSC, body weight and height are routinely measured by trained staff on calibrated scales at almost every medical office visit. In pediatrics and family practice, staff must complete a Web-based training session and successfully pass a certification process that includes knowledge of preparing patients for measuring weight and height and their competency is assessed. Data on weight and height will be extracted from all medical encounters. Biologically implausible values for weight and height data will be excluded [18,19]. Body mass index (BMI; kg/m²) will be used as untransformed BMI instead of sex-specific BMI-for-age percentiles developed by the Centers for Disease Control and Prevention [20] because estimates are more interpretable [21-23].

Other Outcomes

Childhood asthma and atopic disease will be extracted from electronic medical records. Pediatric asthma is defined as (1)

physician-diagnosed asthma (*International Classification of Diseases*, 9th revision, Clinical Modification codes ICD-9-CM 493.xx, ICD-10 J45.xx) and at least 2 prescriptions specific to asthma medication (beta-agonists or asthma controller medications or their combination) in year 1 and 2 after diagnosis or (2) physician-diagnosed wheezing (ICD-9-CM 786.07, ICD-10 R06.2) and at least 2 prescriptions specific to asthma medication (beta-agonists or asthma controller medications or their combination) in year 1 and 2 after diagnosis. Atopic disease is defined as physician-diagnosed allergic rhinitis (ICD-9-CM 477.x, ICD-10 J30.9), asthma, or atopic dermatitis (ICD-9-CM 691.8, ICD-10 L20.xx). Other outcomes may be added over time.

Demographic and Other Factors

Race and ethnicity information was obtained from health plan electronic medical records and administrative and birth records before 2011. As part of the implementation of meaningful use requirements for electronic medical records [24], self-reported race and ethnicity was collected systematically from members starting 2011. Typically, new and current members were asked to complete a self-report form that included separate questions for both their race and ethnicity. These forms were included in both membership applications and at clinical outpatient visits. The choices for race and ethnicity recorded were standardized across health care systems and followed national recommendations for mutually exclusive race categories [25,26]. Regardless of the race category endorsed, patients self-reporting Hispanic ethnicity were considered Hispanic according to recommendations from a national survey of Hispanics living in the United States that Hispanic people considered themselves a race of people and not an ethnicity [27]. If a patient's records contained 2 or more race categories (rather than a single category of *mixed race*), they were assigned the least prevalent race category in the US population. For example, if a patient indicated that they were both Native Hawaiian and Pacific Islander and non-Hispanic black, they were categorized as Native Hawaiian or Pacific Islander in our analyses. This was done to maximize our ability to understand differences in diagnoses and treatment for the least represented racial and ethnic minority patients. This is a convention used across many health care organizations using a standardized virtual data warehouse [28]. If race and ethnicity were missing, the available language preferences were used to impute race and ethnicity for Hispanics and Asians. We categorized race and ethnicity as non-Hispanic white (white), Hispanic (regardless of race), non-Hispanic black (black), Asian and Pacific Islander (API), and other or unknown race or ethnicity.

Neighborhood-level (based on census tract) education, neighborhood-level household income, and the neighborhood proportion of individuals below poverty line were used to indicate socioeconomic status. These population-level indicators were estimated by geocoding cohort members' addresses to 2010 US census block data [29]. Maternal education (individual-level data) is available from birth records. We also included insurance coverage through government health care assistance programs such as Medicaid as an additional proxy for socioeconomic status.

Gestational age is based on the clinical estimate of gestational age as recorded in the maternal electronic medical records [30]. Fetal growth is defined on the basis of the 2000 to 2015 race- and sex-specific nomogram (internal standard) and classified as small-for-gestational age when birth weight is less than the tenth or fifth percentile for gestational age [31,32].

Information on maternal medical and obstetrical history of the index pregnancy includes BMI, gestational weight gain, pregestational and gestational diabetes, and chronic and gestational hypertension. Maternal asthma is defined as physician-diagnosed asthma (ICD-9-CM 493.xx and ICD-10 J45.xx) before birth.

Breastfeeding was documented in progress notes (unstructured text format) between 2007 and 2010. To extract this information, we developed a natural language processing algorithm [33]. The overall ability of the natural language processing algorithm in accurately extracting breastfeeding status was assessed using manual chart review of a random sample of medical record notes from 500 children. Sensitivity, specificity, and positive and negative predictive values for breastfeeding for >6 months detected by natural language processing were 89%, 89%, and 83% and 93%, respectively [33]. After 2010, breastfeeding information was assessed from surveys administered during or before well-child visit surveys at well-baby health care visits at birth to 4 weeks, 2 months, 4 months, 6 months, 9 months, and 12 months of life [33]. Surveys are completed by the parent guardian; collection modes include patient portal, paper (with later data entry by medical support staff), and tablet computers in the waiting room. All survey answers are structured data fields embedded in electronic medical records [34].

Statistical Analysis

For analyses presented here, we compared clinical and demographic characteristics between *in-utero* antibiotic exposure groups using descriptive statistical methods including Pearson chi-square test or Fisher exact test (if data are sparse) for categorical variables and using analysis of variance or the Kruskal-Wallis test for continuous variables depending on the distribution. Maternal BMI before pregnancy was categorized as <18.5, 18.5 to 22.4, 22.5 to 24.9, 25.0 to 29.9, 30.0 to 34.9, 35.0 to 39.9, and ≥ 40 kg/m². The start of prenatal care was divided into a first visit <3, 4 to 6, >6 months of gestation and no care visits. Retention in the health plan was calculated as the proportion of children with health care coverage at any time within a certain year. All analyses were performed using SAS Enterprise Guide 5.1 (SAS Institute).

Results

The study cohort was comprised 114,464 male and 108,967 female infants born in KPSC hospitals between 2007 and 2015 to 177,666 mothers. About 67,050 out of 223,431 infants (30.00%) were born via cesarean section, whereas 17,191 out of 223,431 (7.69%) were born preterm. Approximately half of the infants were non-Hispanic whites ([Multimedia Appendix 1](#)). Almost 1 out of 10 infants (n=20,071, 8.98%) had insurance coverage through government health care assistance programs. Most mothers (n=199,099, 89.11%) initiated their prenatal care

at KPSC in their first trimester of pregnancy; about 22.52% of mothers (n=50,312) were obese with 9.59% of mothers (n=21,436) having a BMI ≥ 35 kg/m².

The *in-utero* exposure to antibiotics was frequent with 42,511 out of 223,431 (19.03%) of infants exposed during the antepartum period, 66,896 out of 223,431 (29.94%) during the intrapartum period, and 3731 out of 223,431 (1.67%) exposed during both the antepartum and intrapartum periods. About one-third of infants (76711 out of 223431, 34.33%) were not exposed to antibiotics *in-utero* (Multimedia Appendix 1). Compared with non-Hispanic white infants, black infants were more likely to be exposed to antibiotics *in-utero* overall; Hispanic infants were more likely to be exposed to antibiotics during pregnancy, and API infants were more likely to be exposed to antibiotics during the intrapartum period. Infants born preterm, with insurance coverage through government health care assistance programs, born to older mothers, born to

mothers with a higher BMI, and born to mothers who smoked during pregnancy were more likely to be exposed to antibiotics *in-utero*.

The 5-year retention of infants in the health plan was over 80% (Table 1) and it has been increasing steadily since 2007. Retention was the lowest for infants with unknown race or ethnicity and highest for Hispanic infants. The retention of infants did not differ between infants with and without insurance coverage through government health care assistance programs.

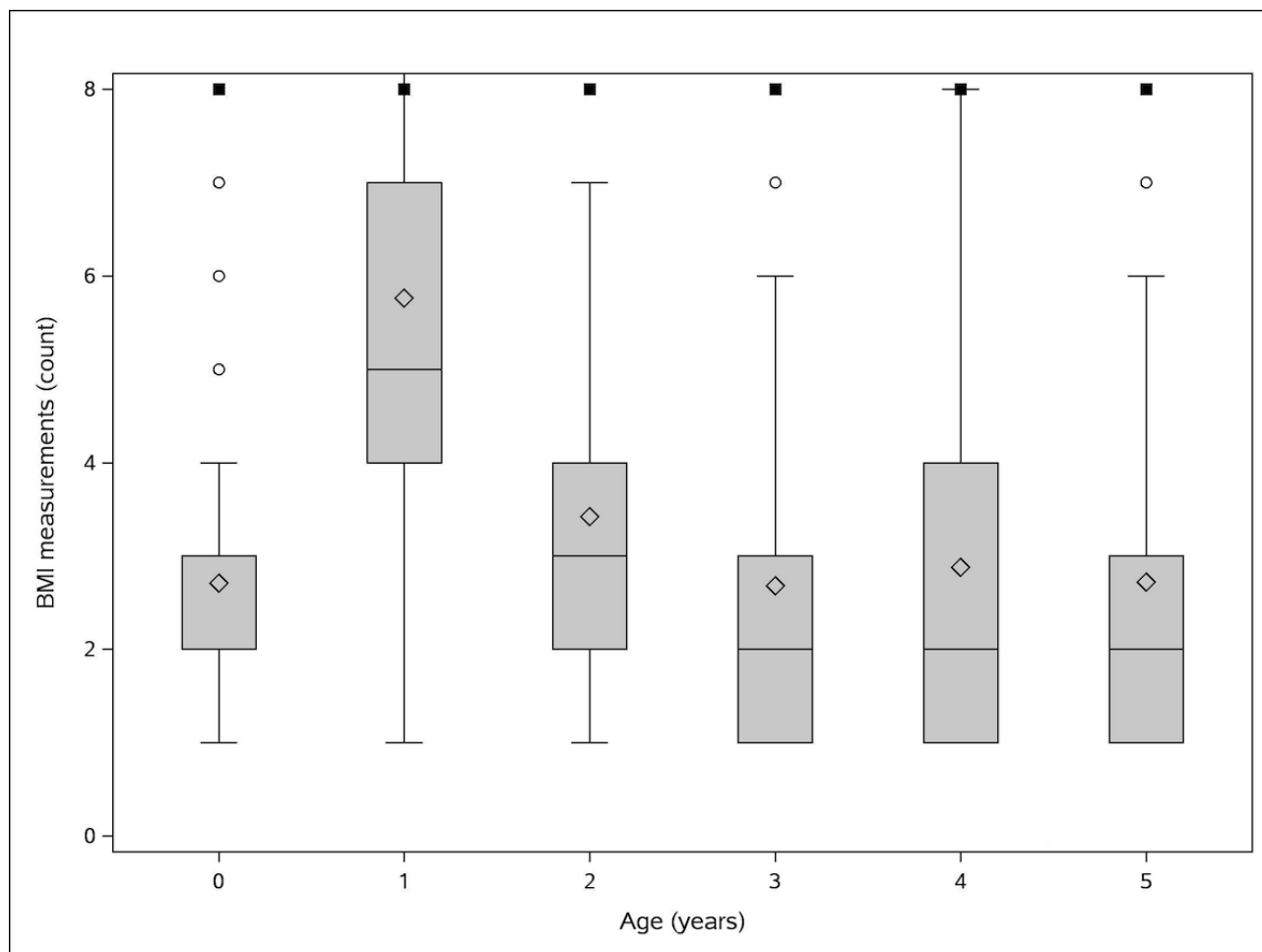
During the neonatal period, infants had a median of 3 BMI measurements recorded and during their first year of life, a median of 5 BMI measurements (Figure 3). The number of recorded BMI measurements per child and year then slowly declined to 2 in the fifth year of life. The availability of BMI measures was consistent across all birth cohorts from 2007 to 2015 (data not shown).

Table 1. Retention of infants by birth cohort, race and ethnicity, and government health care assistance.

Variable	Retention (years), n (%)			
	Baseline	1	3	5
Birth cohort				
2007	22,397 (10.02)	22,375 (99.90)	18,769 (83.80)	17,402 (77.70)
2008	23,242 (10.40)	23,219 (99.90)	19,849 (85.40)	18,245 (78.50)
2009	23,066 (10.32)	23,066 (100.00)	19,814 (85.90)	18,061 (78.30)
2010	23,294 (10.43)	23,294 (100.00)	19,916 (85.50)	18,542 (79.60)
2011	24,365 (10.90)	24,341 (99.90)	20,759 (85.20)	19,638 (80.60)
2012	25,621 (11.47)	25,595 (99.90)	22,085 (86.20)	20,753 (81.00)
2013	25,632 (11.47)	25,632 (100.00)	22,505 (87.80)	— ^a
2014	26,985 (12.08)	26,985 (100.00)	23,774 (88.10)	—
2015	28,829 (12.90)	28,800 (99.90)	—	—
Race and ethnicity				
White	63,085 (28.23)	63,085 (100.00)	52,991 (84.00)	49,017 (77.70)
Hispanic	105,699 (47.31)	105,593 (99.90)	92,698 (87.70)	88,153 (83.40)
Black	18,934 (8.47)	18,915 (99.90)	16,529 (87.30)	15,621 (82.50)
Asian and Pacific Islander	27,937 (12.50)	27,937 (100.00)	24,389 (87.30)	23,048 (82.50)
Others or Unknown	7776 (3.48)	7768 (99.90)	6182 (79.50)	5669 (72.90)
Government health care assistance				
No	203,360 (91.02)	203,157 (99.90)	175,703 (86.40)	165,128 (81.20)
Yes	20,071 (8.98)	20,071 (100.00)	17,241 (85.90)	16,418 (81.80)

^aNot applicable.

Figure 3. Box-and-whisker plot of frequency of body mass index measures per child by age (Age 0 includes the neonatal period defined as the first 28 days of life. Plot boxes reflect the interquartile range (IQR; 25th and 75th percentile) as box limits, median (blue line), and mean (blue diamond). Whiskers reflect the minimum and maximum within 1.5 x IQR. Outliers (black circles) were cut at a maximum of 8 measurements). BMI: body mass index.



Discussion

In total, 2 out of 3 infants included in the FAX study were exposed to antibiotics *in-utero*; the exposure primarily occurred during the intrapartum period. The use of antibiotics during pregnancy is a risk-versus-benefit decision because untreated infections are associated with significant risk for the unborn child [1,35,36]. Owing to the widespread use of antibiotics, understanding the short- and long-term risks of *in-utero* exposure to antibiotics is an important public health issue. Considering the high proportion of infants exposed, even small individual-level health risks from antibiotic exposure could result in significant population-level effects. Possible adverse childhood outcomes include microbiome disruption [37], obesity [38,39], and infections [40,41]. Future interventions can be targeted to attenuate the risk [42-47].

To address current gaps in the knowledge about the health consequences of *in-utero* antibiotic exposure, we created a large cohort study of infants with racial, ethnic and socioeconomic diversity. The large sample size is particularly useful to support the study of rare outcomes and smaller population segments defined by race and socioeconomic status. Available clinical information is robust and reflects *real-world* information that clinicians and health plans use to document health care rather

than research-quality data collected at prespecified study intervals [48].

Weight and height were frequently measured and recorded in the electronic medical records for calculation of BMI [19]. The frequency of BMI measurements per child together with the large sample size will allow us to model nonlinear trajectories of BMI or identify distinct BMI trajectories. We will be able to model these trajectories for the overall cohort and for the strata of children defined by the *in-utero* exposure to antibiotics ante- and intrapartum.

Several challenges for studies using data from the FAX cohort are noted. The use of routinely measured clinical weight and height may increase variation, which may bias potential risks toward the null. However, this bias will be compensated by the large sample size. Another source of variation is the variation in medical practice. In an ideal world, acute medical conditions such as infections are treated according to published recommendations. This may not always be the case in clinical practice. On the contrary, practice variation and the varying probability to be treated can be addressed in analyses by using appropriate statistical methods. In fact, practice variation can add knowledge about real-world settings, which can be readily translated into clinical practice.

Missing values may be frequent in routinely collected electronic medical record data and may not always be missing at random but they reflect real-world settings. The data compiled for the proposed study were collected for routine clinical care and not specifically for research purposes. However, most information such as race, ethnicity, and breastfeeding were collected for almost all patients [33,49]. To address any possible bias because of missing baseline or follow-up outcomes or covariates, we will examine baseline characteristics to determine if there are any systematic differences between the groups with and without missing data. If differences are found, appropriate estimation methods can be used to account for biases because of missing data, such as multiple imputations. Although addressing these challenges poses difficulty in the proposed research, the use of real-world clinical data also represents a key strength of the study.

Another potential challenge is the possibility of attrition because of patients leaving the health plan. KPSC is an open health care plan and members can enroll and disenroll. However, retention of members in the health plan, especially in the targeted age group, is high. To better understand the effects of attrition on the cohort characteristics, we will compare the characteristics (eg, demographics and BMI) of those who remain enrolled in KPSC and those who discontinued.

The current cohort of children will provide a unique opportunity to address key questions regarding the long-term sequelae of *in-utero* exposure to antibiotics in real-world data. The cohort shows a high retention rate and provides data from multiple medical visits over time, allowing us to model the trajectories of BMI over time.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Characteristics of infants born 2007-2015 and enrolled in the Fetal Antibiotic EXposure Study.

[[PDF File \(Adobe PDF File\), 74KB - resprot_v8i7e12065_app1.pdf](#)]

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Abbreviations

- API:** Asian and Pacific Islander
- BMI:** body mass index
- FAX:** Fetal Antibiotic EXposure
- GBS:** group B streptococcal
- KPSC:** Kaiser Permanente Southern California

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